

ESCOBAR - URIBE ASOCIADOS

A B O G A D O S

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2472/P

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES
E. S. D.

Re: Expediente No. 02.041.350

Solicitud de Patente en nombre de
McNEIL-PPC, INC.

SUPERINDUSTRIA Y COMERCIO

Radicación: 02041350 00000002 Folios: 219
Fecha (AND): 2002-04-14 16:22:01
Trámite: 002 PATENTES D 1 REGISTRO/ 329 COMPLETEN
El presente es un extracto de los datos de la solicitud de patente.

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en Bogotá, en la Carrera 11 A No. 94-76 Of. 305, obrando como apoderada de la sociedad McNEIL-PPC, INC., solicitante de la patente de la referencia, anexo al presente memorial los siguientes documentos:

1. Copia certificada de la solicitud de Patente Número 10/122,531 presentada en los Estados Unidos de América el día 15 de abril de 2002, con la debida traducción de lo pertinente, incluyendo el capítulo reivindicatorio.
2. Copia certificada de la solicitud de Patente Número 10/122,999 presentada en los Estados Unidos de América el día 12 de abril de 2002, con la debida traducción de lo pertinente, incluyendo el capítulo reivindicatorio.
3. Copia certificada de la solicitud de Patente Número 60/325,726 presentada en los Estados Unidos de América el día 28 de septiembre de 2001, con la debida traducción de lo pertinente, incluyendo el capítulo reivindicatorio.
4. Copia certificada de la solicitud de Patente Número 60/291,127 presentada en los Estados Unidos de América el día 15 de mayo de 2001, con la debida traducción de lo pertinente, incluyendo el capítulo reivindicatorio.

A este mismo respecto, debe tenerse en cuenta que en la primera página de las copias certificadas anteriormente mencionadas la Oficina de Patentes correspondiente certificó la fecha de presentación de estas solicitudes, cumpliéndose de esta forma todos y cada uno de los requisitos establecidos en el inciso segundo del artículo 10 de la Decisión 486 de la Comisión de la Comunidad Andina.

Señor Superintendente,



JIMENA ESCOBAR URIBE
C.C.39.779.452 de usaquén
T.P. 68228

ESTADOS UNIDOS DE AMERICA
A TODOS AQUELLOS A QUIENES EL PRESENTE LLEGUE:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS
UNIDOS
Oficina de Patentes y Marcas de los Estados Unidos

Junio 14, 2002

La presente es para certificar que el anexo es una copia fiel de los registros de la Oficina de Patentes y Marcas de los Estados Unidos, de los documentos de la solicitud de patente identificada más adelante, que cumplieron con los requerimientos para concederse una fecha de presentación de acuerdo con 35 USC 111.

Número de Solicitud: 10/122,531

Fecha de Presentación: Abril 15, 2002

Por la autoridad del
Comisionado de Patentes y Marca

(fdo) P. SWAIN
Oficial Certificador
Sello oficial de la Oficina de Patentes y Marcas de los
Estados Unidos de América

REIVINDICACIONES

1. Una composición formadora de película formada por:
 - 5 a) un formador de película seleccionado entre el grupo formado por un almidón céreo de maíz, dextrina de tapioca, derivado de un almidón de maíz céreo, derivado de dextrina de tapioca, y sus mezclas;
 - b) un espesador seleccionado entre el grupo formado por sucrosa, dextrosa, fructosa, y sus mezclas; y
 - 10 c) un plastificante,en donde la composición posee un lustre superficial por lo menos de 150 al aplicarse mediante recubrimiento por inmersión a un sustrato.
2. Una composición formadora de película formada por:
 - 15 a) un formador de película de almidón hidroxipropílico;
 - b) un espesador seleccionado entre el grupo formado por kappa carrageno, iota carrageno, maltodextrina, goma gelificante, agar, almidón gelificante, y derivados y mezclas de los mismos;
 - y

c) un plastificante,

en donde la composición posee un lustre superficial por lo menos de 150 al aplicarse mediante recubrimiento por inmersión a un sustrato.

- 5 3. La composición de la reivindicación 1, en la cual los plastificantes se seleccionan entre el grupo formado por polietilén glicol, glicerina, sorbitol, citrato trietillico, citrato tributílico, sebacato dibutílico, aceites vegetales, agentes activos de superficie, propilénglicol, monoacetato de glicerol, diacetato de glicerol, triacetato de glicerol, gomas naturales, y sus mezclas.
- 10
4. La composición de la reivindicación 2, en donde el plastificante se selecciona entre el grupo formado por glicerina, propilénglicol, polietilénglicol, alcoholes de azúcar y sus derivados y mezclas de los mismos.
- 15
5. La composición de la reivindicación 1, en donde el plastificante es glicerina.

6. La composición de la reivindicación 1, en donde el plastificante es glicerina y el espesador es sucrosa.
- 5 7. La composición de la reivindicación 1, en donde la composición está formada por, con base en el peso total seco de la composición,
 - 10 a) desde aproximadamente 40 por ciento hasta alrededor de 60 por ciento de un formador de película seleccionado entre el grupo formado por un almidón cáreo de maíz, dextrina de tapioca, derivado de un almidón cáreo de maíz, derivado de dextrina de tapioca, y sus mezclas;
 - b) desde aproximadamente 10 por ciento hasta alrededor de 20 por ciento de sucrosa; y
 - c) desde aproximadamente 20 por ciento hasta alrededor de 25 por ciento de glicerina.
- 15 8. La composición de la reivindicación 7, en donde la composición está formada por, con base en el peso total seco de la composición,
 - a) desde aproximadamente 50 por ciento hasta alrededor de 55 por ciento de un formador de película seleccionado entre el

- grupo formado por un almidón de maíz céreo, dextrina de tapioca, derivado de un almidón de maíz céreo, derivado de dextrina de tapioca, y sus mezclas;
- 5 b) desde aproximadamente 5 por ciento hasta alrededor de 25 por ciento de sucrosa; y
- c) desde aproximadamente 15 por ciento hasta alrededor de 30 por ciento de glicerina.
- 9. La composición de la reivindicación 7 que comprende adicionalmente
- 10 un intensificador de peso seleccionado entre el grupo formado por simeticona, polisorbato 80, y sus mezclas.
- 10. La composición de la reivindicación 7, que comprende adicionalmente,
- 15 con base en el peso total de la composición, hasta aproximadamente 14 por ciento de un agente para comunicar color.
- 11. Una forma de dosificación para suministrar agentes activos, comprendiendo dicha forma un recubrimiento exterior, dicho

recubrimiento exterior comprendiendo la composición de la reivindicación 6.

- 5
12. Una forma de dosificación farmacéutica que comprende un recubrimiento exterior de la composición de la reivindicación 7.
- 10
13. Una forma de dosificación farmacéutica que comprende un núcleo, un subrecubrimiento que cubre sustancialmente dicho núcleo, y un recubrimiento exterior que cubre sustancialmente dicho subrecubrimiento, en donde el recubrimiento exterior está formado por la composición de la reivindicación 7.
- 15
14. La forma de dosificación de la reivindicación 13 en donde el subrecubrimiento se selecciona entre el grupo formado por hidroxipropilmetilcelulosa, aceite de castor, maltodextrinas, polietilenglicol, polisorbato 80, y sus mezclas.

15. La forma de dosificación de la reivindicación 13, en donde el subrecubrimiento está formado por, con base en el peso seco total del subrecubrimiento,
- 5 a) desde aproximadamente 2 por ciento hasta alrededor de 8 por ciento de hidroxipropilmetilcelulosa; y
- b) desde aproximadamente 0,1 por ciento hasta alrededor de 1 por ciento de aceite de castor.
- 10 16. La forma de dosificación de la reivindicación 13, en donde el subrecubrimiento está formado por, con base en el peso seco total del subrecubrimiento,
- 15 a) desde aproximadamente 25 por ciento hasta alrededor de 40 por ciento de hidroxipropilmetilcelulosa;
- b) desde aproximadamente 50 por ciento hasta alrededor de 20 por ciento de maltodextrina; y
- c) desde aproximadamente 5 por ciento hasta alrededor de 10 por ciento de PEG 400.

17. La forma de dosificación de la reivindicación 13 en donde el subrecubrimiento está formado por, con base en el peso seco total del subrecubrimiento,
 - a) desde aproximadamente 20 por ciento hasta alrededor de 50 por ciento de hidroxietilcelulosa;
 - b) desde aproximadamente 45 por ciento hasta alrededor de 75 por ciento de maltodextrina; y
 - c) desde aproximadamente 1 por ciento hasta alrededor de 10 por ciento de PEG 400.
18. Una dispersión acuosa formada por la composición de la reivindicación 7.
19. La forma de dosificación de la reivindicación 13, que comprende una cantidad efectiva de un ingrediente farmacéutico activo, en donde dicha forma de dosificación satisface los requisitos de disolución de USP para formas de desprendimiento inmediato de dicho ingrediente farmacéutico activo.

20. Una dispersión acuosa formada por la composición de la reivindicación 7.
21. La dispersión acuosa de la reivindicación 20, que comprende, con base en el peso total de la dispersión:
- a) desde aproximadamente 5 por ciento hasta alrededor de 15 por ciento de sucrosa;
 - b) desde aproximadamente 10 por ciento hasta alrededor de 15 por ciento de glicerina; y
 - c) desde aproximadamente 20 por ciento hasta alrededor de 35 por ciento de un formador de película seleccionado entre el grupo formado por un almidón céreo de maíz, dextrina de tapioca, derivado de un almidón céreo de maíz, derivado de dextrina de tapioca, y sus mezclas.
22. El método de hacer tabletas recubiertas a partir de las dispersiones acuosas de la reivindicación 20, que comprende recubrir por inmersión tabletas en la dispersión acuosa bajo condiciones suficientes.

23. Una forma de dosificación farmacéutica que comprende un núcleo y un recubrimiento;
cubriendo sustancialmente dicho recubrimiento dicho núcleo, en donde dicho recubrimiento está formado por la composición de la reivindicación 6.
- 5
24. Un medicamento simulado similar a cápsula, que comprende:
- a. un núcleo que tiene un primero y un segundo extremo,
 - b. una primera capa de recubrimiento que tiene un primer color provisto sobre dicho primer extremo de dicho núcleo;
 - c. una segunda capa de recubrimiento que tiene un segundo color sobre dicho segundo extremo de dicho núcleo, dicho primer color es diferente a dicho segundo color;
- 10
- en donde por lo menos una de dichas primera capa de recubrimiento y segunda capa de recubrimiento está formada por una composición de capa de recubrimiento formada por la composición de la reivindicación 6.
- 15

25. El medicamento de la reivindicación 24 en donde al menos una capa de recubrimiento está formada por, con relación al peso seco total de tal capa de recubrimiento,
- 5 a) desde aproximadamente 40 por ciento hasta alrededor de 60 por ciento de un formador de película seleccionado entre almidón de maíz céreo, dextrina de tapioca, y derivados, y mezclas de los mismos;
- b) desde aproximadamente 10 por ciento hasta alrededor de 20 por ciento de sucrosa; y
- 10 c) desde aproximadamente 20 por ciento hasta alrededor de 25 por ciento de glicerina.
26. El medicamento de la reivindicación 25 que comprende adicionalmente una capa de subrecubrimiento que cubre
- 15 sustancialmente dicho núcleo de tableta, provista dicha capa de subrecubrimiento entre dicho núcleo de tableta y dicha primera capa de recubrimiento y dicha segunda capa de recubrimiento.

27. El medicamento de la reivindicación 26, en donde el subrecubrimiento comprende materiales seleccionados entre el grupo formado por éteres de celulosa, plastificantes, polícarbohidratos, pigmentos, opacificantes y sus mezclas.

5

28. La composición de la reivindicación 2, en donde la composición está formada por, con base en el peso total seco de la composición,

- a) desde aproximadamente 25 por ciento hasta alrededor de 80 por ciento de almidón hidroxipropílico;
- 10 b) desde aproximadamente 0.1 por ciento hasta alrededor de 33 por ciento de un espesador seleccionado entre el grupo formado por kappa carrageno, iota carrageno, maltodextrina, goma gelante, agar, almidón gelificante, y sus mezclas; y
- c) desde aproximadamente 11 por ciento hasta alrededor de 60
- 15 por ciento de un plastificante seleccionado entre el grupo formado por glicerina, propilenglicol, polietilenglicol, alcoholes de azúcar y sus mezclas.

29. Una forma de dosificación para suministrar agentes activos, comprendiendo dicha forma un recubrimiento exterior, comprendiendo dicho recubrimiento exterior la composición de la reivindicación 4.
- 5 30. Una forma de dosificación farmacéutica que comprende un núcleo, un subrecubrimiento que cubre sustancialmente dicho núcleo, y un recubrimiento exterior que cubre sustancialmente dicho subrecubrimiento, en donde el recubrimiento exterior está formado por la composición de la reivindicación 4.
- 10 31. Un medicamento similar a cápsula simulada que comprende:
- a. un núcleo que tiene un primer extremo y un segundo extremo,
 - b. una primera capa de recubrimiento que tiene un primer color provisto sobre dicho primer extremo de dicho núcleo;
 - 15 c. una segunda capa de recubrimiento que tiene un segundo color sobre dicho segundo extremo de dicho núcleo, en donde dicho primer color es diferente a dicho segundo color;
- en donde por lo menos una de dichas primera capa de recubrimiento y segunda capa de recubrimiento está formada por una composición de

capa de recubrimiento formada por la composición de la reivindicación 4.

- 5
32. La composición de la reivindicación 2, en donde los plastificantes se seleccionan entre el grupo formado por polietilenglicol, glicerina, sorbitol, citrato de trietilo, citrato de tributilo, sebecato de dibutilo, aceites vegetales, agentes activos de superficie, polietilenglicol, monoacetato de glicerol, diacetato de glicerol, triacetato de glicerol, gomas naturales y sus mezclas.
- 10
33. La composición de la reivindicación 2, en donde el plastificante es glicerina.
- 15
34. La composición de la reivindicación 2, en donde el almidón gelificante es fosfato hidroxipropílico de almidón.
35. La composición de la reivindicación 2, en donde el almidón gelificante es un almidón hidrolizado.

PA 852987

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

June 14, 2002

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 10/122,531

FILING DATE: April 15, 2002

**By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS**



**P. SWAIN
Certifying Officer**

Please type a plus sign (+) inside this box ☒

04-16-02

109

UTILITY
PATENT APPLICATION
TRANSMITTAL

Attorney Docket No.

MCP-309

First Inventor

Cynthia Gulian et al.

Title

DIP COATING COMPOSITIONS CONTAINING STARCH OR DEXTRIN

Express Mail Label No.

EV 065841588 US

APPLICATION ELEMENTS

ADDRESS TO:

Commissioner for Patents
Box Patent Application
Washington, DC 20231

See MPEP Chapter 800 concerning utility patent application contents.

1. ☒ Fee Transmittal Form (e.g., PTO/SB/17)
(submit an original and a duplicate for fee processing)

2. ☐ Applicant claims small entity status.

3. ☒ Specification [Total Pages - 38]

(Preferred arrangement set forth below)

- Descriptive Title of the Invention
- Cross Reference to Related Applications
- Statement Regarding Fed sponsored R&D
- Reference to sequence listing, a table, or a computer program listing appendix
- Background of the Invention
- Brief Summary of the Invention
- Brief Description of the Drawings (if filed)
- Detailed Description
- Claim(s)
- Abstract of the Disclosure

4. ☐ Drawing(s)/35 USC 113 [Total Sheets]

5. Oath or Declaration [Total Pages - 4]

a. ☒ Unexecuted

b. ☐ Copy from a prior application (37 CFR 1.63(d))
(for continuation/divisional with Box 18 completed)

1. ☐ DELETION OF INVENTOR(S)

Signed statement attached detailing
inventor(s) named in the prior application,
see 37 CFR 1.63(d)(2) and 1.33(b).

6. ☐ Application Data Sheet. See 37 CFR 1.78

7. ☐ CD-ROM or CD-R in duplicate, large table or
Computer Program (Appendix)

8. Nucleotide and/or Amino Acid Sequence
Submission (if applicable, all necessary)

a. ☐ Computer Readable Form (CRF)

b. ☐ Specification Sequence Listing on:

i. ☐ CD-ROM or CD-R (2 copies); or

ii. ☐ paper

c. ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

9. ☐ Assignment Papers (cover sheet & document(s))

10. ☐ 37 CFR 3.73(b) Statement ☐ Power of Attorney
(when there is an assignee)

11. ☐ English Translation Document (if applicable)

12. ☐ Information Disclosure Statement

(IDS)/PTO-1449 ☐ Copies of IDS Citations

13. ☐ Preliminary Amendment

14. ☒ Return Receipt Postcard (MPEP 503)

(Should be specifically itemized)

15. ☐ Certified Copy of Priority Document(s)

(if foreign priority is claimed)

16. ☐ Request and Certifications under 35 U.S.C. 122

(b)(2)(B)(i). Applicant must attach form
PTO/SB/35 or its equivalent.

17. ☒ Other (Express Mail Certificate)

18. ☐ If a CONTINUING APPLICATION, check appropriate box and supply the requisite information below and in a preliminary amendment, or in an Application Data Sheet under 37 CFR 1.78:

☒ Continuation-in-Part (CIP) of prior appl. No.: 10/ (N/A) (Atty. Docket MCP-303), filed April 12, 2002.

Prior application information: Examiner Group Art Unit:

For CONTINUATION or DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 5b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

19. CORRESPONDENCE ADDRESS

☒ Customer Number or Bar Code Label 000027777 or ☐ Correspondence Address below

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Address: Johnson & Johnson

One Johnson & Johnson Plaza

New Brunswick, NJ 08933-7003 USA

20. TELEPHONE CONTACT

Please direct all telephone calls or telefaxes to Michele G. Mangini at:

Telephone: (732) 524-2810

Fax: (732) 524-2808

21. SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

NAME

Michele G. Mangini

Reg. No. 38,808

SIGNATURE

Michele Mangini

DATE

April 15, 2002

04/15/02

10122531-041502

1036 U.S. PT
10/12/02
04/15/02

FEE TRANSMITTAL	Complete if Known	
	Application Number	
	Filing Date	April 15, 2002
	First Named Inventor	Cynthia Gulian et al.
	Group Art Unit	
	Examiner Name	
	Attorney Docket Number	MCP-309

FEE CALCULATION

CLAIMS AS FILED

(1)	(2)	(3)	(4)	(5)
FOR:	NUMBER FILED	NUMBER EXTRA	RATE	BASIC FEE \$740.00
TOTAL CLAIMS	35 - 20 =	15	x 18.00	\$ 270.00
INDEPENDENT CLAIMS	2 - 3 =	0	x 84.00	\$ 0.00
MULTIPLE DEPENDENT CLAIMS	☐	N/A	\$280.00	
			TOTAL FEES	\$1010.00

METHOD OF PAYMENT

- ☒ Please charge Deposit Account No. 10-0750/MCP-309/MGM in the amount of \$1010.00. Three copies of this sheet are enclosed.
- ☒ The Commissioner is hereby authorized to charge any additional fees which may be required in connection with the filing of this communication, or credit any overpayment, to Account No. 10-0750/MCP-309/MGM. Three copies of this sheet are enclosed.

SUBMITTED BY:		Complete (if applicable)	
Typed or Printed Name	Michèle G. Mangini	Reg. No. 36,806	
Signature		Date: 4/15/02	Deposit Account No. 10-0750

10122531.041502

IN THE UNITED STATES
PATENT AND TRADEMARK OFFICE

Applicant: Cynthia Gulian et al.

For : DIP COATING COMPOSITIONS CONTAINING STARCH OR
DEXTRIN

Express Mail Certificate

"Express Mail" mailing number: EV 065841588 US

Date of Deposit: April 15, 2002

I hereby certify that this complete application (including 36 specification pages and 35 claims), an unexecuted Declaration and Power of Attorney and Patent Application Transmittal (2 pp.), is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner for Patents, Box Patent Applications, Washington, D.C. 20231.

An executed Combined Declaration and Power of Attorney will be submitted to the United States Patent and Trademark Office upon receipt of the U.S. Serial Number for this patent application.

Karen Hall-Morgan

(Typed or printed name of person mailing paper or fee)

Karen Hall-Morgan

(Signature of person mailing paper or fee)

10122531.041502

DIP COATING COMPOSITIONS CONTAINING STARCH OR DEXTRIN

5

CROSS-REFERENCE TO RELATED APPLICATION

This Application is a continuation in part of United States Application Number _____ (Attorney Docket No. MCP 303) filed 12 April 2002, which claimed the benefit of
10 United States Application Number 60/291,127 filed on 15 May 2001 and United States Application Number 60/325,726 filed 28 September 2001, which are all incorporated by reference in their entireties herein.

FIELD OF THE INVENTION

15 This invention relates to novel, water soluble, gelatin-free compositions for dip coating substrates, such as tablets and capsules, and methods for producing such dosage forms. This invention further relates to a method for increasing the weight gain of a water soluble, gelatin-free, film forming coating on a dip-coated tablet or caplet.

20 **BACKGROUND OF THE INVENTION**

During most of this century, hard gelatin capsules were a popular dosage form for prescription and over-the-counter (OTC) drugs. The ability to combine capsule halves having different colors provided manufacturers with a unique means of distinguishing various pharmaceutical products. Many patients preferred capsules over tablets, perceiving them as being
25 easier to swallow. This consumer preference prompted pharmaceutical manufacturers to market certain products in capsule form even when they were also available in tablet form.

Generally, empty hard gelatin capsules are manufactured using automated equipment. This equipment employs rows of stainless steel pins, mounted on bars or plates, which are dipped into a gelatin solution maintained at a uniform temperature and fluidity. The pins are then
30 withdrawn from the gelatin solution, rotated, and then inserted into drying kline through which a strong blast of filtered air with controlled humidity is forced. A crude capsule half is thus formed over each pin during drying. Each capsule half is then stripped, trimmed to uniform length, filled and joined to an appropriate mating half.

An alternative to capsule products are caplets, which are solid, oblong tablets that are
35 often coated with various polymers such as cellulose ethers to improve their aesthetics, stability, and swallowability. Typically, such polymers are applied to the tablets either from solution in organic solvents, or from aqueous dispersion via spraying. However, such spray-coated tablets lack the shiny surface and elegance of the hard gelatin capsules. Additionally, it is not commercially feasible to spray-coat a tablet with a different color coating on each end.

40 Another alternative to capsule products are "gelcaps," which are elegant, shiny, consumer-preferred dosage forms that are prepared by dipping each half of an elongated tablet in two different colors of gelatin solution. See United States Patent Nos.: 4,820,524; 5,538,125;

MCP-309

1012251.041502

5,685,589; 5,770,225; 5,198,227; and 5,286,233, which are all incorporated by reference herein. A similar dosage form, commercially available as a "geltab," is prepared by dipping each half of a round, convex tablet into different colors of gelatin solution, as described in United States Patent Nos. 5,228,916, US5,436,026 and US5,679,406, which are all incorporated by reference herein.

As used herein, such "gelcaps" and "geltabs" shall be included within the broader term, "tablets."

However, the use of gelatin as a pharmaceutical coating material presents certain disadvantages and limitations, including the potential for decreased dissolution rate after extended storage due to cross-linking of the gelatin, potential for microbial contamination of the gelatin solution during processing, and long processing times due to extensive drying requirements.

Further, the energy-related costs associated with gelatin coatings tend to be high since the gelatin material is typically applied to the substrates at an elevated temperature of at least about 40°C in order to maintain fluidity of the gelatin, while the substrates are maintained at about 50°C in order to minimize microbial growth.

Various attempts have been made to produce gelatin-free hard shell capsules. For example, WO 00/18835 discloses the combination of starch ethers or oxidized starch and hydrocolloids for use in preparing hard capsule shells via conventional dip molding processing. See also U.S. Pat. No. 4,001,211 (capsules prepared via pin dip coating with thermogelled methylcellulose ether compositions). However, due to potential tampering concerns, hard gelatin capsules are no longer a preferred delivery system for consumer (over-the-counter) pharmaceuticals, dietary supplements, or other such products. Additionally, the properties of an ideal composition into which steel pins are to be dipped then dried to form hard capsule shells thereon are not necessarily the same as those for dipping tablets to form a coating thereon. For example, relevant physical properties such as viscosity, weight-gain, film thickness, tensile strength, elasticity, and moisture content will differ between compositions for hard capsule formation and for coating tablets. See e.g., U.S. Pat. No. 1,787,777 (Optimal temperatures of the substrate and coating solution, residence times in the solution, and drying conditions differ.)

One disadvantage associated with dipping tablets or capsules into a non-gelatin coating system is that the resulting coatings often lack adequate tensile strength, plasticity, hardness, and thickness. Moreover, the inclusion of plasticizers into such non-gelatin coating systems often results in tablets having soft, tacky coatings without a hardness sufficient to maintain their shape or smoothness during handling. In addition, many non-gelatin compositions do not adhere to the tablet substrate in an amount sufficient to uniformly cover the tablet after a single dipping. Further, many non-gelatin compositions lack the sufficient rheological properties necessary to maintain uniform color dispersion throughout the dipping and drying process. Although attempts have been made to improve the rheological properties of these compositions by, for example, increasing their solids content in order to increase viscosity. However, such compositions often disadvantageously resulted in undesirable coating aesthetics such as surface roughness, decreased gloss, and non-uniform coating thickness.

It is desirable to find a dip coating material, which not only produces a similar elegant, shiny, high gloss, consumer-preferred dosage form similar to that of gelatin-coated forms, but which is absent the limitations of gelatin, particularly those noted above.

SUMMARY OF THE INVENTION

The present invention provides for a film forming composition comprised of, consisting of, and/or consisting essentially of:

a) a film former selected from the group consisting of waxy maize starch, tapioca dextrin, derivative of a waxy maize starch, derivative of a tapioca dextrin, and mixtures thereof;

b) a thickener selected from the group consisting of sucrose, dextrose, fructose, and mixtures thereof; and

c) a plasticizer,

wherein the composition possesses a surface gloss of at least 150 when applied via dip coating to a substrate.

Another embodiment of the present invention is directed to a film forming composition comprised of, consisting of, and/or consisting essentially of:

a) a hydroxypropyl starch film former;

b) a thickener selected from the group consisting of kappa carrageenan, iota carrageenan, maltodextrin, gellan gum, agar, gelling starch, and derivatives and mixtures thereof; and

c) a plasticizer,

wherein the composition possesses a surface gloss of at least 150 when applied via dip coating to a substrate.

We have found that when a dosage form is coated with the composition of the present invention, the result is an elegant, shiny, high gloss, consumer-preferred dosage form similar to that of a gelatin-coated form, but which lacks the limitations associated with gelatin, particularly those noted above. We have also found that when such a composition is used in dip coating and spray coating operations, it does not inhibit the dissolution of the active coated therewith. Further, we have found that the color uniformity of dosage forms coated with such compositions is improved upon the addition of a weight gain enhancer thereto.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, "capsules" refer to hard shell compartments that enclose a doseable ingredient. "Tablets," as used herein, refer to compressed or molded solid dosage forms of any shape or size. "Caplets," as used herein, refer to solid, oblong-shaped tablets. "Gelcaps" refer to solid caplets having a glossy gelatinous coating, and "galtabs" refer to solid tablets having flat sides, convex opposing faces, and a glossy gelatinous coating. "Hardness" as used herein in connection with films or coatings indicates the resistance of the film/coating to deformation upon impact. "Water soluble," as used herein in connection with non-polymeric materials, shall mean

from sparingly soluble to very soluble, i.e., not more than 100 parts water required to dissolve 1 part of the non-polymeric, water soluble solute. See Remington, "The Science and Practice of Pharmacy," pages 208 – 209 (2000). "Water soluble," as used herein in connection with polymeric materials, shall mean that the polymer swells in water and can be dispersed at the molecular level to form a homogeneous dispersion or colloidal "solution." "Surface gloss" as used herein, shall refer to amount of light reflectance as measured at a 80 degree incident angle using the method set forth in Example 7 herein.

Dimethicone is a well known pharmaceutical material consisting of linear siloxane polymers containing repeating units of the formula $-(CH_2)_nSiO-$, stabilized with trimethylsiloxy end blocking units of the formula $[(CH_3)_3SiO-]$. Simethicone is the mixture of dimethicone and silicon dioxide. For the purposes of this invention, the two materials may be used interchangeably.

The first embodiment of this invention is directed to water soluble, substantially gelatin-free, film forming compositions for dip coating tablets or manufacturing capsules via a dip molding process. One composition comprises, consists of, and/or consists essentially of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose; and a thickener, such as a hydrocolloid, e.g., xanthan gum or carrageenan. In another embodiment, the composition comprises, consists of, and/or consists essentially of a film former such as a modified starch selected from waxy maize starch, tapioca dextrin, and derivatives and mixtures thereof; a thickener selected from sucrose, dextrose, fructose, maltodextrin, polydextrose, and derivatives and mixtures thereof; and a plasticizer, e.g., polyethylene glycol, propylene glycol, vegetable oils such as castor oil, glycerin, and mixtures thereof. In another embodiment, the composition comprises, consists of, and/or consists essentially of a film former such as hydroxypropyl starch; a thickener selected from kappa or iota carrageenan, maltodextrin, gellan gum, agar, gelling starches, and derivatives and mixtures thereof; and a plasticizer. In yet another embodiment, the composition comprises, consists of, and/or consists essentially of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose; and optionally a plasticizer, such as vegetable oils, e.g., castor oil; and may optionally be substantially free of thickeners such as hydrocolloids, e.g. xanthan gum. In yet another embodiment, the composition comprises, consists of, and/or consists essentially of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose; an extender, such as polycarbohydrates, e.g. maltodextrin; and optionally a plasticizer, such as glycols, e.g., polyethylene glycol; and may optionally be substantially free of thickeners such as hydrocolloids, e.g. xanthan gum. As used herein, "substantially gelatin-free" shall mean less than about 1 percent, e.g. less than about 0.5 percent, of gelatin in the composition, and "substantially free of thickeners" shall mean less than about 1 percent, e.g. less than about 0.01 percent, of thickeners in the composition.

Any film former known in the art is suitable for use in film forming composition of the present invention. Examples of suitable film formers include, but are not limited to, polyvinylalcohol (PVA), hydroxypropyl starch, hydroxyethyl starch, pullulan, methylcellulose, carboxymethyl starch, methylcellulose, hydroxypropylcellulose (HPC), hydroxyethylmethylcellulose (HEMC), hydroxypropylmethylcellulose (HPMC), hydroxybutylmethylcellulose (HBMG),

hydroxyethylcellulose (HEEC), hydroxyethylhydroxypropylmethyl cellulose (HEMPMC), methacrylic acid copolymers, methacrylate ester copolymers, polyvinyl alcohol and polyethylene glycol copolymers, proteins such as whey protein, egg albumin, casein, casein isolates, soy protein and soy protein isolates, pre-gelatinized starches, film-forming modified starches, and copolymers, derivatives and mixtures thereof.

One suitable hydroxypropylmethylcellulose compound is "HPMC 2910", which is a cellulose ether having a degree of substitution of about 1.9 and a hydroxypropyl molar substitution of 0.23, and containing, based upon the total weight of the compound, from about 29% to about 30% methoxyl and from about 7% to about 12% hydroxypropyl groups. HPMC 2910 is commercially available from the Dow Chemical Company under the tradename, "Methocel E." "Methocel E5," which is one grade of HPMC-2910 suitable for use in the present invention, has a viscosity of about 4 to 6 cps (4 to 6 millipascal-seconds) at 20 °C in a 2% aqueous solution as determined by a Ubbelohde viscometer. Similarly, "Methocel E8," which is another grade of HPMC-2910 suitable for use in the present invention, has a viscosity of about 5 to 7 cps (5 to 7 millipascal-seconds) at 20 °C in a 2% aqueous solution as determined by a Ubbelohde viscometer. "Methocel E16," which is another grade of HPMC-2910 suitable for use in the present invention, has a viscosity of about 15000 cps (15 millipascal-seconds) at 20 °C in a 2% aqueous solution as determined by a Ubbelohde viscometer. As used herein, "degree of substitution" shall mean the average number of substituent groups attached to an anhydroglucose ring, and "hydroxypropyl molar substitution" shall mean the number of moles of hydroxypropyl per mole anhydroglucose.

One suitable polyvinyl alcohol and polyethylene glycol copolymer is commercially available from BASF Corporation under the tradename "Kollcoat IR".

As used herein, "modified starches" include starches that have been modified via crosslinking and/or other chemical modification for improved stability or optimized performance, or physical modification for improved solubility properties or optimized performance. Examples of chemically-modified starches are well known in the art and typically include those starches that have been chemically treated to cause replacement of some of its hydroxyl groups with either ester or ether groups. Crosslinking, as used herein, may occur in modified starches when two hydroxyl groups on neighboring starch molecules are chemically linked. As used herein, "pre-gelatinized starches" or "instantized starches" refers to physically modified starches that have been pre-wetted, then dried to enhance their cold-water solubility. Suitable modified starches are commercially available from several suppliers such as, for example, A.E. Staley Manufacturing Company, and National Starch & Chemical Company.

A suitable film forming modified starch includes the pre-gelatinized waxy maize derivative starches that are commercially available from National Starch & Chemical Company under the tradenames, "Purity Gum" and "FilmSet", and derivatives, copolymers, and mixtures thereof. Such waxy maize starches typically contain, based upon the total weight of the starch, from about 0 percent to about 18 percent of amylose and from about 100 percent to about 88 percent of amylopectin.

Another suitable film forming modified starch includes the hydroxypropylated starches, in which some of the hydroxyl groups of the starch have been etherified with hydroxypropyl groups, usually via treatment with propylene oxide. One example of a suitable hydroxypropyl starch that possesses film-forming properties is available from Grain Processing Company under the tradename, "Pure-Cote B790".

Suitable film forming tapioca dextrins include those available from National Starch & Chemical Company under the tradename, "Crystal Gum" or "K-4484," and derivatives thereof such as modified food starch derived from tapioca, which is available from National Starch and Chemical under the tradename, "Purity Gum 40," and copolymers and mixtures thereof.

Any thickener known in the art is suitable for use in the film forming composition of the present invention. Examples of such thickeners include but are not limited to hydrocolloids such as alginates, agar, guar gum, locust bean gum, kappa carrageenan, iota carrageenan, tara, gum arabic, tragacanth, pectin, xanthan gum, gellan gum, maltodextrin, galactomannan, pustulan, laminarin, scleroglucan, gum arabic, inulin, pectin, wheatan, rhamnan, zooglan, methylcellulose, chitin, cyclodextrin, chitosan, clays, gelling starches such as acid hydrolyzed starches and derivatives and mixtures thereof. Additional suitable thickeners include sucrose, dextrose, fructose, maltodextrin, polydextrose, and the like, and derivatives and combinations thereof.

Suitable xanthan gums include those available from C.P. Kelco Company under the tradename, "Keltrol 1000," "Xantrol 180," or "K9B310."

Suitable clays include smectites such as bentonite, kaolin, and laponite; magnesium trisilicate, magnesium aluminum silicate, and the like, and derivatives and mixtures thereof.

"Acid-hydrolyzed starch," as used herein, is one type of modified starch that results from treating a starch suspension with dilute acid at a temperature below the gelatinization point of the starch. During the acid hydrolysis, the granular form of the starch is maintained in the starch suspension, and the hydrolysis reaction is ended by neutralization, filtration and drying once the desired degree of hydrolysis is reached. As a result, the average molecular size of the starch polymers is reduced. Acid-hydrolyzed starches (also known as "thin boiling starches") tend to have a much lower hot viscosity than the same native starch as well as a strong tendency to gel when cooled.

"Gelling starches," as used herein, include those starches that, when combined with water and heated to a temperature sufficient to form a solution, thereafter form a gel upon cooling to a temperature below the gelation point of the starch. Examples of gelling starches include, but are not limited to, acid hydrolyzed starches such as that available from Grain Processing Corporation under the tradename, "Pure-Set B950"; hydroxypropyl distarch phosphate such as that available from Grain Processing Corporation under the tradename, "Pure-Gel B990", and mixtures thereof.

Any plasticizer known in the pharmaceutical art is suitable for use in the present invention, and may include, but not be limited to polyethylene glycol; glycerin; sugar alcohols; triethyl citrate; tributyl citrate; dibutyl sebacate; vegetable oils such as castor oil; surfactants such as polysorbates, sodium lauryl sulfates, and dioctyl-sodium sulfosuccinates; propylene glycol; mono acetate of glycerol; diacetate of glycerol; triacetate of glycerol; natural gums and mixtures

thereof. Suitable sugar-alcohols include sorbitol, mannitol, xylitol, maltitol, erythritol, lactitol, and mixtures thereof. In solutions containing a cellulose ether film former, an optional plasticizer may be present in an amount, based upon the total weight of the solution, from about 0 percent to about 40 percent.

5 In one embodiment, the film forming composition for dip coating substrates may be substantially free of gelatin, i.e., e.g. contains less than about 1%, or less than about 0.01% of gelatin.

10 In another embodiment, the film forming composition for dip coating substrates may be substantially free of bovine derived materials, i.e., e.g. contains less than about 1%, or less than about 0.01% of bovine derived materials.

In embodiments wherein a cellulose ether film former is used in the composition, the film forming composition for dip coating substrates may be substantially free of hydrocolloids, i.e., e.g. contains less than about 1%, or less than about 0.01% of hydrocolloids.

15 In yet another embodiment, the film forming composition for dip coating substrates may be substantially free of plasticizers, i.e., e.g. contains less than about 1%, or less than about 0.01% of plasticizers.

20 In one embodiment, the film forming composition for dip coating substrates contains, based upon the total dry solids weight of the composition, from about 95 percent to less than about 100 percent, e.g. from about 95 percent to about 99.5 percent, of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose; and from about 0.5 percent to about 5 percent of a thickener such as a hydrocolloid, e.g., xanthan gum.

25 In another embodiment, the film forming composition for dip coating substrates contains, based upon the total dry solids weight of the composition, from about 40 percent to about 60 percent, e.g. from about 50 percent to about 55 percent, of a modified starch, e.g. a waxy maize starch, a tapioca dextrin, and/or mixtures and derivatives thereof; from about 15 percent to about 30 percent, e.g., from about 20 percent to about 25 percent of a plasticizer, e.g., glycerin, polyethylene glycol, propylene glycol, castor oil, and mixtures thereof; and from about 5 percent to about 25 percent, e.g., from about 10 percent to about 20 percent, of a thickener, e.g., sucrose, dextrose, fructose, maltodextrin, polydextrose, and mixtures thereof.

30 In yet another embodiment, the film forming composition for dip coating substrates contains, based upon the total dry solids weight of the composition, from about 25 percent to about 80 percent, e.g. from about 50 to about 75 percent, of a film former such as a chemically modified starch, e.g. hydroxypropyl starch; from about 0.10 percent to about 33 percent, e.g. from about 0.15 percent to about 1 percent, or from about 10 percent to about 25 percent of a thickening agent; and from about 11 percent to about 60 percent, e.g. from about 20 percent to about 40 percent of a plasticizer.

35 In one embodiment wherein the film former is a chemically modified starch, the thickener may be selected from the group consisting of kappa or iota carrageenan, maltodextrin, gellan gum, agar, gelling starch and derivatives and mixtures thereof.

In one embodiment wherein the film former is a chemically modified starch, the plasticizer may be selected from the group consisting of glycerin, propylene glycol, polyethylene glycol, sugar alcohols and derivatives and mixtures thereof.

In one embodiment, the film forming composition for dip coating substrates contains, based upon the total dry solids weight of the composition, from about 95 percent to about 100 percent, e.g. from about 97 percent to about 100 percent, of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose.

In another embodiment, the film forming composition for dip coating substrates contains, based upon the total dry solids weight of the composition, from about 95 percent to about 100 percent, e.g. from about 97 percent to about 100 percent, of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose, and is substantially free of hydrocolloids, i.e., e.g. contains less than about 1%, or less than about 0.01% of hydrocolloids.

In yet another embodiment, the film forming composition for dip coating substrates contains, based upon the total dry solids weight of the composition, from about 95 percent to about 100 percent, e.g. from about 97 percent to about 100 percent, of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose; and from about 0.1 percent to about 1.0 percent, e.g. from about 0.25 percent to about 0.5 percent of a plasticizer such as vegetable oils, e.g. Castor Oil.

In yet another embodiment, the film forming composition for dip coating substrates contains, based upon the total dry solids weight of the composition, from about 5 percent to about 99 percent, e.g. from about 80 percent to about 90 percent, or from about 80 percent to about 90 percent of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose; from about 1 percent to about 80 percent, e.g. from about 5 percent to about 50 percent or from about 5 percent to about 40 percent of an extender, such as polycarbohydrates, e.g. maltodextrin; and from about 0.1 percent to about 20 percent, e.g. from about 2.5 percent to about 15 percent of a plasticizer such as glycols, e.g. polyethylene glycol. Examples of suitable dry compositions are disclosed in, for example, United States Patent Nos. 5,470,581 and 5,183,808, which are incorporated by reference herein.

These film forming compositions are typically in the form of a dispersion for ease of dip coating substrates therein. Such dispersions contain a solvent in an amount, based upon the total weight of the dispersion, from about 30 percent to about 97 percent, for example, from about 80 percent to about 82 percent or from about 40 percent to about 75 percent. Examples of suitable solvents include, but are not limited to water; alcohols such as methanol, ethanol, and isopropanol; organic solvents such as methylene chloride, acetone, and the like; and mixtures thereof. In one embodiment, the solvent is water. The resulting film forming dispersion typically possesses a solids level of, based upon the total weight of the film forming dispersion, from about 3 percent to about 70 percent, for example, from about 8 percent to about 20 percent or from about 25 percent to about 60 percent.

In one embodiment, the film forming composition for dip coating substrates contains, based upon the total wet weight of the dipping dispersion composition, from about 5 percent to

about 20 percent, e.g. from about 8 percent to about 15 percent or from about 10 percent to about 14 percent, of a film former such as hydroxypropylmethylcellulose and from about 0.05 percent to about 0.2 percent, e.g. from about 0.08 percent to about 0.16 percent or from about 0.1 percent to about 0.14 percent, of a thickener such as xanthan gum.

5 In another embodiment, the film forming composition for dip coating substrates contains, based upon the total wet weight of the dipping dispersion composition, from about 20 percent to about 35 percent, e.g. from about 25 percent to about 30 percent, of a film former such as waxy maize starch, tapioca dextrin, and/or derivatives and mixtures thereof; from about 5 percent to about 20 percent, e.g., from about 10 percent to about 15 percent of a plasticizer such as glycerin,
10 polyethylene glycol, propylene glycol, castor oil, and mixtures thereof; and from about 5 percent to about 15 percent of a thickener selected from sucrose, fructose, dextrose, maltodextrin, polydextrose, and mixtures thereof.

In yet another embodiment, the film forming composition for dip coating substrates contains, based upon the total wet weight of the dipping dispersion composition, from about 15
15 percent to about 30 percent, e.g. from about 20 to about 25 percent, of a film former such as a chemically modified starch, e.g. hydroxypropyl starch; from about 0.05 percent to about 10 percent, e.g. from about 0.15 percent to about 7 percent of a thickening agent; and from about 5 percent to about 20 percent, e.g. from about 8 percent to about 12 percent of a plasticizer.

In yet another embodiment, the film forming composition for dip coating substrates
20 contains, based upon the total wet weight of the dipping dispersion composition, from about 5 percent to about 25 percent, e.g. from about 8 percent to about 20 percent or from about 10 to about 16 percent, of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose.

In yet another embodiment, the film forming composition for dip coating substrates contains, based upon the total wet weight of the dipping dispersion composition, from about 5
25 percent to about 25 percent, e.g. from about 8 percent to about 20 percent or from about 10 to about 16 percent, of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose, and is substantially free of hydrocolloids, i.e., e.g. contains less than about 1%, or less than about 0.01% of hydrocolloids.

In yet another embodiment, the film forming composition for dip coating substrates
30 contains, based upon the total wet weight of the dipping dispersion composition, from about 5 percent to about 25 percent, e.g. from about 8 percent to about 20 percent or from about 10 to about 16 percent, of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose; and from about 0.001 percent to about 0.1 percent, e.g. from about 0.01 percent to about 0.09 percent of a plasticizer such as vegetable oils, e.g. castor oil.

In yet another embodiment, the film forming composition for dip coating substrates
35 contains, based upon the total wet weight of the dipping dispersion composition, from about 1 percent to about 21 percent, e.g. from about 10 percent to about 19 percent or from about 16 percent to about 19 percent, of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose; from about 0.1 percent to about 17 percent, e.g. from about 1
40 percent to about 11 percent or from about 1 percent to about 8 percent of an extender, such as

polycarbohydrates, e.g. maltodextrin; and from about 0.02 percent to about 4 percent, e.g. from about 0.5 percent to about 3 percent of a plasticizer such as glycols, e.g. polyethylene glycol.

Optionally, the composition for dipping may further comprise other ingredients such as, based upon the total weight of the dipping solution, from about 0 percent to about 2 percent preservatives such as methylparaben and propylparaben, from about 0 percent to about 14 percent opacifying agents such as titanium dioxide, and/or from about 0 percent to about 14 percent colorants. See *Remington's Practice of Pharmacy*, Martin & Cook, 17th ed., pp. 1625 - 30, which is herein incorporated by reference.

Any coloring agent suitable for use in pharmaceutical applications may be used in the present invention and may include, but not be limited to azo dyes, quinophthalone dyes, triphenylmethane dyes, xanthene dyes, indigoid dyes, iron oxides, iron hydroxides, titanium dioxide, natural dyes, and mixtures thereof. More specifically, suitable colorants include, but are not limited to patent blue V, acid brilliant green BS, red 2G, azorubine, ponceau 4R, amaranth, D&C red 33, D+C red 22, D+C red 28, D+C red 28, D+C yellow 10, FD+C yellow 5, FD+C yellow 6, FD+C red 3, FD+C red 40, FD+C blue 1, FD+C blue 2, FD+C green 3, brilliant black BN, carbon black, iron oxide black, iron oxide red, iron oxide yellow, titanium dioxide, riboflavin, carotenes, anthocyanines, turmeric, cochineal extract, chlorophyllin, canthaxanthin, caramel, betanin, and mixtures thereof.

In one embodiment, each end of the tablet or capsule may be coated with dip coatings of different colors to provide a distinctive appearance for specialty products. See United States Patent No. 4,820,524, which is incorporated by reference herein.

In one embodiment, the pharmaceutical dosage form is comprised of a) a core containing an active ingredient; b) an optional first coating layer comprised of a subcoating that substantially covers the core; and c) a second coating layer on the surface of the first coating layer, the second coating layer comprised of the dip coating composition of the present invention. As used herein, "substantially covers" shall mean at least about 95 percent of the surface area of the core is covered by the subcoating.

In an alternate embodiment, a first active ingredient may be contained in the first coating layer, and the core may contain a second active ingredient and/or an additional amount of the first active ingredient. In yet another embodiment, the active ingredient may be contained in the first coating layer, and the core may be substantially free, i.e., less than about 1 percent, e.g. less than about 0.1 percent, of active ingredient.

The use of subcoatings is well known in the art and disclosed in, for example, United States Patent Nos. 3,185,626, which is incorporated by reference herein. Any composition suitable for film-coating a tablet may be used as a subcoating according to the present invention. Examples of suitable subcoatings are disclosed in United States Patent Nos. 4,683,256, 4,543,370, 4,643,894, 4,828,841, 4,725,441, 4,802,924, 5,630,671, and 6,274,162, which are all incorporated by reference herein. Additional suitable subcoatings include one or more of the following ingredients: cellulose ethers such as hydroxypropylmethylcellulose, hydroxypropylcellulose, and hydroxyethylcellulose; polycarbohydrates such as xanthan gum,

starch, and maltodextrin; plasticizers including for example, glycerin, polyethylene glycol, propylene glycol, dibutyl sebacate, triethyl citrate, vegetable oils such as castor oil, surfactants such as polysorbate-80, sodium lauryl-sulfate and dioctyl-sodium sulfosuccinate; polycarbohydrates, pigments, and opacifiers.

5 In one embodiment, the subcoating may be comprised of, based upon the total weight of the subcoating, from about 2 percent to about 8 percent, e.g. from about 4 percent to about 6 percent of a water-soluble cellulose ether and from about 0.1 percent to about 1 percent, castor oil, as disclosed in detail in United States Patent No. 5,658, 589, which is incorporated by reference herein. In another embodiment, the subcoating may be comprised of, based upon the total weight
10 of the subcoating, from about 20 percent to about 50 percent, e.g., from about 25 percent to about 40 percent of HPMC; from about 45 percent to about 75 percent, e.g., from about 50 percent to about 70 percent of maltodextrin; and from about 1 percent to about 10 percent, e.g., from about 5 percent to about 10 percent of PEG 400.

15 The dried subcoating typically is present in an amount, based upon the dry weight of the core, from about 0 percent to about 5 percent. The dried dip coating layer typically is present in an amount, based upon the dry weight of the core and the optional subcoating, from about 1.5 percent to about 10 percent.

20 The average thickness of the dried dip coating layer typically is from about 40 to about 400 microns. However, one skilled in the art would readily appreciate without undue experimentation that the dip coating thickness may be varied in order to provide a smoother, easier to swallow, dosage form or to achieve a desired dissolution profile. Moreover, the thickness of dipped film coatings may vary at different locations on the substrate depending upon its shape. For example, the thickness of the coating at an edge or corner of a substrate may be as much as 50 percent to 70 percent less than the thickness of the coating at the center of a major face of the substrate.
25 This difference can be minimized by, for example, use of a thicker subcoating, or use of dipping compositions that result in higher weight gains on the substrate.

In embodiments wherein a thicker dip coating is desired, we have found that an effective amount of a weight gain enhancer selected from the group consisting of simethicone, polysorbate 80 and mixtures thereof, may be added to a film forming composition comprised, consisting of,
30 and/or consisting essentially of a film former and an optional thickener such as a hydrocolloid. The weight gain enhancer is used in an amount sufficient to increase the weight gain of the coating solution, e.g. by at least about 10 percent, by at least about 20%, or by at least about 30 % on a substrate when dried. The percent weight gain increase is determined based upon the difference between the total weight of the coated substrate with the coating composition including the weight
35 gain enhancer, and the total weight of an coated equivalent substrate, which has been coated under similar processing conditions with a coating composition that does not include an effective amount of weight gain enhancer.

In one embodiment, the film former is a cellulose ether such as HPMC, and the thickener is a hydrocolloid such as xanthan gum and the weight gain enhancer is simethicone.

A suitable film forming composition capable of achieving increased weight gain of dip coating on a substrate may contain, based upon the total dry weight of the film forming composition, from about 40 percent to about 99.9 percent, e.g. from about 95 percent to about 99.5 percent, or from about 40 percent to about 80 percent of a film former; from about 0 percent to about 80 percent, e.g. from about 0 percent to about 10 percent, or from about 0.5 percent to about 5 percent, or from about 10 percent to about 25 percent of a thickener; and from about 0.01 percent to about 0.25 percent, e.g. from about 0.03 percent to about 0.15 percent of a weight gain enhancer. When aesthetics of the final tablet are of particular concern, it is recommended to not use greater than about 0.25 percent of a weight gain enhancer. As shown above, the amount of thickener suitable for use in the composition will vary depending upon, for example, the particular thickener selected and the desired properties of the coating. For example, when xanthan gum is the thickener of choice, the amount of xanthan gum thickener may range, based upon the total dry weight of the film forming composition, from about 0.5 percent to about 5 percent.

The film forming compositions of the present invention may be prepared by combining the film former, the thickener, and any optional ingredients such as plasticizers, preservatives, colorants, opacifiers, the weight gain enhancer, or other ingredients with the solvent using a high shear mixer until homogeneous under ambient conditions. In embodiments wherein a waxy maize starch derivative is used as a film former, the mixture may be heated to a temperature of about 60 °C to about 90 °C for faster dispersion of the ingredients. Alternatively, the film former and thickener may be preblended as dry powders, followed by addition of the resulting powder blend to the water and optional weight gain enhancer with high speed mixing. In order to remove substantially all of the bubbles from the resulting mixture, the pressure may then be decreased to about 5 inches Hg while reducing the mixing speed in order to avoid creating a vortex therein. Any other additional optional ingredients may then be added thereto at constant mixing.

It has surprisingly been found that substrates may be dipped into such solutions of the present invention using the same equipment and similar range of process conditions as used for the production of dip molded, gelatin-coated tablets. For example, both tablets and hard capsules may be coated using the aqueous dispersions of the present invention via known gelatin-dipping process parameters and equipment. Details of such equipment and processing conditions are known in the art and are disclosed at, for example, United States Patent No. 4,820,524, which is incorporated by reference herein. Advantageously, because the coating solutions of the present invention are fluid at room temperature and are less susceptible to microbial growth than gelatin compositions, the dip coating process may occur under ambient temperature and pressure conditions.

The tablets dip coated with the composition of the present invention may contain one or more active agents. The term "active agent" is used herein in a broad sense and may encompass any material that can be carried by or entrained in the system. For example, the active agent can be a pharmaceutical, nutraceutical, vitamin, dietary supplement, nutrient, herb, foodstuff, dyestuff, nutritional, mineral, supplement, or favoring agent or the like and combinations thereof.

The active agents useful herein can be selected from classes from those in the following therapeutic categories: ace-inhibitors; alkaloids; antacids; analgesics; anabolic agents; anti-anginal drugs; anti-allergy agents; anti-arrhythmia agents; antiasthmatics; antibiotics; anticholesterolemics; anticonvulsants; anticoagulants; antidepressants; antidiarrheal preparations; anti-emetics; 5 antihistamines; antihypertensives; anti-infectives; anti-inflammatory; antilipid agents; antineoplasics; anti-migraine agents; anti-nauseants; antipsychotics; antistroke agents; antithyroid preparations; anabolic drugs; antioesity agents; antiparasitics; antipsychotics; antipyretics; antispasmodics; antithrombotics; antitumor agents; antitussives; antulcer agents; anti-uricemic agents; anxiolytic agents; appetite stimulants; appetite suppressants; beta-blocking agents; bronchodilators; 10 cardiovascular agents; cerebral dilators; chelating agents; cholecystakinin antagonists; chemotherapeutic agents; cognition activators; contraceptives; coronary dilators; cough suppressants; decongestants; deodorants; dermatological agents; diabetes agents; diuretics; emollients; enzymes; erythropoietic drugs; expectorants; fertility agents; fungicides; gastrointestinal agents; growth regulators; hormone replacement agents; hyperglycemic agents; hypoglycemic agents; ion-exchange resins; laxatives; migraine treatments; mineral supplements; 15 mucolytics; narcotics; neuroleptics; neuromuscular drugs; non-steroidal anti-inflammatory (NSAIDs); nutritional additives; peripheral vasodilators; polypeptides; prostaglandins; psychotropics; renin inhibitors; respiratory stimulants; sedatives; steroids; stimulants; sympatholytics; thyroid preparations; tranquilizers; uterine relaxants; vaginal preparations; vasoconstrictors; vasodilators; vertigo agents; vitamins; wound healing agents; and others.

Active agents that may be used in the invention include, but are not limited to: acetaminophen; acetic acid; acetylsalicylic acid, including its buffered forms; acrivastine; albuterol and its sulfate; alcohol; alkaline phosphatase; allantoin; aloe; aluminum acetate, carbonate, 25 chlorhydrate and hydroxide; alproazolam; amino acids; aminobenzoic acid; amoxicillin; ampicillin; amesacrine; amesalog; anethole; ascorbic acid; aspartame; astemizole; atenolol; azetidine and its maleate; bacitracin; balsam peru; BCNU (carmustine); beclomethasone dipropionate; benzocaine; benzoic acid; benzophenones; benzoyl peroxide; benzoquinamide and its hydrochloride; bethanechol; biotin; bisacodyl; bismuth subacetylolate; borneyl acetate; bromopheniramine and its maleate; buspirone; caffeine; calamine; calcium carbonate, casinate and hydroxide; camphor; 30 captopril; cascara sagrada; castor oil; cefaclor; cefadroxil; cephalosin; cetirizine and its hydrochloride; cetirizine; cetyl alcohol; cetylpyridinium chloride; chelated minerals; chloramphenicol; chlorcyclizine hydrochloride; chlorhexidine gluconate; chloroxylenol; chloropentastatin; chlorpheniramine and its maleates and tannates; chlorpromazine; cholestyramine resin; choline bitartrate; chondrogenic stimulating protein; cimetidine; cinnamedrine hydrochloride; citalopram; citric acid; clarithromycin; clemastine and its fumarate; clonidine; 35 clorifibrate; cocoa butter; cod liver oil; codeine and its fumarate and phosphate; cortisone acetate; ciprofloxacin HCl; cyanocobalamin; cyclizine hydrochloride; cyproheptadine; dantrolene; dexbromopheniramine maleate; dextromethorphan and its hydrohalides; diazepam; dibucaine; dichlorophenazone; diclofen and its alkali metal sales; diclofenac sodium; digoxin; 40 dihydroergotamine and its hydrogenates/mesylates; diltiazem; dimethicone; dioxibenzene;

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- diphenhydramine and its citrate; diphenhydramine and its hydrochloride; divalproex and its alkali metal salts; docosate calcium, potassium, and sodium; doxycycline hydrate; doxylamine succinate; dronabinol; efavirenz; enalapril; enoxacin; ergotamine and its tartrate; erythromycin; estroplaste; ethinyl estradiol; ephedrine; epinephrine bitartrate; erythropoietin; eucalyptol; famotidine;
- 5 fenoprofen and its metal salts; ferrous fumarate, gluconate and sulfate; fexofenadine; fluoxetine; folic acid; fosphenytoin; 5-fluorouracil (5-FU); fluoxetine; flurbiprofen; furosemide; gabapentin; gentamicin; gemfibrozil; glipizide; glycerine; glyceryl stearate; granisetron; griseofulvin; growth hormone; guaifenesin; hexylresorcinol; hydrochlorothiazide; hydrocodone and its tartrates;
- 10 hydrocortisone and its acetate; 8-hydroxyquinoline sulfate; hydroxyzine and its pamoate and hydrochloride salts; ibuprofen; indomethacin; inositol; insulin; iodine; ipsecac; iron; isosorbide and its mono- and dinitrates; isoxicam; ketamine; kaolin; ketoprofen; lactic acid; lanolin; lecithin; leuprolide acetate; lidocaine and its hydrochloride salt; lifinopril; liothrin; loperamide; loratadine; lovastatin; luteinizing hormone; LHRH (luteinizing hormone replacement hormone); magnesium carbonate, hydroxide, salicylate, and triacetate; meclizine; metenamic acid; meclofenamic acid;
- 15 meclofenamate sodium; medroxyprogesterone acetate; methenamine mandelate; menthol; meperidine hydrochloride; metaproterenol sulfate; methscopolamine and its nitrates; methsergide and its maleate; methyl nicotinate; methyl salicylate; methyl cellulose; methazindide; metoclopramide and its helides/hydrates; metronidazole; metoprolol tartrate; miconazole nitrate; mineral oil; minoxidil; morphine; naproxen and its alkali metal sodium salts; nifedipine; neomycin
- 20 sulfate; niacin; niacinamide; nicotine; nicotinamide; nimesulide; nitroglycerine; nonoxonyl-9; norethindrone and its acetate; nystatin; octoxynol; octoxynol-9; octyl dimethyl PABA; octyl methoxycinnamate; omega-3 polyunsaturated fatty acids; omeprazole; ondansetron and its hydrochloride; oxolinic acid; oxybenzone; oxytriphylline; para-aminobenzoic acid (PABA); padimate-O; paramethadione; pentastatin; peppermint oil; pentaerythritol tetranitrate; pentobarbital sodium;
- 25 perphenazine; phenelzine sulfate; phenindamine and its tartrate; pheniramine maleate; phenobarbital; phenol; phenolphthalein; phenylephrine and its tannates and hydrochlorides; phenylpropanolamine; phenytoin; pirfenone; piroxicam and its salts; polymixin B sulfate; potassium chloride and nitrate; prazepam; procainamide hydrochloride; procaterol; promethazine and its hydrochloride; propoxyphene and its hydrochloride and napsylate; pramiracetin; pramoxine and its
- 30 hydrochloride salt; prochlorperazine and its maleate; propranolol and its hydrochloride; promethazine and its hydrochloride; propanolol; pseudoephedrine and its sulfates and hydrochlorides; pyridoxine; pyrolamine and its hydrochlorides and tannates; quinine; quinidine gluconate and sulfate; quinine; ranitidine; resorcinol; riboflavin; salicylic acid; scopolamine; sesame oil; shark liver oil; simethicone; sodium bicarbonate, citrate, and fluoride;
- 35 sodium monofluorophosphate; sucralose; sulfanethoxazole; sulfasalazine; sulfur; sumatriptan and its succinate; tacrine and its hydrochloride; theophylline; terfenadine; thialthylperazine and its maleate; timolol and its maleate; thioferidone; tramadol; trimetrexate; triazolam; tretinoin; tetracycline hydrochloride; tolmetin; tolnaftate; triclosan; trimethobenzamide and its hydrochloride; tripiennamine and its hydrochloride; triprolidine hydrochloride; undecylenic acid; vancomycin;
- 40 verapamil HCl; vidarabine phosphate; vitamins A, B, C, D, B₁, B₂, B₆, B₁₂, E, and K; witch hazel;

xylometazoline hydrochloride; zinc; zinc sulfate; zinc undecylenate. Active agents may further include, but are not limited to food acids; insoluble metal and mineral hydroxides, carbonates, oxides, polycarbophils, and salts thereof; adsorbates of active drugs on a magnesium trisilicate base and on a magnesium aluminum silicate base, and mixtures thereof. Mixtures and pharmaceutically acceptable salts of these and other actives can be used.

In one embodiment, the dosage forms coated with the dip coatings of the present invention provided for immediate release of the active ingredient, i.e. the dissolution of the dosage form conformed to USP specifications for immediate release tablets containing the particular active ingredient employed. For example, for acetaminophen tablets, USP 24 specifies that in pH 5.8 phosphate buffer, using USP apparatus 2 (paddles) at 50 rpm, at least 80% of the acetaminophen contained in the dosage form is released therefrom within 30 minutes after dosing, and for ibuprofen tablets, USP 24 specifies that in pH 7.2 phosphate buffer, using USP apparatus 2 (paddles) at 50 rpm, at least 80% of the ibuprofen contained in the dosage form is released therefrom within 60 minutes after dosing. See USP 24, 2000 Version, 19 - 20 and 856 (1999).

We have unexpectedly found that the coatings formed by dipping substrates into the compositions of the present invention possessed excellent properties comparable to those possessed by gelatin coatings, e.g. crack resistance, hardness, thickness, color uniformity, smoothness, and gloss. Typically, the coatings of the present invention possessed a surface gloss of greater than about 150, e.g. greater than about 190 or greater than about 210 when measured according to the method set forth in example 7 herein.

In addition, tablets dip coated with the compositions of the present invention were superior to tablets dip coated with conventional gelatin-based coatings in several important ways. First, tablets dip coated with the compositions of the present invention advantageously retained acceptable dissolution characteristics for the desired shelf-life and storage period at elevated temperature and humidity conditions. In particular, the cellulose-ether based compositions according to the present invention were also advantageously more resistant to microbial growth, which thereby enabled a longer shelf-life or use-life of the dipping solution as well as a reduction in manufacturing cost. Second, the sugar-thickened dipping dispersions according to the present invention beneficially employed a lower water content relative to that of gelatin-containing dispersions, which thereby enabled a shorter drying cycle time. Although the water content of the other dipping dispersions of the present invention may have been higher than that typically found in gelatin-based dipping solutions, the cellulose-ether based compositions of the present invention surprisingly required a shorter drying cycle time relative to that for gelatin-containing compositions. Third, the dried coatings comprised of the compositions of the present invention also surprisingly and advantageously contained fewer air bubbles relative to the amount present in dried, gelatin based dipping compositions. Fourth, unlike dip processing with gelatin-containing compositions, substrates may optionally be dipped in the solutions of the present invention at room temperature, which is economically more beneficial. Fifth, the dip coated compositions of the present invention possessed a higher degree of glossiness relative to similar coatings applied via spray coating methods known in the art. The dip coated compositions of the present invention also possessed a

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similar degree of glossiness relative to that possessed by gelatin-containing dip or enrobing coatings, which are currently viewed as the industry benchmark for high gloss coatings. See, e.g., United States Patent No. 6,274,162 (Typical gloss readings for standard, commercially available gel-dipped or gelatin enrobed tablets range from about 200 to 240 gloss units, gloss readings for standard, commercially available sugar-coated medicaments range from 177 to 209 gloss units, and gloss readings for a new, high-gloss coating system range from about 148 to about 243 gloss units.).

We have further unexpectedly found that the addition of an effective amount of weight gain enhancer to a film forming composition comprised of film former and hydrocolloid not only significantly increased the resulting dry weight of the dip coating on a substrate, but it also improved the color uniformity of the coating.

The invention illustratively disclosed herein suitably may be practiced in the absence of any component, ingredient, or step which is not specifically disclosed herein. Several examples are set forth below to further illustrate the nature of the invention and the manner of carrying it out. However, the invention should not be considered as being limited to the details thereof.

EXAMPLES

Example 1.) Preparation of Subcoating Dispersions

An aqueous dispersion containing the ingredients set forth in Table A was prepared by combining all of the ingredients in a beaker under ambient conditions.

Table A: Aqueous Dispersion Subcoating Composition

Ingredient	Part *
HPMC (2910, 5 mPa) from Dow Chemical Company under the tradename, "Methocel E-5"	20
Castor oil	1
Water	241.5
Total Coating Solution	262.5
% solids in coating solution	8%

* expressed in terms of part by weight unless otherwise noted

Additional aqueous dispersions containing the ingredients in Table B were similarly prepared:

Table B: Aqueous Dispersion Subcoating Compositions

Ingredient	Ex 1A**	Ex 1B	Ex 1C	Ex 1D	Ex 1E
HPMC 2910, 5 mPa	20	40	40	28	28
Castor oil	1	0	0	0	0
water	212.3	566.67	566.67	566.67	566.67
maltodextrin	0	53	53	67	67

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PEG 400	0	7	7	5	5
Hydroxy-ethylcellulose*	0	0	0	0	0
Total coating solution	233.3	666.67	666.67	666.67	666.67
Wt % solids in coating solution	9%	15%	15	15	15

* Available from Aqualon, under the tradename, "Natrocol 250L"
** all values expressed in terms of parts by weight unless otherwise noted

Additional aqueous dispersions containing the ingredients in Table C were similarly prepared:

5 **Table C: Aqueous Dispersion Subcoating Compositions**

Ingredient	Ex 1F**	Ex 1G	Ex 1H
water	666.67	666.67	660.4
maltodextrin	71	71	0
Castor oil	0	0	0.13
HPMC (1910, 5mPas)	0	0	32.4
PEG 400	5	5	0
Hydroxy-ethylcellulose*	24	24	0
Total coating solution	666.67	666.67	722.9
Wt % solids in coating solution	15%	15%	4.5%

* Available from Aqualon, under the tradename, "Natrocol 250L"
** all values expressed in terms of parts by weight unless otherwise noted

Example 2.) Preparation of Subcoated Tablets

10 Compressed tablets were prepared in accordance with the procedure set forth in Example 1 of United States Patent No. 5,658,589 ("589 Patent"), which was incorporated by reference herein.

15 The dispersion of Example 1 was then applied onto the compressed tablets via spraying in accordance with the procedure set forth in the examples of the '589 Patent . As shown in Table D below, the dried subcoated tablets possessed an average 2% to 4% weight gain relative to the weight of the subcoating-free tablets.

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This process was repeated with additional compressed tablets, but with the substitution of each, respective subcoating dispersion produced in Example 1A to 1H for that of Example 1. The percentage weight gain of the dried subcoated tablets are set forth below in Table D:

5 Table D: % Weight Gain of Dried Subcoated Tablets

<u>Example Number</u>	<u>% Weight Gain</u>
1A	2
1B	2
1C	4
1D	2
1E	4
1F	2
1G	4
1H	4

Example 3) Preparation of HPMC Coated Tablets

Aqueous HPMC dipping solutions containing the ingredients set forth in Table E were prepared:

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Table E: Composition of HPMC Dipping Solutions

Ingredient	Ex 3A (g)	Ex 3B (g)	Ex 3C (g)	Ex 3D (%)	Ex 3E (%)	Ex 3F (%)
HPMC E5	32.5	0	32.5	10	11	14
Water	200	200	200	89.89	88.879	85.85
HPMC (2910, 15mPa)	0	20	0		0	0
Xanthan gum	0	0	0	0.11	0.121	0.15
PEG 400	0	0	8	0	0	0
% (wt.) solids in dipping solution	14	9	17	10.11	11.121	14.15

* all values expressed in terms of weight (g) unless otherwise noted

5 Example 3A: Preparation Of Dipping Solution of Example 3A: HPMC was dispersed into 200 ml of deionized water at a temperature of 70 °C. After adding about 1 wt % FD&C blue dye thereto, the solution was mixed until homogeneous. The solution was then cooled to a temperature of about 22 °C.

10 Example 3B: Preparation of Dipping Solution of Example 3B: The procedure of Example 3A was repeated, but with substitution of HPMC (2910, 15mPa) for the HPMC E5.

Example 3C: Preparation Of Dipping Solution of Example 3C: HPMC was dispersed into 200 ml of deionized water at a temperature of 70 °C. After adding the PEG 400 thereto, the solution was mixed until homogeneous. The solution was then cooled to a temperature of about 22 °C.

15 Example 3D: Preparation Of Dipping Solution of Example 3D: HPMC and xanthan gum were added to purified water at a temperature of 80 °C until the powder was dispersed. After discontinuing the heat, the solution was divided into two parts. 4.35 wt. % of a yellow color dispersion available from Colorcon, Inc. under the tradename, "Opatint Yellow DD-2115" was added to the first part and mixed at a low speed until dispersed. 5.8% of a green color dispersion available from Colorcon, Inc. under the tradename, "Opatint Green DD-11000" was added to the second part and mixed at a low speed until dispersed. The two dispersed solutions were then stored under ambient conditions for about 12 hours.

25 Example 3E: Preparation Of Dipping Solution of Example 3E: The procedure of Example 3D was repeated, but using the components of Example 3E.

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Example 3F: Preparation Of Dipping Solution of Example 3F: The procedure of Example 3D was repeated, but using the components of Example 3F.

Example 3G: Preparation of Hand-Dipped Dip Coated Tablets: The subcoated tablets prepared in accordance with Example 2 using the subcoating produced in Example 1H were hand-dipped into the dipping solutions of Example 3A for a dwell time of 1 second, removed from the dipping solution, then dried under ambient conditions.

This procedure was repeated, but with substitution of the dipping solutions of Examples 3B and 3C, respectively, for the dipping solution of Example 3A.

An observation of the resulting coatings showed the following:

Tablets Coated with Coating of Ex. 3A: The coatings were smooth, hard, and shiny, and had no bubbles or cracking. However, the coatings were non-uniform and thin, with land areas not well-covered. Upon exposure to ambient conditions for a six month period, no cracks were seen in the coatings.

Tablets Coated with Coating of Ex. 3B: The coating were shiny, with few bubbles and no cracking. The coatings were more uniform and rough relative to those of Example 3A. The coatings were also somewhat tacky and thin, with land areas not well-covered. Upon exposure to ambient conditions for a six month period, no cracks were seen in the coatings.

Tablets Coated with Coating of Ex. 3C: The coatings were shiny with few bubbles and no cracking. The coatings were more uniform and rough relative to those of Example 3A. The coatings were also somewhat tacky and thin, with land areas not well-covered. Upon exposure to ambient conditions for a six month period, no cracks were seen in the coatings.

Example 3H: Preparation of Production Scale Dipped Tablets: Additional subcoated tablets prepared in accordance with Example 2 using the subcoating produced in Example 1H were coated with the resulting dipping solution of Examples 3D using a commercial grade gel-dipping machine in accordance with the procedure described in United States Patent No. 4,820,524, which is incorporated by reference herein.

This procedure was repeated, but with substitution of the dipping solutions of Examples 3E and 3F, respectively, for the dipping solution of Example 3D.

The average percentage weight gain of the dried dipped coatings were as set forth in Table F:

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Table F: Weight Gain of Dried Dip Coating

<u>Example</u>	<u>% Wt. Gain of Dried Coating*</u>
Ex. 3D	0.75 – 2.28
Ex. 3E	1.9 – 3.52
Ex. 3F	3.2 – 5.8

* Relative to weight of dried subcoating and core

5 This example showed that the addition of xanthan gum to the HPMC dipping solution provided a viscosity enhancement to the dip coating, and thus an increased weight gain of the dip coating on the tablets.

Example 3I: Preparation of Dipping Solution of Example 3I

10 The procedure of Example 3D was repeated, but using the components of Example 3I, as set forth in Table M:

Table M: Composition of HPMC Dipping Solutions

<u>Ingredient</u>	<u>Ex 3I *(g)</u>	<u>Ex 3J (g)</u>
HPMC E5	14	12
Water	85.89	87.88
HPMC (2810, 15mPs)	0	0
Xanthan gum	0.11	0.12
PEG 400	0	0
% (wt.) solids in dipping solution	14.11	12.12

* all values expressed in terms of weight (g) unless otherwise noted

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Example 3J: Preparation of Dipping Solution of Example 3J

 The procedure of Example 3D was repeated, but using the components of Example 3J, as set forth in Table M above.

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Example 4) Preparation of Pre-gelatinized Starch-Containing Dip Coating Solutions

 Dipping solutions comprised of the components set forth in Table G were prepared by dispersing 75 g of the modified waxy maize starch into 200 ml of water under ambient conditions with mixing:

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Table G: Pre-gelatinized starch-containing Dipping solutions

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Component/Other	Example 4A*	Example 4B
Modified waxy maize starch (Purity® Gum 59)	75	125
water	200	200
Total weight of solution	275	325
Wt % solids in dipping solution	27	38

* all values expressed in terms of weight (g) unless otherwise noted

Dipping solutions comprised of the components set forth in Table H below were prepared by dispersing all of the components into 200 ml of water under ambient conditions with mixing until the resulting solution was clear.

5

Table H: Pre-gelatinized starch-containing Dipping solutions With Simethicone of Example 4C

Component	Tradename	Supplier	Amount used *
Modified waxy maize starch	Purity ® Gum 59	National Starch & Chemical Co.	125
Simethicone	Antifoam®		2
Colloidal silicone dioxide	Aerosil ® A200		8
Glycerin	—	—	63.5
Sucrose	—	—	38
colorant	Opatint®		6.9
water	—	—	200
Total solids			241.4
TOTAL solution (w/ 55% solids)			441.1

* all values expressed in terms of weight (mg) unless otherwise noted

Each side of the subcoated tablets prepared in accordance with Example 2 using the subcoating produced in Example 1H were hand-dipped into the dipping solution of Example 4A for a dwell time of about 1 second, pulled up, then dried under ambient conditions.

10

This procedure was repeated, but with substitution of the dipping solution of Example 4B for the dipping solution of Example 4A and with about a 3 day period between the completion of production of the dipping solution and the commencement of dip coating process.

This procedure was further repeated, but with substitution of the dipping solutions of Example 4C for the dipping solution of Example 4A and with about a 12 hour period between the completion of production of the dipping solution and the commencement of dip coating process.

15

An observation of the resulting coatings showed the following:

Tablets Coated With Dipping Solution of Ex. 4A: The coatings were very shiny, hard, smooth, even, and not tacky or cracked. However, the coatings were too thin, and land areas were not covered. No cracking after exposure to ambient conditions for a period of 6 months.

20

Tablets Coated With Dipping Solution of Ex. 4B: The coatings were smooth and shiny. Initially the land areas were covered; however, the coatings cracked after exposure to ambient conditions for a period of 6 months.

Tablets Coated With Dipping Solution of Ex. 4C: The coatings possessed excellent shine and cover, and were smooth with no cracks. No cracking after exposure to ambient conditions for a period of 2 months.

Example 5) Preparation of Pre-Gelatinized Starch-Containing Dip Coating Solutions

The procedure set forth in Example 4C is repeated, but without the inclusion of simethicone. Prior to coating the substrate, the solution is exposed to a vacuum pressure of 5 inches Hg in order to remove substantially all of the visible bubbles from the solution. The resulting coating possesses excellent shine and cover, and is smooth with no cracks.

Example 6) Effect of Simethicone on Coating Weight Gain

The following dip coating solutions set forth in Table I were prepared to illustrate the effect of simethicone as a weight gain enhancer. Amounts are percent based on the total weight of coating solution.

Table I Dip Coating Solutions

Ingredient	6A	6B	6C	6D	6E
HPMC 2910, 5mPs	12	12	12	12	12
Xanthan Gum	1	1	1	1	1
Simethicone	0	0.035	0.07	0.14	0.25
Yellow color dispersion***	6	6	6	6	6
Water	81	80.985	80.93	80.86	80.75

*** Yellow color dispersion was "Opalint"® No. DD2125 obtained from Colorcon, Inc.

Dipping solutions A through E, above, were prepared in the following manner: Purified water was heated to about 35°C. HPMC and xanthan gum were added while mixing using a laboratory scale electric mixer (Janke and Kunkel, IKA Labortechnik, Staufen, Germany) with propeller blade at approximately 1000 rpm until the powders appeared uniformly dispersed. Heating was discontinued, and the resulting dispersion was allowed to stand overnight at room temperature. Simethicone and yellow color dispersion were then added with mixing at approximately 500 rpm.

Subcoated cores, prepared according to the method of example 1A, were pre-weighed, then dipped in solutions A, B, C, D, and E, above for a dwell time of about 2 seconds, pulled up, then dried at ambient conditions (about 22 °C). The cores were dipped simultaneously in sets of 7.

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Three separate sets of seven cores were dipped in each solution A through E. The average weight gain was determined from the triplicate sets of dipped cores from each coating solution. Resulting weight gains were as follows in Table J:

Table J – Average Weight Gain

Dipping Solution	6A	6B	6C	6D	6E
Average weight gain from dip coat (mg/tablet)	13.3	20.8	22.3	23.7	19.1

Example 7) Surface Gloss Measurement of Coated Tablets

Tablets made according to the preceding examples were tested for surface gloss using an instrument available from TriCor Systems Inc. (Elgin, IL) under the tradename, "Tri-Cor Model 805A/806H Surface Analysis System" and generally in accordance with the procedure described in "TriCor Systems WGLOSS 3.4 Model 805A/806H Surface Analysis System Reference Manual" (1996), which is incorporated by reference herein, except as modified below.

This instrument utilized a CCD camera detector, employed a flat diffuse light source, compared tablet samples to a reference standard, and determined average gloss values at a 60 degree incident angle. During its operation, the instrument generated a grey-scale image, wherein the occurrence of brighter pixels indicated the presence of more gloss at that given location.

The instrument also incorporated software that utilized a grouping method to quantify gloss, i.e., pixels with similar brightness were grouped together for averaging purposes.

The "percent full scale" or "percent ideal" setting (also referred to as the "percent sample group" setting), was specified by the user to designate the portion of the brightest pixels above the threshold that will be considered as one group and averaged within that group. "Threshold", as used herein, is defined as the maximum gloss value that will not be included in the average gloss value calculation. Thus, the background, or the non-glossy areas of a sample were excluded from the average gloss value calculations. The method disclosed in K. Fagley and C. Vesey, "The Effect of Tablet Shape on the Perception of High Gloss Film Coating Systems", which is available at www.colorcon.com as of 18 March, 2002 and incorporated by reference herein, was used in order to minimize the effects resulting from different tablet shapes, and thus report a metric that was comparable across the industry. (Selected the 50% sample group setting as the setting which best approximated analogous data from tablet surface roughness measurements.).

After initially calibrating the instrument using a calibration reference plate (190-228; 294 degree standard; no mask, rotation 0, depth 0), a standard surface gloss measurement was then created using gel-coated caplets available from McNEIL-PPC, Inc. under the tradename, "Extra Strength Tylenol Gelcaps." The average gloss value for a sample of 112 of such gel-coated

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caplets was then determined, while employing the 25 mm full view mask (190-280), and configuring the instrument to the following settings:

- Rotation: 0
- Depth: 0.25 inches
- Gloss Threshold: 95
- % Full Scale: 50%
- Index of Refraction: 1.57

The average surface gloss value for the reference standard was determined to be 260, using the 50% Ideal (50% full scale) setting.

Samples of coated tablets prepared according to the preceding examples were then tested in accordance with the same procedure. The surface gloss values at the 50% Ideal setting that were obtained are summarized in Table K below.

Table K: Gloss values of coated tablets

Example No.	3D	3I	3J	4C	6B
Type of coating	dipped	dipped	dipped	poured film	dipped
No. of tablets tested	48	48	51	plate	3
Gloss Value(% Ideal at 50)	234	247	229	259	221

Additional samples of other, commercially available gel coated tablets were also tested in accordance with the same procedure and compared to the same standard. The results are summarized in Table L below.

Table L: Gloss values of commercially available coated tablets

Product	Motrin IB * Caplet (white)	Excedrin* * Aspirin free Caplets (red)	Excedrin ** Migraine Geltab (green side)	Excedrin ** Migraine Geltab (white side)	Extra Strength Tylenol Geltabs * (yellow side)	Extra Strength Tylenol Geltabs * (red side)
Type of coating	sprayed film	sprayed film	gelatin enrobed	gelatin enrobed	dipped	dipped
No. of tablets tested	41	40	10	10	112	112
Gloss Value(% Ideal at 50)	125	119	270	264	268	268

* Available from McNEIL-PPC, Inc.
 ** Available from Bristol-Myers, Squibb, Inc.

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This Example showed that the tablets coated with the compositions of the present invention possessed a high surface gloss value that either was comparable to or exceeded that possessed by commercially available gelatin coated tablets. In contrast, typical sprayed films possessed a substantially lower surface gloss, e.g. 119 to 125 in this Example.

Example 8: Preparation of Coated tablets

Example 8A: Preparation of Tablets Spray Coated With Opadry® II Subcoating

122.8 kg (18% w/w) of a prepared blend containing HPMC 2910-6cP, maltodextrin, HPMC2910-3cP, HPMC2910-50cP, and PEG-400 (commercially available from Colorcon Inc., West Point, PA as "Opadry® II") was added with mixing into 559.7 kg (82% w/w) of 35°C purified water in a conventional pressure pot, and mixed with an air-driven propeller-type Lightnin mixer at a speed of 500 rpm. After the powder was completely added, the dispersion was mixed at 500 rpm for 2 hours, then allowed to stand without mixing at ambient conditions for 12 hours.

The resulting film coating dispersion was then applied onto compressed acetaminophen tablets, which were prepared in accordance with the procedure set forth in Example 1 of US Patent No. 5,658,569 ("569 Patent"), which is incorporated by reference herein, via spraying in accordance with the procedure set forth in the examples of the '569 patent. The resulting spray-coated tablets possessed a 4% weight gain relative to the weight of the uncoated tablet cores.

Examples 8B: Preparation of Tablets Spray Coated with HPMC / Castor Oil Subcoating

88.4 kg (9% w/w) of hydroxypropyl methylcellulose 2910, 5mPa and 0.347 kg (0.04% w/w) of castor Oil were mixed into 593.8 kg (91% w/w) of purified water at 35°C in a tank with mixer (Lee Industries) at a speed of 1750 rpm. After the powder was completely added, the mixer speed was increased to 3500 rpm for 15 minutes. The mixer speed was then reduced to 1750 rpm while the pressure was reduced to 15 inches of water for 2 hours to deaerate the dispersion.

The resulting film coating dispersion was then applied onto the compressed acetaminophen tablets of Example 8A via spraying in accordance with the procedure set forth above in Example 8A. The resulting spray coated tablets possessed a 4% weight gain relative to the weight of the uncoated tablet cores.

Example 8C: Preparation of Tablets Dip Coated with HPMC/Castor Oil dipping solutions

A dipping solution comprised of the components set forth in Table M below was produced:

Table M: HPMC/Castor Oil Clear Dipping Solutions

Example	A&B	C&D	E&F
HPMC 2910 5mPa	9%	13%	13%
Castor Oil	0.04%	0.05%	0.05%
Purified Water	90.96%	86.95%	86.95%

Purified water was heated to 80° C, then added to a Lee Jacketed mix tank while mixing at a speed of 1750 rpm. After HPMC 2910, 5mPa and castor oil were added thereto with mixing, the mixer speed was increased to 3500 rpm for 15 minutes. The mixer speed was then reduced to 1750 rpm while the temperature of the dispersion was reduced to 35 °C and the pressure was reduced to 15 inches water for deaeration. After mixing the dispersion for 2 hours, the resulting dispersion remained under constant pressure conditions for an additional 3 hours without mixing.

The colorant of Example 8C-a was then added to 96 kg of the resulting clear dipping solutions with mixing at a 1750 rpm speed in the amounts set forth in Table N below :

Table N: HPMC/Castor Oil Colored Dipping Solutions

Example	8C-a	8C-b	8C-c	8C-d	8C-e	8C-f
Colorant	Opatint (DD-1781)	Opatint (DD-2125)	Opatint (DD-1781)	Opatint (DD-2125)	Opatint (DD-10518)	Opatint (DD-18000)
Amount of colorant (kg)	2.700	2.570	2.700	2.570	4.072	2.175
Color	red	yellow	red	yellow	blue	white
Visc/Temp	490 cps @40C	518 cps @40C	612cps @30C	457cps @30C	351cps @40C	319cps @40C
Dipping Temp	40C	40C	30C	30C	40C	40C
Weight Gain in dipping (mg/tablet)	18	18	28	28	20	20
Gloss	229	229	249	228	238	233

This procedure was independently repeated for each of the colorants set forth above in Table N.

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Subcoated tablets, which were prepared in accordance with the procedure set forth above in Example 8A, were dip-coated with the dip-coating solution prepared in accordance with Example 8C-a and 8C-b using a commercial grade gel-dipping machine and in accordance with the procedure described in United States Patent No. 4,820,524, which is incorporated by reference herein, using the dipping solution temperatures reported in the table above. This procedure was independently repeated on subcoated tablets, which were prepared in accordance with the procedure set forth above in Example 8B, for each of the colored dipping solutions 8C-c through 8C-f in Table N above.

A visual comparison of the dip-coated tablets prepared according to examples 8C-a and 8C-b with those prepared in accordance with Examples 8C-c through 8C-f revealed that the former did not possess complete coating coverage around the edges of the tablets. By contrast, the dip-coated tablets prepared according to examples 8C-c through 8C-f possessed a superior good coating coverage around the tablet edges. This indicated that a weight gain of 18 mg per gelcap (such as that produced by the 9% HPMC formula of examples 8C-a and 8C-b) was insufficient for the HPMC/Castor Oil dipping formula, while a weight gain of 20 to 26 mg per gelcap/gelcap (such as that produced by the 13% HPMC formula of examples 8C-c through 8C-f) provided good coverage.

In addition, a visual comparison of the HPMC/Castor Oil dip-coated tablets of Examples 8C-c through 8C-f and the HPMC/Xanthan Gum dip-coated tablets of Examples 3I and 3J indicated that the former possessed superior gloss and surface smoothness. The superior gloss and smoothness were likely attributed to the inclusion of castor oil in the dip coating.

Example 9: Preparation of Tablets Dip Coated with HPMC/Maltodextrin/PEG dipping solutions

143.3 kg (21% w/w) of the Opadry® II blend of Example 8A was added into 539.2 kg (79% w/w) of 35°C purified water while mixing at a speed of 3500 rpm for 15 minutes. The mixer speed was then decreased to 1750 rpm, and the tank evacuated to 30 PSIA to degerate the solution for 5 hours. 2.70 kg of Colorant (Opatint® Red DD-1781, from Colorcon Inc.) was then added to 96 kg of the clear dipping solution while mixing at a speed of 1750 rpm. 2.570 kg of Colorant (Opatint® Yellow DD-2125, from Colorcon Inc.) was then added to a second 96 kg portion of the clear dipping solution while mixing at a speed of 1750 rpm until dispersed.

Subcoated tablets, which were prepared in accordance with the procedure and materials set forth above in Example 8B, were dip-coated with the dip-coating solution prepared in accordance with this Example using a commercial grade gel-dipping machine and in accordance with the procedure described in United States Patent No. 4,820,524, which is incorporated by reference herein, using a dipping solution temperature of 30°C. The viscosity of the dipping solutions was 807 cPs at 30°C for the yellow solution, and 677 cPs at 30°C for the red solution. An average weight gain of about 27 mg/gelcap was obtained.

Seventy-two (72) dipped gel caps produced in accordance with this Example were tested for surface gloss in accordance with the procedure set forth in Example 7. The average surface gloss for these dipped gelcaps was 268 gloss units.

Example 10: Preparation of Tablets Dip Coated with HPMC/Carrageenan dipping solutions

88.4 kg (13% w/w) of HPMC 2910-5 mPs, 0.347 kg of Castor Oil (0.05% w/w), and 0.68 kg (0.1% w/w) of kappa Carrageenan-911 were added into a tank containing 500 kg (87% w/w) of 80°C purified water while mixing at a speed of 1750 rpm. After the addition was complete, the mixer speed was increased to 3500 rpm for 15 minutes. The mixer speed was then decreased to 1750 rpm, and the tank evacuated to 15 inches of water to deaerate the solution for 2 hours. Mixing was then stopped, and the dispersion was allowed to stand at constant pressure for an additional 3 hours. 2.175 kg of Colorant (Opalint® White DD-16000, from Colorcon Inc.) was then added to 88 kg of the clear dipping solution while mixing at a speed of 1750 rpm. 4.072 kg of Colorant (Opalint® Blue DD-10516, from Colorcon Inc.) was then added to a second 88 kg portion of the clear dipping solution while mixing at a speed of 1750 rpm until dispersed.

Subcoated tablets, which were prepared in accordance with the procedure and materials set forth above in Example 8B, were dip-coated with the dip-coating solution prepared in accordance with this Example using a commercial grade gel-dipping machine and in accordance with the procedure described in United States Patent No. 4,820,524, which is incorporated by reference herein, using a dipping solution temperature of 40°C. An average weight gain of about 20 mg/gelcap was obtained.

Eighty-eight (88) dipped gel caps produced in accordance with this Example were tested for surface gloss in accordance with the procedure set forth in Example 7. The average surface gloss for these dipped gelcaps was 232 gloss units.

Example 11: Preparation of tablets dip coated with hydroxypropyl starch containing dipping solution.

92.5 g of hydroxypropylated modified dent corn starch ("Pure-Cote B790", Grain Processing Corporation) was added to a tank containing 300g of 80°C purified water while mixing with a Kika-Werk RW 20 DZM motor fitted with a 4 cm propeller blade at a speed of 650 rpm for 30 minutes. 7.5 g of Gellan Gum ("Kelco gel", Kelco) was then added thereto with constant mixing for 15 min. 2.6g of colorant ("Opalint Red DD-1761" Colorcon) was then added into the 80C solution with constant mixing for 15 min. The resulting solution contained the ingredients set forth below in Table O:

Table O: Hydroxypropyl Starch Based Dipping Solutions

Component	Trade name	Supplier	Amount Used*
Hydroxypropyl Starch	Pure-Cote B790	Grain Processing Corporation	82.5
Gellan Gum	Kelcogel	Kelco	7.5
Colorant	Opalint Red	Colorcon	2.6
Water	N/A	N/A	300

*All values expressed in terms of weight (grams) unless otherwise stated

5 Subcoated tablets, which were prepared in accordance with the procedure and materials set forth above in Example 6B, were dipped by hand in the resulting solution at 22°C, then dried at ambient conditions for 18 hours. An average weight gain of about 47 mg/gelcap was obtained.

Dipped gel caps produced in accordance with this Example were then tested for surface gloss in accordance with the procedure set forth in Example 7. The average surface gloss for these dipped gellabs was 229 gloss units.

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We claim:

1. A film forming composition comprised of:

a) a film former selected from the group consisting of a waxy maize starch, tapioca dextrin, derivative of a waxy maize starch, derivative of tapioca dextrin, and mixtures thereof;

b) a thickener selected from the group consisting of sucrose, dextrose, fructose, and mixtures thereof; and

c) a plasticizer,

wherein the composition possesses a surface gloss of at least 150 when applied via dip coating to a substrate.

2. A film forming composition comprised of:

a) a hydroxypropyl starch film former;

b) a thickener selected from the group consisting of kappa carrageenan, iota carrageenan, maltodextrin, gellan gum, agar, gelling starch, and derivatives and mixtures thereof; and

c) a plasticizer,

wherein the composition possesses a surface gloss of at least 150 when applied via dip coating to a substrate.

3. The composition of claim 1, wherein the plasticizers are selected from the group consisting of polyethylene glycol, glycerin, sorbitol, triethyl citrate, tributyl citrate, dibutyl sebacate, vegetable oils, surfactants, propylene glycol, mono acetate of glycerol, diacetate of glycerol, triacetate of glycerol, natural gums, and mixtures thereof.

4. The composition of claim 2 wherein the plasticizer is selected from the group consisting of glycerin, propylene glycol, polyethylene glycol, sugar alcohols and derivatives and mixtures thereof.

5. The composition of claim 1 wherein the plasticizer is glycerin.

6. The composition of claim 1 wherein the plasticizer is glycerin and the thickener is sucrose.

7. The composition of claim 1, wherein the composition is comprised of, based upon the total dry weight of the composition,

a) from about 40 percent to about 60 percent of a film former selected from the group consisting of a waxy maize starch, tapioca dextrin, derivative of a waxy maize starch, derivative of tapioca dextrin, and mixtures thereof;

b) from about 10 percent to about 20 percent of sucrose; and

c) from about 20 percent to about 25 percent of glycerin.

8. The composition of claim 7, wherein the composition is comprised of, based upon the total dry weight of the composition,

a) from about 50 percent to about 55 percent of a film former selected from the group consisting of a waxy maize starch, tapioca dextrin, derivative of a waxy maize starch, derivative of tapioca dextrin, and mixtures thereof;

b) from about 5 percent to about 25 percent of sucrose; and

c) from about 15 percent to about 30 percent of glycerin.

9. The composition of claim 7 further comprising a weight enhancer selected from the group consisting of simethicone, polysorbate 80, and mixtures thereof.

10. The composition of claim 7 further comprising, based upon the total weight of the composition, up to about 14 percent of a coloring agent.

11. A dosage form for delivering active agents, said form comprising an outer coating, said outer coating comprising the composition of claim 6.

12. A pharmaceutical dosage form comprising an outer coating of the composition of claim 7.

13. A pharmaceutical dosage form comprising a core, a subcoating substantially covering said core, and an outer coating substantially covering said subcoating, wherein the outer coating is comprised of the composition of claim 7.

14. The dosage form of claim 13 wherein the subcoating is selected from the group consisting of hydroxypropylmethyl cellulose, castor oil, maltodextrin, polyethylene glycol, polysorbate 80, and mixtures thereof.

15. The dosage form of claim 13 wherein the subcoating is comprised of, based upon the total dry weight of the subcoating,

a) from about 2 percent to about 8 percent hydroxypropylmethylcellulose; and

b) from about 0.1 percent to about 1 percent castor oil.

16. The dosage form of claim 13 wherein the subcoating is comprised of, based upon the total dry weight of the subcoating,

a) from about 25 percent to about 40 percent hydroxypropylmethylcellulose;

b) from about 50 percent to about 20 percent maltodextrin; and

c) from about 5 percent to about 10 percent PEG 400.

17. The dosage form of claim 13 wherein the subcoating is comprised of, based upon the total dry weight of the subcoating,

- a) from about 20 percent to about 50 percent hydroxyethylcellulose;
- b) from about 45 percent to about 75 percent maltodextrin; and
- c) from about 1 percent to about 10 percent PEG 400.

18. A tablet dip coated with the film forming composition according to claim 7.

19. The dosage form of claim 13, comprising an effective amount of a pharmaceutical active ingredient, wherein said dosage form meets USP dissolution requirements for immediate release forms of said pharmaceutical active ingredient.

20. An aqueous dispersion comprised of the composition of claim 7.

21. The aqueous dispersions of claim 20 comprising, based upon the total weight of the dispersion:

- a) from about 5 percent to about 15 percent of sucrose;
- b) from about 10 percent to about 15 percent of glycerin; and
- c) from about 20 percent to about 35 percent of a film former selected from the group consisting of a waxy maize starch, tapioca dextrin, derivative of a waxy maize starch, derivative of tapioca dextrin, and mixtures thereof.

22. A method of making coated tablets from the aqueous dispersions of claim 20 comprising dip coating tablets in the aqueous dispersion under conditions sufficient.

23. A pharmaceutical dosage form comprising a core and a coating;
said coating substantially covering said core, wherein said coating is comprised of the composition of claim 6.

24. A simulated capsule-like medicament comprising:

- a. a core having a first and a second end,
- b. a first coating layer having a first color provided on said first end of said core;
- c. a second coating layer having a second color on said second end of said core, said first color is different than said second color;

wherein at least one of said first coating layer and second coating layer is comprised of a coating layer composition comprised of the composition of claim 6.

25. The medicament of claim 24 wherein at least one coating layer is comprised of, based upon the total dry weight of that coating layer,

- a) from about 40 percent to about 60 percent of a film former selected from waxy maize starch, tapioca dextrin, and derivatives, and mixtures thereof;
- b) from about 10 percent to about 20 percent of sucrose; and
- c) from about 20 percent to about 25 percent of glycerin.

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26. The medicament of claim 25 further comprising a subcoating layer substantially covering said tablet core, said subcoating layer provided between said tablet core and said first coating layer and said second coating layer.

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27. The medicament of claim 26 wherein the subcoating comprises materials selected from the group consisting of cellulose ethers, plasticizers, polycarbohydrates, pigments, opacifiers, and mixtures thereof.

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28. The composition of claim 2, wherein the composition is comprised of, based upon the total dry weight of the composition,

- a) from about 25 percent to about 60 percent of hydroxypropyl starch;
- b) from about 0.1 percent to about 33 percent of a thickener selected from the group consisting of kappa carrageenan, iota carrageenan, maltodextrin, gellan gum, agar, gelling starch, and mixtures thereof; and
- c) from about 11 percent to about 60 percent of a plasticizer selected from the group consisting of glycerin, propylene glycol, polyethylene glycol, sugar alcohols and mixtures thereof.

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29. A dosage form for delivering active agents, said form comprising an outer coating, said outer coating comprising the composition of claim 4

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30. A pharmaceutical dosage form comprising a core, a subcoating substantially covering said core, and an outer coating substantially covering said subcoating, wherein the outer coating is comprised of the composition of claim 4.

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31. A simulated capsule-like medicament comprising:

- a. a core having a first and a second end,
- b. a first coating layer having a first color provided on said first end of said core;
- c. a second coating layer having a second color on said second end of said core, said first color is different than said second color;

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wherein at least one of said first coating layer and second coating layer is comprised of a coating layer composition comprised of the composition of claim 4.

32. The composition of claim 2, wherein the plasticizers are selected from the group consisting of polyethylene glycol, glycerin, sorbitol, triethyl citrate, tributyl citrate, dibutyl sebacate, vegetable oils,

surfactants, propylene glycol, mono acetate of glycerol, diacetate of glycerol, triacetate of glycerol, natural gums, and mixtures thereof.

33. The composition of claim 2 wherein the plasticizer is glycerin.

34. The composition of claim 2 wherein the gelling starch is hydroxypropyl distarch phosphate.

35. The composition of claim 2 wherein the gelling starch is an acid hydrolyzed starch.

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ABSTRACT OF THE INVENTION

Water soluble, gelatin-free dip coatings for tablets and capsules comprising sucrose, glycerin and pre-gelatinized starch and/or tapioca dextrin or comprising hydroxypropyl starch, thickener, and plasticizer.

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DECLARATION - Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)	
60/291,127 60/325,728	15 May 2001 28 September 2001	☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status
10/ (N/A) (Atty. Docket MCP-303)	12 April 2002	Pending

I hereby appoint:

☒ Practitioners at Customer Number **000027777** --

AND

☐ Practitioner(s) named below:

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as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.			
NAME OF SOLE OR FIRST INVENTOR:		☐ A petition has been filed for this unsigned inventor	
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.			
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Mailing Address 80 Annamaria Drive			
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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City Randolph	State NJ	ZIP 07869	Country U.S.A.

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ESTADOS UNIDOS DE AMERICA
A TODOS AQUELLOS A QUIENES EL PRESENTE LLEGUE:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS
UNIDOS
Oficina de Patentes y Marcas de los Estados Unidos

Junio 14, 2002

La presente es para certificar que el anexo es una copia fiel de los registros de la Oficina de Patentes y Marcas de los Estados Unidos, de los documentos de la solicitud de patente identificada más adelante, que cumplieron con los requerimientos para concederse una fecha de presentación de acuerdo con 35 USC 111.

Número de Solicitud: 10/122,999

Fecha de Presentación: Abril 12, 2002

Por la autoridad del
Comisionado de Patentes y Marca

(fdo) N. WOODSON
Oficial Certificador
Sello oficial de la Oficina de Patentes y Marcas de los
Estados Unidos de América

REIVINDICACIONES

1. Una composición soluble en agua para cubrir por inmersión un substrato formada por:
 - a) hidroxipropilmetil celulosa; y
 - 5 b) un espesador seleccionado entre el grupo formado por goma de xantano, carrágeno y sus mezclas,en donde la composición tiene un lustre superficial por lo menos de 150 al aplicarse mediante recubrimiento por inmersión a un substrato.
- 10 2. La composición de la reivindicación 1, en donde la composición está formada por, con base en el peso total seco de la composición,
 - a) desde aproximadamente 95 por ciento hasta menos de aproximadamente 100 por ciento de hidroxipropilmetil celulosa; y
 - 15 b) desde aproximadamente 0,5 por ciento hasta alrededor de 5 por ciento de un espesador seleccionado entre el grupo formado por goma de xantano, carrágeno, y sus mezclas.
- 20 3. La composición de la reivindicación 1, en donde la composición está formada por, con base en el peso total seco de la composición,
 - a) desde aproximadamente 95 por ciento hasta alrededor de 99,5 por ciento de hidroxipropilmetil celulosa; y

b) desde aproximadamente 0,5 por ciento hasta alrededor de 5 por ciento de goma de xantano.

4. La composición de la reivindicación 2, que comprende adicionalmente,
5 con base en el peso seco total de la composición, hasta aproximadamente 40 por ciento de plastificantes.

5. La composición de la reivindicación 4 en donde los plastificantes se
seleccionan entre el grupo formado por polietilenglicol, glicerina,
10 sorbitol, citrato de trietilo, citrato de tributilo, cebacato de dibutilo, aceites vegetales, agentes activos de superficie, propilenglicol, monoacetato de glicerol, diacetato de glicerol, triacetato de glicerol, gomas naturales, y sus mezclas.

15 6. La composición de la reivindicación 4, en donde los plastificantes se seleccionan entre el grupo formado por glicerina, polietilenglicol, propilenglicol, aceite de castor, y sus mezclas.

7. La composición de la reivindicación 2 que comprende adicionalmente,
20 con base en el peso seco total de la composición, hasta aproximadamente 14 por ciento de un agente colorante.

8. La composición de la reivindicación 7, en donde el agente colorante se selecciona entre el grupo formado por azo colorantes, colorantes de quinoxalina, colorantes de trifenilmetano, colorantes de xantano, colorantes de indigoide, óxidos de hierro, hidróxidos de hierro, dióxido de titanio, colorantes naturales, y sus mezclas.
9. Una forma de dosificación para suministrar un agente activo, comprendiendo la forma un recubrimiento exterior, comprendiendo dicho recubrimiento exterior la composición de la reivindicación 2.
10. Una forma de dosificación farmacéutica que comprende un recubrimiento exterior de la composición de la reivindicación 2.
11. Una forma de dosificación farmacéutica que comprende un núcleo, un subrecubrimiento que cubre sustancialmente dicho núcleo, y un recubrimiento exterior que cubre sustancialmente dicho subrecubrimiento, en donde el recubrimiento exterior está formado por la composición de la reivindicación 2.
12. La forma de dosificación recubierta de la reivindicación 11, en donde el subrecubrimiento comprende materiales seleccionados entre el grupo

formado por éteres de celulosa, plastificantes, polícarbohidratos, pigmentos, opacificantes, y sus mezclas.

5 13. La forma de dosificación recubierta de la reivindicación 11 en donde el subrecubrimiento comprende materiales seleccionados entre el grupo formado por hidroxipropilmetil celulosa, aceite de castor, polietilén glicol, polisorbato 80, maltodextrina, y sus mezclas.

10 14. La forma de dosificación de la reivindicación 11 en donde el subrecubrimiento está formado por, con base en el peso seco total del subrecubrimiento,

15 a) desde aproximadamente 2 por ciento hasta alrededor de 8 por ciento de un éter de celulosa soluble en agua seleccionado entre el grupo formado por hidroxipropilmetil celulosa, hidroxipropil celulosa, hidroxietil celulosa y sus mezclas,

b) desde aproximadamente 0,1 por ciento hasta alrededor de 1 por ciento de aceite de castor.

20 15. La forma de dosificación de la reivindicación 11, en donde el subrecubrimiento está formado por, con base en el peso seco total del subrecubrimiento,

- a) desde aproximadamente 4 por ciento hasta alrededor de 6 por ciento de hidroxipropilmetil celulosa; y
- b) desde aproximadamente 0,1 por ciento hasta alrededor de 1 por ciento de aceite de castor.

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16. La forma de dosificación de la reivindicación 15, en donde la hidroxipropilmetil celulosa tiene una viscosidad de aproximadamente 5000 cps en una solución acuosa que contiene 2 por ciento en peso de hidroxipropilmetil celulosa.

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17. La forma de dosificación de la reivindicación 11 en donde el subrecubrimiento está formado por, con base en el peso seco total del subrecubrimiento,

- a) desde aproximadamente 20 por ciento hasta alrededor de 50 por ciento de hidroxipropilmetil celulosa;
- b) desde aproximadamente 45 por ciento hasta alrededor de 75 por ciento de maltodextrina;
- c) desde aproximadamente 1 por ciento hasta alrededor de 10 por ciento de PEG 400.

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18. La forma de dosificación recubierta de la reivindicación 11, en donde el recubrimiento está formado por, con base en el peso seco total de el substrato,
 - a) desde aproximadamente 25 por ciento hasta alrededor del 40 por ciento de hidroxietilcelulosa;
 - b) desde aproximadamente 50 por ciento hasta alrededor de 70 por ciento de maltodextrina;
 - c) desde aproximadamente 5 por ciento hasta aproximadamente 10 por ciento de PEG 400.
19. Una tableta recubierta con la composición formadora de película de acuerdo con la reivindicación 2.
20. La forma de dosificación recubierta de la reivindicación 11, que comprende adicionalmente una cantidad efectiva de un ingrediente farmacéutico activo, en donde dicha forma de dosificación satisface los requisitos de disolución de la USP para formas de desprendimiento inmediato de dicho ingrediente farmacéutico activo.
21. Una dispersión acuosa de la composición de la reivindicación 2, para la manufactura de tabletas recubiertas por inmersión.

22. La dispersión acuosa de la reivindicación 21 formada por, sobre la base peso total de la dispersión acuosa,
- a) desde aproximadamente 10 por ciento hasta alrededor de 14 por ciento de hidroxipropilmetil celulosa; y
- 5 b) desde aproximadamente 0,1 por ciento hasta alrededor de 0,14 por ciento de goma de xantano.
23. La composición de la reivindicación 1, la cual es sustancialmente libre de gelatina.
- 10
24. El uso de la dispersión acuosa de la reivindicación 21 para la fabricación de tabletas recubiertas por inmersión.
25. Una forma de dosificación farmacéutica que comprende un núcleo y un recubrimiento, cubriendo sustancialmente dicho recubrimiento dicho núcleo y teniendo un lustre superficial aproximadamente de 150; en donde dicho recubrimiento comprende la composición de la reivindicación 1.
- 15
- 20 26. La composición de la reivindicación 2, que comprende adicionalmente un agente mejorador de peso, seleccionado entre el grupo formado por simeticona, polisorbato 80, y sus mezclas.

27. Un medicamento simulado en forma de a cápsula, que comprende:
- a. un núcleo que tiene un primero y un segundo extremo,
 - b. una primera capa de recubrimiento que tiene un primer color provisto sobre dicho primer extremo de dicho núcleo;
 - 5 c. una segunda capa de recubrimiento que tiene un segundo color sobre dicho segundo extremo de dicho núcleo, dicho primer color es diferente a dicho segundo color;
- en donde por lo menos una de dichas primera capa de recubrimiento y segunda capa de recubrimiento comprende la composición de la
- 10 reivindicación 1.
28. El medicamento de la reivindicación 27 en donde al menos una de dicha primera capa de recubrimiento y dicha segunda capa de recubrimiento está formada por una composición de recubrimiento,
- 15 estando formada dicha composición de recubrimiento por, con base en el peso seco total de la composición de recubrimiento,
- a) desde aproximadamente 95 por ciento hasta menos de aproximadamente 100 por ciento de hidroxipropilmetilcelulosa; y
 - b) desde aproximadamente 0,5 por ciento hasta alrededor de 5 por
- 20 ciento de goma de xantano.

29. El medicamento de la reivindicación 28 que comprende adicionalmente una capa de subrecubrimiento que cubre sustancialmente dicho núcleo de tableta, provista dicha capa de subrecubrimiento entre dicho núcleo de tableta y dicha primera capa de recubrimiento y dicha segunda capa de recubrimiento.
30. El medicamento de la reivindicación 29, en donde el subrecubrimiento comprende materiales seleccionados entre el grupo formado por éteres de celulosa, plastificantes, polícarbohidratos, pigmentos, opacificantes y sus mezclas.
31. Una composición soluble en agua para recubrir por inmersión un sustrato formado por:
- a) hidroxipropilmetil celulosa; y
 - b) aceite de castor,
- en donde la composición comprende un lustre superficial de por lo menos 150 al aplicarse mediante recubrimiento por inmersión a un sustrato.
32. Una forma de dosificación farmacéutica que comprende un núcleo y un recubrimiento, cubriendo sustancialmente dicho recubrimiento

dicho núcleo; en donde dicho recubrimiento comprende la composición de la reivindicación 31.

33. El uso de la composición de la reivindicación 31, para la manufactura
5 de tabletas recubiertas por inmersión.

34. Una composición soluble en agua para recubrir por inmersión un
substrato, formada por:

a) hidroxipropilmetil celulosa; y

10 b) maltodextrina,

en donde la composición posee un lustre superficial por lo menos de
150 al aplicarse mediante recubrimiento por inmersión a un substrato.

35. La composición de la reivindicación 34, que comprende
15 adicionalmente polietilenglicol.

36. Una forma de dosificación farmacéutica que comprende un núcleo y
un recubrimiento, cubriendo sustancialmente dicho recubrimiento
dicho núcleo; en donde dicho recubrimiento comprende la composición
20 de la reivindicación 34.

37. El uso de la composición de la reivindicación 34 para la fabricación de tabletas recubiertas por inmersión.
38. La composición soluble en agua de la reivindicación 1, en donde la
5 composición está formada por, con base en el peso seco total de la composición:
- a) más de aproximadamente 95 por ciento y menos de aproximadamente 99,5 por ciento de hidroxipropilmetil celulosa;
y
- 10 b) más de aproximadamente 0,5 por ciento y menos de aproximadamente 5 por ciento de carrágeno, en donde la composición posee un lustre superficial por lo menos de 150 al aplicarse mediante recubrimiento por inmersión a un substrato.
- 15 39. Una forma de dosificación farmacéutica que comprende un núcleo y un recubrimiento, cubriendo dicho recubrimiento sustancialmente dicho núcleo; en donde dicho recubrimiento comprende la composición de la reivindicación 38.
- 20 40. El uso de la composición de la reivindicación 38 para la fabricación de tabletas recubiertas por inmersión.

PA 852970



THE UNITED STATES OF AMERICA

~~TO ALL TO WHOM THESE PRESENTS SHALL COME:~~

UNITED STATES DEPARTMENT OF COMMERCE

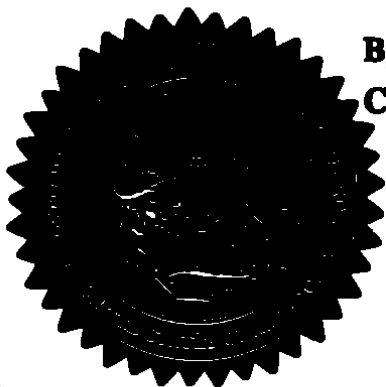
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June 14, 2002

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 10/122,999

FILING DATE: April 12, 2002



By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS


N. WOODSON
Certifying Officer

Please type a plus sign (+) inside this box ☒UTILITY
PATENT APPLICATION
TRANSMITTAL

Attorney Docket No.

MCP-303

First Inventor

Cynthia Gulian et al.

Title

DIP COATING COMPOSITIONS CONTAINING CELLULOSE
ETHERS

Express Mail Label No.

EV 085841702 US

(only for new nonprovisional applications under 37 CFR
1.52(b))

APPLICATION ELEMENTS

ADDRESS TO:

Commissioner for Patents
Box Patent Application
Washington, DC 20231See MPEP Chapter 600 concerning utility patent application
contents.1. ☒ Fee Transmittal Form (e.g., PTO/SB/17)
(submit an original and a duplicate for fee processing)2. ☐ Applicant claims small entity status.3. ☒ Specification [Total Pages - 34]

(Preferred arrangement set forth below)

- Descriptive Title of the Invention

- Cross Reference to Related Applications

- Statement Regarding Fed sponsored R&D

- Reference to sequence listing, a table, or a
computer program listing appendix

- Background of the Invention

- Brief Summary of the Invention

- Brief Description of the Drawings (if filed)

- Detailed Description

- Claim(s)

- Abstract of the Disclosure

4. ☐ Drawing(s) (35 USC 113) [Total Sheets - 0]

5. Oath or Declaration [Total Pages - 5]

a. ☒ Unexecutedb. ☐ Copy from a prior application (37 CFR 1.63(d))
(for continuation/divisional with Box 18 completed)i. ☐ DELETION OF INVENTOR(S)Signed statement attached deleting
inventor(s) named in the prior application,
see 37 CFR 1.63(d)(2) and 1.33(b).6. ☐ Application Data Sheet. See 37 CFR 1.7618. ☐ If a CONTINUING APPLICATION, check appropriate box and supply the requisite information below and in a
preliminary amendment, or in an Application Data Sheet under 37 CFR 1.76:☐ Continuation ☐ Divisional ☐ Continuation-in-Part (CIP) of prior application No.: , filed

Prior application information: Examiner Group Art Unit:

For CONTINUATION or DIVISIONAL APPS only: The entire disclosure of the prior application, from which an
oath or declaration is supplied under Box 5b, is considered a part of the disclosure of the accompanying
continuation or divisional application and is hereby incorporated by reference. The incorporation can only be
relied upon when a portion has been inadvertently omitted from the submitted application parts.

19. CORRESPONDENCE ADDRESS

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New Brunswick, NJ 08933-7003 USA

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21. SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

NAME

Michele G. Mangini

Reg. No. 36,806

SIGNATURE



DATE

April 12, 2002

FEE TRANSMITTAL	<i>Complete if Known</i>	
	Application Number	
	Filing Date	April 12, 2002
	First Named Inventor	Cynthia Gullan et al.
	Group Art Unit	
	Examiner Name	
	Attorney Docket Number	MCP-303

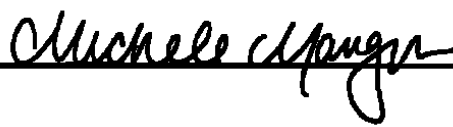
FEE CALCULATION

CLAIMS AS FILED

(1)	(2)	(3)	(4)	(5)
FOR:	NUMBER FILED	NUMBER EXTRA	RATE	BASIC FEE \$740.00
TOTAL CLAIMS	40 - 20 =	20	x 18.00	\$ 380.00
INDEPENDENT CLAIMS	3 - 3 =	0	x 84.00	\$ 0.00
MULTIPLE DEPENDENT CLAIMS	☐	N/A	\$280.00	
			TOTAL FEES	\$1100.00

METHOD OF PAYMENT

- ☒ Please charge Deposit Account No. 10-0750/MCP-303/MGM in the amount of \$1,100.00. Three copies of this sheet are enclosed.
- ☒ The Commissioner is hereby authorized to charge any additional fees which may be required in connection with the filing of this communication, or credit any overpayment, to Account No. 10-0750/MCP-303/MGM. Three copies of this sheet are enclosed.

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Typed or Printed Name	Michele G. Mangini	Reg. No. 38,808
Signature		Deposit Account No. 10-0750
	Date: 4/12/02	

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FEE TRANSMITTAL	<i>Complete if Known</i>	
	Application Number	
	Filing Date	April 12, 2002
	First Named Inventor	Cynthia Gullan et al.
	Group Art Unit	
	Examiner Name	
	Attorney Docket Number	MCP-303

FEE CALCULATION

CLAIMS AS FILED

(1)	(2)	(3)	(4)	(5)
FOR:	NUMBER FILED	NUMBER EXTRA	RATE	BASIC FEE
				\$740.00
TOTAL CLAIMS	40 - 20 =	20	x 18.00	\$ 360.00
INDEPENDENT CLAIMS	3 - 3 =	0	x 84.00	\$ 0.00
MULTIPLE DEPENDENT CLAIMS	☐	N/A	\$280.00	
			TOTAL FEES	\$1100.00

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SUBMITTED BY:		<i>Complete (if applicable)</i>	
Typed or Printed Name	Michèle G. Mengini	Reg. No. 38,808	
Signature	<i>Michèle G. Mengini</i>	Date: 4/12/02	Deposit Account No. 10-0750

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DOCKET NO. MCP-303

IN THE UNITED STATES
PATENT AND TRADEMARK OFFICE

Applicant: Cynthia Gulian et al.

For : DIP COATING COMPOSITIONS CONTAINING CELLULOSE ETHERS

Express Mail Certificate

"Express Mail" mailing number: EV 065841702 US

Date of Deposit: April 12, 2002

I hereby certify that this complete application (including 34 specification pages and 40 claims), an unexecuted Declaration and Power of Attorney and Patent Application Transmittal (2 pp.), is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner for Patents, Box Patent Applications, Washington, D.C. 20231.

An executed Combined Declaration and Power of Attorney will be submitted to the United States Patent and Trademark Office upon receipt of the U.S. Serial Number for this patent application.

Karen Hall-Morgan

(Typed or printed name of person mailing paper or fee)

Karen Hall Morgan

(Signature of person mailing paper or fee)

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DIP COATING COMPOSITIONS CONTAINING CELLULOSE ETHERS

CROSS-REFERENCE TO RELATED APPLICATION

This Application claims the benefit of United States Application Number 60/291,127 filed on 15 May 2001 and United States Application Number 60/325,726 filed 28 September 2001, which are both incorporated by reference in their entireties herein.

FIELD OF THE INVENTION

This invention relates to novel, water soluble, gelatin-free compositions for dip coating substrates, such as tablets and capsules, and methods for producing such dosage forms. This invention further relates to a method for increasing the weight gain of a water soluble, gelatin-free, film forming coating on a dip-coated tablet or caplet.

BACKGROUND OF THE INVENTION

During most of this century, hard gelatin capsules were a popular dosage form for prescription and over-the-counter (OTC) drugs. The ability to combine capsule halves having different colors provided manufacturers with a unique means of distinguishing various pharmaceutical products. Many patients preferred capsules over tablets, perceiving them as being easier to swallow. This consumer preference prompted pharmaceutical manufacturers to market certain products in capsule form even when they were also available in tablet form.

Generally, empty hard gelatin capsules are manufactured using automated equipment. This equipment employs rows of stainless steel pins, mounted on bars or plates, which are dipped into a gelatin solution maintained at a uniform temperature and fluidity. The pins are then withdrawn from the gelatin solution, rotated, and then inserted into drying kilns through which a strong blast of filtered air with controlled humidity is forced. A crude capsule half is thus formed over each pin during drying. Each capsule half is then stripped, trimmed to uniform length, filled and joined to an appropriate mating half.

An alternative to capsule products are caplets, which are solid, oblong tablets that are often coated with various polymers such as cellulose ethers to improve their aesthetics, stability, and swallowability. Typically, such polymers are applied to the tablets either from solution in organic solvents, or from aqueous dispersion via spraying. However, such spray-coated tablets lack the shiny surface and elegance of the hard gelatin capsules. Additionally, it is not commercially feasible to spray-coat a tablet with a different color coating on each end.

Another alternative to capsule products are "gelcaps," which are elegant, shiny, consumer-preferred dosage forms that are prepared by dipping each half of an elongated tablet in two different colors of gelatin solution. See United States Patent Nos.: 4,820,524; 5,536,125; 5,685,688; 5,770,225; 5,196,227; and 5,296,233, which are all incorporated by reference herein. A similar dosage form, commercially available as a "geltab," is prepared by dipping each half of a

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round, convex tablet into different colors of gelatin solution, as described in United States Patent Nos. 5,228,916, US5,436,026 and US5,679,406, which are all incorporated by reference herein. As used herein, such "gelcaps" and "gelabs" shall be included within the broader term, "tablets."

However, the use of gelatin as a pharmaceutical coating material presents certain disadvantages and limitations, including the potential for decreased dissolution rate after extended storage due to cross-linking of the gelatin, potential for microbial contamination of the gelatin solution during processing, and long processing times due to extensive drying requirements. Further, the energy-related costs associated with gelatin coatings tend to be high since the gelatin material is typically applied to the substrates at an elevated temperature of at least about 40°C in order to maintain fluidity of the gelatin, while the substrates are maintained at about 50°C in order to minimize microbial growth.

Various attempts have been made to produce gelatin-free hard shell capsules. For example, WO 00/18835 discloses the combination of starch ethers or oxidized starch and hydrocolloids for use in preparing hard capsule shells via conventional dip molding processing. See also U.S. Pat. No. 4,001,211 (capsules prepared via pin dip coating with thermogelled methylcellulose ether compositions). However, due to potential tampering concerns, hard gelatin capsules are no longer a preferred delivery system for consumer (over-the-counter) pharmaceuticals, dietary supplements, or other such products. Additionally, the properties of an ideal composition into which steel pins are to be dipped then dried to form hard capsule shells thereon are not necessarily the same as those for dipping tablets to form a coating thereon. For example, relevant physical properties such as viscosity, weight-gain, film thickness, tensile strength, elasticity, and moisture content will differ between compositions for hard capsule formation and for coating tablets. See e.g., U.S. Pat. No. 1,787,777 (Optimal temperatures of the substrate and coating solution, residence times in the solution, and drying conditions differ.)

One disadvantage associated with dipping tablets or capsules into a non-gelatin coating system is that the resulting coatings often lack adequate tensile strength, plasticity, hardness, and thickness. Moreover, the inclusion of plasticizers into such non-gelatin coating systems often results in tablets having soft, tacky coatings without a hardness sufficient to maintain their shape or smoothness during handling. In addition, many non-gelatin compositions do not adhere to the tablet substrate in an amount sufficient to uniformly cover the tablet after a single dipping. Further, many non-gelatin compositions lack the sufficient rheological properties necessary to maintain uniform color dispersion throughout the dipping and drying process. Although attempts have been made to improve the rheological properties of these compositions by, for example, increasing their solids content in order to increase viscosity. However, such compositions often disadvantageously resulted in undesirable coating aesthetics such as surface roughness, decreased gloss, and non-uniform coating thickness.

It is desirable to find a dip coating material, which not only produces a similar elegant, shiny, high gloss, consumer-preferred dosage form similar to that of gelatin-coated forms, but which is absent the limitations of gelatin, particularly those noted above.

SUMMARY OF THE INVENTION

The present invention provides for a film forming composition for dip coating a substrate comprising, consisting of, and/or consisting essentially of:

- a) hydroxypropylmethyl cellulose; and
- b) a thickener selected from the group consisting of xanthan gum, carrageenan, and mixtures thereof,

wherein the composition possesses a surface gloss of at least 150 when applied via dip coating to a substrate.

Another embodiment of the present invention is directed to a water soluble composition for dip-coating a substrate comprising, consisting of, and/or consisting essentially of:

- a) hydroxypropylmethyl cellulose; and
- b) castor oil,

wherein the composition possesses a surface gloss of at least 150 when applied via dip coating to a substrate.

Another embodiment of the present invention is directed to a water soluble composition for dip-coating a substrate comprising, consisting of, and/or consisting essentially of:

- a) hydroxypropylmethyl cellulose; and
- b) maltodextrin,

wherein the composition possesses a surface gloss of at least 150 when applied via dip coating to a substrate.

We have found that when a dosage form is coated with the composition of the present invention, the result is an elegant, shiny, high gloss, consumer-preferred dosage form similar to that of a gelatin-coated form, but which lacks the limitations associated with gelatin, particularly those noted above. We have also found that when such a composition is used in dip coating and spray coating operations, it does not inhibit the dissolution of the active coated therewith. Further, we have found that the color uniformity of dosage forms coated with such compositions is improved upon the addition of a weight gain enhancer thereto.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, "capsules" refer to hard shell compartments that enclose a doseable ingredient. "Tablets," as used herein, refer to compressed or molded solid dosage forms of any shape or size. "Caplets," as used herein, refer to solid, oblong-shaped tablets. "Gelcaps" refer to solid caplets having a glossy gelatinous coating, and "geltabs" refer to solid tablets having flat sides, convex opposing faces, and a glossy gelatinous coating. "Hardness" as used herein in connection with films or coatings indicates the resistance of the film/coating to deformation upon impact. "Water soluble," as used herein in connection with non-polymeric materials, shall mean from sparingly soluble to very soluble, i.e., not more than 100 parts water required to dissolve 1 part of the non-polymeric, water soluble solute. See Remington, "The Science and Practice of

Pharmacy," pages 208 - 209 (2000). "Water soluble," as used herein in connection with polymeric materials, shall mean that the polymer swells in water and can be dispersed at the molecular level to form a homogeneous dispersion or colloidal "solution." "Surface gloss" as used herein, shall refer to amount of light reflectance as measured at a 60 degree incident angle using the method set forth in Example 7 herein.

Dimethicone is a well known pharmaceutical material consisting of linear siloxane polymers containing repeating units of the formula $-(CH_3)_2SiO-$, stabilized with trimethylsiloxy and blocking units of the formula $[(CH_3)_3SiO-]$. Dimethicone is the mixture of dimethicone and silicon dioxide. For the purposes of this invention, the two materials may be used interchangeably.

The first embodiment of this invention is directed to water soluble, substantially gelatin-free, film forming compositions for dip coating tablets or manufacturing capsules via a dip molding process. One composition comprises, consists of, and/or consists essentially of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose; and a thickener, such as a hydrocolloid, e.g., xanthan gum or carrageenan. In another embodiment, the composition comprises, consists of, and/or consists essentially of a film former such as a modified starch selected from waxy maize starch, tapioca dextrin, and derivatives and mixtures thereof; a thickener selected from sucrose, dextrose, fructose, maltodextrin, polydextrose, and derivatives and mixtures thereof; and a plasticizer, e.g., polyethylene glycol, propylene glycol, vegetable oils such as castor oil, glycerin, and mixtures thereof. In yet another embodiment, the composition comprises, consists of, and/or consists essentially of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose; and optionally a plasticizer, such as vegetable oils, e.g., castor oil; and may optionally be substantially free of thickeners such as hydrocolloids, e.g. xanthan gum. In yet another embodiment, the composition comprises, consists of, and/or consists essentially of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose; an extender, such as polycarbohydrates, e.g. maltodextrin; and optionally a plasticizer, such as glycols, e.g., polyethylene glycol; and may optionally be substantially free of thickeners such as hydrocolloids, e.g. xanthan gum. As used herein, "substantially gelatin-free" shall mean less than about 1 percent, e.g. less than about 0.5 percent, of gelatin in the composition, and "substantially free of thickeners" shall mean less than about 1 percent, e.g. less than about 0.01 percent, of thickeners in the composition.

Any film former known in the art is suitable for use in film forming composition of the present invention. Examples of suitable film formers include, but are not limited to, polyvinylalcohol (PVA), hydroxypropyl starch, hydroxyethyl starch, pullulan, methylcellulose, carboxymethyl starch, methylcellulose, hydroxypropylcellulose (HPC), hydroxyethylmethylcellulose (HEMC), hydroxypropylmethylcellulose (HPMC), hydroxybutylmethylcellulose (HBMC), hydroxyethylethylcellulose (HEEC), hydroxyethylhydroxypropylmethyl cellulose (HEMPMC), pre-gelatinized starches, and polymers and derivatives and mixtures thereof.

One suitable hydroxypropylmethylcellulose compound is "HPMC 2910", which is a cellulose ether having a degree of substitution of about 1.9 and a hydroxypropyl molar substitution of 0.23, and containing, based upon the total weight of the compound, from about 29% to about

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30% methoxyl and from about 7% to about 12% hydroxypropyl groups. HPMC 2910 is commercially available from the Dow Chemical Company under the tradename, "Methocel E." "Methocel E5," which is one grade of HPMC-2910 suitable for use in the present invention, has a viscosity of about 4 to 6 cps (4 to 6 millipascal-seconds) at 20 °C in a 2% aqueous solution as determined by a Ubbelohde viscometer. Similarly, "Methocel E6," which is another grade of HPMC-2910 suitable for use in the present invention, has a viscosity of about 5 to 7 cps (5 to 7 millipascal-seconds) at 20 °C in a 2% aqueous solution as determined by a Ubbelohde viscometer. "Methocel E15," which is another grade of HPMC-2910 suitable for use in the present invention, has a viscosity of about 15000 cps (15 millipascal-seconds) at 20 °C in a 2% aqueous solution as determined by a Ubbelohde viscometer. As used herein, "degree of substitution" shall mean the average number of substituent groups attached to a anhydroglucose ring, and "hydroxypropyl molar substitution" shall mean the number of moles of hydroxypropyl per mole anhydroglucose.

As used herein, "modified starches" include starches that have been modified by crosslinking, chemically modified for improved stability, or physically modified for improved solubility properties. As used herein, "pre-gelatinized starches" or "instantized starches" refers to modified starches that have been pre-wetted, then dried to enhance their cold-water solubility. Suitable modified starches are commercially available from several suppliers such as, for example, A.E. Staley Manufacturing Company, and National Starch & Chemical Company. One suitable modified starch includes the pre-gelatinized waxy maize derivative starches that are commercially available from National Starch & Chemical Company under the tradenames, "Purity Gum" and "FilmSet", and derivatives, copolymers, and mixtures thereof. Such waxy maize starches typically contain, based upon the total weight of the starch, from about 0 percent to about 18 percent of amylose and from about 100 percent to about 88 percent of amylopectin.

Suitable tapioca dextrans include those available from National Starch & Chemical Company under the tradename, "Crystal Gum" or "K-4484," and derivatives thereof such as modified food starch derived from tapioca, which is available from National Starch and Chemical under the tradename, "Purity Gum 40," and copolymers and mixtures thereof.

Any thickener known in the art is suitable for use in the film forming composition of the present invention. Examples of such thickeners include but are not limited to hydrocolloids such as alginates, agar, guar gum, locust bean, carrageenan, tara, gum arabic, tragacanth, pectin, xanthan, gellan, maltodextrin, galactomannan, pustulan, laminarin, scleroglucan, gum arabic, inulin, pectin, wheatan, rhaman, zooglan, methylan, chitin, cyclodextrin, chitosan, and derivatives and mixtures thereof. Additional suitable thickeners include sucrose, dextrose, fructose, maltodextrin, polydextrose, and the like, and derivatives and combinations thereof.

Suitable xanthan gums include those available from C.P. Kelco Company under the tradename, "Keltrol 1000," "Xantrol 180," or "K98310."

Any plasticizer known in the pharmaceutical art is suitable for use in the present invention, and may include, but not be limited to polyethylene glycol; glycerin; sorbitol; triethyl citrate; tributyl citrate; dibutyl sebacate; vegetable oils such as castor oil; surfactants such as polysorbates, sodium lauryl sulfates, and dioctyl-sodium sulfosuccinates; propylene glycol; mono acetate of

glycerol; diacetate of glycerol; triacetate of glycerol; natural gums and mixtures thereof. In solutions containing a cellulose ether film former, an optional plasticizer may be present in an amount, based upon the total weight of the solution, from about 0 percent to about 40 percent.

In one embodiment, the film forming composition for dip coating substrates may be substantially free of gelatin, i.e., e.g. contains less than about 1%, or less than about 0.01% of gelatin.

In another embodiment, the film forming composition for dip coating substrates may be substantially free of bovine derived materials, i.e., e.g. contains less than about 1%, or less than about 0.01% of bovine derived materials.

In embodiments wherein a cellulose ether film former is used in the composition, the film forming composition for dip coating substrates may be substantially free of hydrocolloids, i.e., e.g. contains less than about 1%, or less than about 0.01% of hydrocolloids.

In yet another embodiment, the film forming composition for dip coating substrates may be substantially free of plasticizers, i.e., e.g. contains less than about 1%, or less than about 0.01% of plasticizers.

In one embodiment, the film forming composition for dip coating substrates contains, based upon the total dry solids weight of the composition, from about 95 percent to less than about 100 percent, e.g. from about 95 percent to about 99.5 percent, of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose; and from about 0.5 percent to about 5 percent of a thickener such as a hydrocolloid, e.g., xanthan gum.

In another embodiment, the film forming composition for dip coating substrates contains, based upon the total dry solids weight of the composition, from about 40 percent to about 80 percent, e.g. from about 50 percent to about 55 percent, of a modified starch, e.g. a waxy maize starch, a tapioca dextrin, and/or mixtures and derivatives thereof; from about 15 percent to about 30 percent, e.g., from about 20 percent to about 25 percent of a plasticizer, e.g., glycerin, polyethylene glycol, propylene glycol, castor oil, and mixtures thereof; and from about 5 percent to about 25 percent, e.g., from about 10 percent to about 20 percent, of a thickener, e.g., sucrose, dextrose, fructose, maltodextrin, polydextrose, and mixtures thereof.

In yet another embodiment, the film forming composition for dip coating substrates contains, based upon the total dry solids weight of the composition, from about 95 percent to about 100 percent, e.g. from about 97 percent to about 100 percent, of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose.

In yet another embodiment, the film forming composition for dip coating substrates contains, based upon the total dry solids weight of the composition, from about 95 percent to about 100 percent, e.g. from about 97 percent to about 100 percent, of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose, and is substantially free of hydrocolloids, i.e., e.g. contains less than about 1%, or less than about 0.01% of hydrocolloids.

In yet another embodiment, the film forming composition for dip coating substrates contains, based upon the total dry solids weight of the composition, from about 95 percent to about 100 percent, e.g. from about 97 percent to about 100 percent, of a film former such as a cellulose

ether, e.g., hydroxypropylmethylcellulose; and from about 0.1 percent to about 1.0 percent, e.g. from about 0.25 percent to about 0.5 percent of a plasticizer such as vegetable oils, e.g. Castor Oil.

In yet another embodiment, the film forming composition for dip coating substrates contains, based upon the total dry solids weight of the composition, from about 5 percent to about 99 percent, e.g. from about 50 percent to about 90 percent, or from about 80 percent to about 90 percent of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose; from about 1 percent to about 80 percent, e.g. from about 5 percent to about 50 percent or from about 5 percent to about 40 percent of an extender, such as polycarbohydrates, e.g. maltodextrin; and from about 0.1 percent to about 20 percent, e.g. from about 2.5 percent to about 15 percent of a plasticizer such as glycols, e.g. polyethylene glycol. Examples of suitable dry compositions are disclosed in, for example, United States Patent Nos. 5,470,581 and 6,163,808, which are incorporated by reference herein.

These film forming compositions are typically in the form of a dispersion for ease of dip coating substrates therein. Such dispersions contain a solvent in an amount, based upon the total weight of the dispersion, from about 30 percent to about 97 percent, for example, from about 80 percent to about 82 percent or from about 40 percent to about 75 percent. Examples of suitable solvents include, but are not limited to water; alcohols such as methanol, ethanol, and isopropanol; organic solvents such as methylene chloride, acetone, and the like; and mixtures thereof. In one embodiment, the solvent is water. The resulting film forming dispersion typically possesses a solids level of, based upon the total weight of the film forming dispersion, from about 3 percent to about 70 percent, for example, from about 8 percent to about 20 percent or from about 25 percent to about 60 percent.

In one embodiment, the film forming composition for dip coating substrates contains, based upon the total wet weight of the dipping dispersion composition, from about 5 percent to about 20 percent, e.g. from about 8 percent to about 15 percent or from about 10 percent to about 14 percent, of a film former such as hydroxypropylmethylcellulose and from about 0.05 percent to about 0.2 percent, e.g. from about 0.08 percent to about 0.18 percent or from about 0.1 percent to about 0.14 percent, of a thickener such as xanthan gum.

In another embodiment, the film forming composition for dip coating substrates contains, based upon the total wet weight of the dipping dispersion composition, from about 20 percent to about 35 percent, e.g. from about 25 percent to about 30 percent, of a film former such as waxy maize starch, tapioca dextrin, and/or derivatives and mixtures thereof; from about 5 percent to about 20 percent, e.g., from about 10 percent to about 15 percent of a plasticizer such as glycerin, polyethylene glycol, propylene glycol, castor oil, and mixtures thereof; and from about 5 percent to about 15 percent of a thickener selected from sucrose, fructose, dextrose, maltodextrin, polydextrose, and mixtures thereof.

In yet another embodiment, the film forming composition for dip coating substrates contains, based upon the total wet weight of the dipping dispersion composition, from about 5

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percent to about 25 percent, e.g. from about 8 percent to about 20 percent or from about 10 to about 18 percent, of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose.

In yet another embodiment, the film forming composition for dip coating substrates contains, based upon the total wet weight of the dipping dispersion composition, from about 5 percent to about 25 percent, e.g. from about 8 percent to about 20 percent or from about 10 to about 18 percent, of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose, and is substantially free of hydrocolloids, i.e., e.g. contains less than about 1%, or less than about 0.01% of hydrocolloids.

In yet another embodiment, the film forming composition for dip coating substrates contains, based upon the total wet weight of the dipping dispersion composition, from about 5 percent to about 25 percent, e.g. from about 8 percent to about 20 percent or from about 10 to about 18 percent, of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose; and from about 0.001 percent to about 0.1 percent, e.g. from about 0.01 percent to about 0.09 percent of a plasticizer such as vegetable oils, e.g. castor oil.

In yet another embodiment, the film forming composition for dip coating substrates contains, based upon the total wet weight of the dipping dispersion composition, from about 1 percent to about 21 percent, e.g. from about 10 percent to about 19 percent or from about 16 percent to about 19 percent, of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose; from about 0.1 percent to about 17 percent, e.g. from about 1 percent to about 11 percent or from about 1 percent to about 8 percent of an extender, such as polycarbohydrates, e.g. maltodextrin; and from about 0.02 percent to about 4 percent, e.g. from about 0.5 percent to about 3 percent of a plasticizer such as glycols, e.g. polyethylene glycol.

Optionally, the composition for dipping may further comprise other ingredients such as, based upon the total weight of the dipping solution, from about 0 percent to about 2 percent preservatives such as methylparaben and propylparaben, from about 0 percent to about 14 percent opacifying agents such as titanium dioxide, and/or from about 0 percent to about 14 percent colorants. See *Remington's Practice of Pharmacy*, Martin & Cook, 17th ed., pp. 1825 - 30, which is herein incorporated by reference.

Any coloring agent suitable for use in pharmaceutical applications may be used in the present invention and may include, but not be limited to azo dyes, quinophthalone dyes, triphenylmethane dyes, xanthene dyes, indigoid dyes, iron oxides, iron hydroxides, titanium dioxide, natural dyes, and mixtures thereof. More specifically, suitable colorants include, but are not limited to patent blue V, acid brilliant green BS, red 2G, azorubine, ponceau 4R, amaranth, D&C red 33, D+C red 22, D+C red 28, D+C red 28, D+C yellow 10, FD+C yellow 5, FD+C yellow 6, FD+C red 3, FD+C red 40, FD+C blue 1, FD+C blue 2, FD+C green 3, brilliant black BN, carbon black, iron oxide black, iron oxide red, iron oxide yellow, titanium dioxide, riboflavin, carotenes, anthocyanines, turmeric, cochineal extract, chlorophyllin, canthaxanthin, caramel, betanin, and mixtures thereof.

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In one embodiment, each end of the tablet or capsule may be coated with dip coatings of different colors to provide a distinctive appearance for specialty products. See United States Patent No. 4,820,524, which is incorporated by reference herein.

In one embodiment, the pharmaceutical dosage form is comprised of a) a core containing an active ingredient; b) an optional first coating layer comprised of a subcoating that substantially covers the core; and c) a second coating layer on the surface of the first coating layer, the second coating layer comprised of the dip coating composition of the present invention. As used herein, "substantially covers" shall mean at least about 95 percent of the surface area of the core is covered by the subcoating.

In an alternate embodiment, a first active ingredient may be contained in the first coating layer, and the core may contain a second active ingredient and/or an additional amount of the first active ingredient. In yet another embodiment, the active ingredient may be contained in the first coating layer, and the core may be substantially free, i.e., less than about 1 percent, e.g. less than about 0.1 percent, of active ingredient.

The use of subcoatings is well known in the art and disclosed in, for example, United States Patent Nos. 3,185,826, which is incorporated by reference herein. Any composition suitable for film-coating a tablet may be used as a subcoating according to the present invention. Examples of suitable subcoatings are disclosed in United States Patent Nos. 4,683,258, 4,543,370, 4,643,894, 4,828,841, 4,725,441, 4,802,924, 5,630,871, and 6,274,162, which are all incorporated by reference herein. Additional suitable subcoatings include one or more of the following ingredients: cellulose ethers such as hydroxypropylmethylcellulose, hydroxypropylcellulose, and hydroxyethylcellulose; polycarbohydrates such as xanthan gum, starch, and maltodextrin; plasticizers including for example, glycerin, polyethylene glycol, propylene glycol, dibutyl sebacate, triethyl citrate, vegetable oils such as castor oil, surfactants such as polyorbate-80, sodium lauryl sulfate and dioctyl-sodium sulfosuccinate; polycarbohydrates, pigments, and opacifiers.

In one embodiment, the subcoating may be comprised of, based upon the total weight of the subcoating, from about 2 percent to about 8 percent, e.g. from about 4 percent to about 6 percent of a water-soluble cellulose ether and from about 0.1 percent to about 1 percent, castor oil, as disclosed in detail in United States Patent No. 5,858, 589, which is incorporated by reference herein. In another embodiment, the subcoating may be comprised of, based upon the total weight of the subcoating, from about 20 percent to about 50 percent, e.g., from about 25 percent to about 40 percent of HPMC; from about 45 percent to about 75 percent, e.g., from about 50 percent to about 70 percent of maltodextrin; and from about 1 percent to about 10 percent, e.g., from about 5 percent to about 10 percent of PEG 400.

The dried subcoating typically is present in an amount, based upon the dry weight of the core, from about 0 percent to about 5 percent. The dried dip coating layer typically is present in an amount, based upon the dry weight of the core and the optional subcoating, from about 1.5 percent to about 10 percent.

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The average thickness of the dried dip coating layer typically is from about 40 to about 400 microns. However, one skilled in the art would readily appreciate without undue experimentation that the dip coating thickness may be varied in order to provide a smoother, easier to swallow, dosage form or to achieve a desired dissolution profile. Moreover, the thickness of dipped film coatings may vary at different locations on the substrate depending upon its shape. For example, the thickness of the coating at an edge or corner of a substrate may be as much as 50 percent to 70 percent less than the thickness of the coating at the center of a major face of the substrate. This difference can be minimized by, for example, use of a thicker subcoating, or use of dipping compositions that result in higher weight gains on the substrate.

In embodiments wherein a thicker dip coating is desired, we have found that an effective amount of a weight gain enhancer selected from the group consisting of simethicone, polysorbate 80 and mixtures thereof, may be added to a film forming composition comprised, consisting of, and/or consisting essentially of a film former and an optional thickener such as a hydrocolloid. The weight gain enhancer is used in an amount sufficient to increase the weight gain of the coating solution, e.g. by at least about 10 percent, by at least about 20%, or by at least about 30 % on a substrate when dried. The percent weight gain increase is determined based upon the difference between the total weight of the coated substrate with the coating composition including the weight gain enhancer, and the total weight of an coated equivalent substrate, which has been coated under similar processing conditions with a coating composition that does not include an effective amount of weight gain enhancer.

In one embodiment, the film former is a cellulose ether such as HPMC, and the thickener is a hydrocolloid such as xanthan gum and the weight gain enhancer is simethicone.

A suitable film forming composition capable of achieving increased weight gain of dip coating on a substrate may contain, based upon the total dry weight of the film forming composition, from about 40 percent to about 99.9 percent, e.g. from about 95 percent to about 99.5 percent, or from about 40 percent to about 60 percent of a film former; from about 0 percent to about 60 percent, e.g. from about 0 percent to about 10 percent, or from about 0.5 percent to about 5 percent, or from about 10 percent to about 25 percent of a thickener; and from about 0.01 percent to about 0.25 percent, e.g. from about 0.03 percent to about 0.15 percent of a weight gain enhancer. When aesthetics of the final tablet are of particular concern, it is recommended to not use greater than about 0.25 percent of a weight gain enhancer. As shown above, the amount of thickener suitable for use in the composition will vary depending upon, for example, the particular thickener selected and the desired properties of the coating. For example, when xanthan gum is the thickener of choice, the amount of xanthan gum thickener may range, based upon the total dry weight of the film forming composition, from about 0.5 percent to about 5 percent.

The film forming compositions of the present invention may be prepared by combining the film former, the thickener, and any optional ingredients such as plasticizers, preservatives, colorants, opacifiers, the weight gain enhancer, or other ingredients with the solvent using a high shear mixer until homogeneous under ambient conditions. In embodiments wherein a waxy maize starch derivative is used as a film former, the mixture may be heated to a temperature of about 60

°C to about 90 °C for faster dispersion of the ingredients. Alternatively, the film former and thickener may be preblended as dry powders, followed by addition of the resulting powder blend to the water and optional weight gain enhancer with high speed mixing. In order to remove substantially all of the bubbles from the resulting mixture, the pressure may then be decreased to about 5 inches Hg while reducing the mixing speed in order to avoid creating a vortex therein. Any other additional optional ingredients may then be added thereto at constant mixing.

It has surprisingly been found that substrates may be dipped into such solutions of the present invention using the same equipment and similar range of process conditions as used for the production of dip molded, gelatin-coated tablets. For example, both tablets and hard capsules may be coated using the aqueous dispersions of the present invention via known gelatin-dipping process parameters and equipment. Details of such equipment and processing conditions are known in the art and are disclosed at, for example, United States Patent No. 4,820,624, which is incorporated by reference herein. Advantageously, because the coating solutions of the present invention are fluid at room temperature and are less susceptible to microbial growth than gelatin compositions, the dip coating process may occur under ambient temperature and pressure conditions.

The tablets dip coated with the composition of the present invention may contain one or more active agents. The term "active agent" is used herein in a broad sense and may encompass any material that can be carried by or entrained in the system. For example, the active agent can be a pharmaceutical, nutraceutical, vitamin, dietary supplement, nutrient, herb, foodstuff, dyestuff, nutritional, mineral, supplement, or favoring agent or the like and combinations thereof.

The active agents useful herein can be selected from classes from those in the following therapeutic categories: ace-inhibitors; alkaloids; antacids; analgesics; anabolic agents; anti-anginal drugs; anti-allergy agents; anti-arrhythmia agents; antiasthmatics; antibiotics; anticholesterolemics; anticonvulsants; anticoagulants; antidepressants; antidiarrheal preparations; anti-emetics; antihistamines; antihypertensives; anti-infectives; anti-inflammatory; antilipid agents; antimentics; anti-migraine agents; anti-nauseants; antipsychotics; antistroke agents; antithyroid preparations; anabolic drugs; antiobesity agents; antiparasitics; antipsychotics; antipyretics; antispasmodics; antithrombotics; antitumor agents; antitussives; antilucer agents; anti-uricemic agents; endolytic agents; appetite stimulants; appetite suppressants; beta-blocking agents; bronchodilators; cardiovascular agents; cerebral dilators; chelating agents; cholecystekinin antagonists; chemotherapeutic agents; cognition activators; contraceptives; coronary dilators; cough suppressants; decongestants; deodorants; dermatological agents; diabetes agents; diuretics; emollients; enzymes; erythropoietic drugs; expectorants; fertility agents; fungicides; gastrointestinal agents; growth regulators; hormone replacement agents; hyperglycemic agents; hypoglycemic agents; ion-exchange resins; laxatives; migraine treatments; mineral supplements; mucolytics, narcotics; neuroleptics; neuromuscular drugs; non-steroidal anti-inflammatory (NSAIDs); nutritional additives; peripheral vasodilators; polypeptides; prostaglandins; psychotropics; renin inhibitors; respiratory stimulants; sedatives; steroids; stimulants;

sympatholytics; thyroid preparations; tranquilizers; uterine relaxants; vaginal preparations; vasoconstrictors; vasodilators; vertigo agents; vitamins; wound healing agents; and others.

Active agents that may be used in the invention include, but are not limited to:

acetaminophen; acetic acid; acetylsalicylic acid, including its buffered forms; acrivastine; albuterol
 5 and its sulfate; alcohol; alkaline phosphatase; allantoin; aloe; aluminum acetate, carbonate,
 chlorohydrate and hydroxide; alproazolam; amino acids; aminobenzolic acid; amoxicillin; ampicillin;
 amesacrine; amesalog; anethole; ascorbic acid; aspartame; astemizole; atenolol; azatidine and its
 maleate; bacitracin; balsam peru; BCNU (carmustine); beclomethasone dipropionate; benzocaine;
 10 benzoic acid; benzophenones; benzoyl peroxide; benzquinamide and its hydrochloride;
 bethanechol; biotin; bisacodyl; blamuth subsalicylate; borneyl acetate; brompheniramine and its
 maleate; buspirone; caffeine; calamine; calcium carbonate, caseinate and hydroxide; camphor;
 ceftopril; cascara sagrada; castor oil; cefaclor; cefadroxil; cephalaxin; centriline and its
 hydrochloride; cetirizine; cetyl alcohol; cetylpyridinium chloride; chelated minerals;
 15 chloramphenicol; chlorcyclizine hydrochloride; chlorhexidine gluconate; chloroxylenol;
 chloropentostatin; chlorpheniramine and its maleates and tannates; chlorpromazine;
 cholestyramine resin; choline bitartrate; chondrogenic stimulating protein; cimetidine; cinnamedrine
 hydrochloride; citalopram; citric acid; clarithromycin; clemastine and its fumarate; clonidine;
 clorifibrate; cocoa butter; cod liver oil; codeine and its fumarate and phosphate; cortisone acetate;
 20 ciprofloxacin HCl; cyanocobalamin; cyclizine hydrochloride; cyproheptadine; danthron;
 dexbrompheniramine maleate; dexdromethorphan and its hydrohalides; diazepam; dibucaine;
 dichloralphenazone; diclofen and its alkali metal salts; diclofenac sodium; digoxin;
 dihydroergotamine and its hydrogenates/mesylates; diltiazem; dimethicone; dioxibenzene;
 diphenhydramine and its citrate; diphenhydramine and its hydrochloride; divalproex and its alkali
 metal salts; docusate calcium, potassium, and sodium; doxycycline hydrate; doxylamine succinate;
 25 dronabinol; efaroxan; enalapril; enoxacin; ergotamine and its tartrate; erythromycin; estropipate;
 ethinyl estradiol; ephedrine; epinephrine bitartrate; erythropoietin; eucalyptol; famotidine;
 fenopropfen and its metal salts; ferrous fumarate, gluconate and sulfate; fexofenadine; fluoxetine;
 folic acid; fosphenytoin; 5-fluorouracil (5-FU); fluoxetine; flurbiprofen; furosemide; gabapentin;
 gentamicin; gemfibrozil; glipizide; glycerine; glyceryl stearate; granisetron; griseofulvin; growth
 30 hormone; guaifenesin; hexylresorcinol; hydrochlorothiazide; hydrocodone and its tartrates;
 hydrocortisone and its acetate; 8-hydroxyquinoline sulfate; hydroxyzine and its pamoate and
 hydrochloride salts; ibuprofen; indomethacin; inositol; insulin; iodine; ipecac; iron; isosorbide and
 its mono- and dinitrates; iscodcam; ketamine; kaolin; ketoprofen; lactic acid; lanolin; lecithin;
 leuprolide acetate; lidocaine and its hydrochloride salt; lilefinopril; liletrix; loperamide, loratadine;
 35 lovastatin; luteinizing hormone; LHRH (luteinizing hormone replacement hormone); magnesium
 carbonate, hydroxide, salicylate, and trisilicate; meclizine; mefenamic acid; meclofenamic acid;
 meclofenamate sodium; medroxyprogesterone acetate; methenamine mandelate; menthol;
 meprednise hydrochloride; metaproterenol sulfate; methecopolamine and its nitrates; methsergide
 and its maleate; methyl nicotinate; methyl salicylate; methyl cellulose; metheximide;
 40 metoclopramide and its halides/hydrates; metronidazole; metoprolol tartrate; miconazole nitrate;

mineral oil; minoxidil; morphine; naproxen and its alkali metal sodium salts; nifedipine; neomycin sulfate; niacin; niacinamide; nicotine; nicotinamide; nimesulide; nitroglycerine; nonoxonyl-9; norethindrone and its acetate; nystatin; octoxynol; octoxynol-8; octyl dimethyl PABA; octyl methoxycinnamate; omega-3 polyunsaturated fatty acids; orneprazole; ondansetron and its hydrochloride; oxolinic acid; oxybenzone; oxytriphylline; para-aminobenzoic acid (PABA); pedimate-O; paramethedione; pentastatin; peppermint oil; pentaerythritol tetranitrate; pentobarbital sodium; perphenazine; phenelzine sulfate; phenindamine and its tartrate; pheniramine maleate; phenobarbital; phenol; phenolphthalein; phenylephrine and its tannates and hydrochlorides; phenylpropanolamine; phenytoin; pimenol; piroxicam and its salts; polymixin B sulfate; potassium chloride and nitrate; prazepam; procainamide hydrochloride; procaterol; promethazine and its hydrochloride; propoxyphene and its hydrochloride and napsylate; pramiracetin; pramoxine and its hydrochloride salt; prochlorperazine and its maleate; propranolol and its hydrochloride; promethazine and its hydrochloride; propanolol; pseudoephedrine and its sulfates and hydrochlorides; pyridoxine; pyrolamine and its hydrochlorides and tannates; quinapril; quinidine gluconate and sulfate; quinestral; ralitoline; ranitidine; resorcinol; riboflavin; salicylic acid; scopolamine; sesame oil; shark liver oil; simethicone; sodium bicarbonate, citrate, and fluoride; sodium monofluorophosphate; sucralose; sulfanethoxazole; sulfasalazine; sulfur; sumatriptan and its succinate; tetrine and its hydrochloride; theophylline; terfenadine; thiothipiperazine and its maleate; timolol and its maleate; thioiperidone; tramadol; trimetrexate; triazolam; tretinoin; tetracycline hydrochloride; tolmetin; tolnaftate; triclosan; trimethobenzamide and its hydrochloride; tripelennamine and its hydrochloride; trippidine hydrochloride; undecylenic acid; vancomycin; verapamil HCl; vidarbine phosphate; vitamins A, B, C, D, B₁, B₂, B₆, B₁₂, E, and K; witch hazel; xylometazoline hydrochloride; zinc; zinc sulfate; zinc undecylenate. Active agents may further include, but are not limited to food acids; insoluble metal and mineral hydroxides, carbonates, oxides, polycarbophils, and salts thereof; adsorbates of active drugs on a magnesium trisilicate base and on a magnesium aluminum silicate base, and mixtures thereof. Mixtures and pharmaceutically acceptable salts of these and other actives can be used.

In one embodiment, the dosage forms coated with the dip coatings of the present invention provided for immediate release of the active ingredient, i.e. the dissolution of the dosage form conformed to USP specifications for immediate release tablets containing the particular active ingredient employed. For example, for acetaminophen tablets, USP 24 specifies that in pH 5.8 phosphate buffer, using USP apparatus 2 (paddles) at 50 rpm, at least 80% of the acetaminophen contained in the dosage form is released therefrom within 30 minutes after dosing, and for ibuprofen tablets, USP 24 specifies that in pH 7.2 phosphate buffer, using USP apparatus 2 (paddles) at 50 rpm, at least 80% of the ibuprofen contained in the dosage form is released therefrom within 80 minutes after dosing. See USP 24, 2000 Version, 19 – 20 and 858 (1999).

We have unexpectedly found that the coatings formed by dipping substrates into the compositions of the present invention possessed excellent properties comparable to those possessed by gelatin coatings, e.g. crack resistance, hardness, thickness, color uniformity, smoothness, and gloss. Typically, the coatings of the present invention possessed a surface gloss

of greater than about 150, e.g. greater than about 190 or greater than about 210 when measured according to the method set forth in example 7 herein.

In addition, tablets dip coated with the compositions of the present invention were superior to tablets dip coated with conventional gelatin-based coatings in several important ways. First, tablets dip coated with the compositions of the present invention advantageously retained acceptable dissolution characteristics for the desired shelf-life and storage period at elevated temperature and humidity conditions. In particular, the cellulose-ether based compositions according to the present invention were also advantageously more resistant to microbial growth, which thereby enabled a longer shelf-life or use-life of the dipping solution as well as a reduction in manufacturing cost. Second, the sugar-thickened dipping dispersions according to the present invention beneficially employed a lower water content relative to that of gelatin-containing dispersions, which thereby enabled a shorter drying cycle time. Although the water content of the other dipping dispersions of the present invention may have been higher than that typically found in gelatin-based dipping solutions, the cellulose-ether based compositions of the present invention surprisingly required a shorter drying cycle time relative to that for gelatin-containing compositions. Third, the dried coatings comprised of the compositions of the present invention also surprisingly and advantageously contained fewer air bubbles relative to the amount present in dried, gelatin based dipping compositions. Fourth, unlike dip processing with gelatin-containing compositions, substrates may optionally be dipped in the solutions of the present invention at room temperature, which is economically more beneficial. Fifth, the dip coated compositions of the present invention possessed a higher degree of glossiness relative to similar coatings applied via spray coating methods known in the art. The dip coated compositions of the present invention also possessed a similar degree of glossiness relative to that possessed by gelatin-containing dip or enrobing coatings, which are currently viewed as the industry benchmark for high gloss coatings. See, e.g., United States Patent No. 6,274,162 (Typical gloss readings for standard, commercially available gel-dipped or gelatin enrobed tablets range from about 200 to 240 gloss units, gloss readings for standard, commercially available sugar-coated medicaments range from 177 to 209 gloss units, and gloss readings for a new, high-gloss coating system range from about 148 to about 243 gloss units.).

We have further unexpectedly found that the addition of an effective amount of weight gain enhancer to a film forming composition comprised of film former and hydrocolloid not only significantly increased the resulting dry weight of the dip coating on a substrate, but it also improved the color uniformity of the coating.

The invention illustratively disclosed herein suitably may be practiced in the absence of any component, ingredient, or step which is not specifically disclosed herein. Several examples are set forth below to further illustrate the nature of the invention and the manner of carrying it out. However, the invention should not be considered as being limited to the details thereof.

EXAMPLES

Example 1.) Preparation of Subcoating Dispersions

An aqueous dispersion containing the ingredients set forth in Table A was prepared by combining all of the ingredients in a beaker under ambient conditions.

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Table A: Aqueous Dispersion Subcoating Composition

<u>Ingredient</u>	<u>Part *</u>
HPMC (2910, 5 mPs) from Dow Chemical Company under the tradename, "Methocel E-5"	20
Castor oil	1
Water	241.5
Total Coating Solution	262.5
% solids in coating solution	8%

* expressed in terms of part by weight unless otherwise noted

Additional aqueous dispersions containing the ingredients in Table B were similarly prepared:

Table B: Aqueous Dispersion Subcoating Compositions

<u>Ingredient</u>	<u>Ex 1A**</u>	<u>Ex 1B</u>	<u>Ex 1C</u>	<u>Ex 1D</u>	<u>Ex 1E</u>
HPMC 2910, 5 mPs	20	40	40	28	28
Castor oil	1	0	0	0	0
water	212.3	566.67	566.67	566.67	566.67
maltodextrin	0	53	53	67	67
PEG 400	0	7	7	5	5
Hydroxy-ethylcellulose*	0	0	0	0	0
Total coating solution	233.3	666.67	666.67	666.67	666.67
Wt % solids in coating solution	9%	15%	15	15	15

* Available from Aquaion, under the tradename, "Natrosol 250L"

** all values expressed in terms of parts by weight unless otherwise noted

Additional aqueous dispersions containing the ingredients in Table C were similarly prepared:

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Table C: Aqueous Dispersion Subcoating Compositions

Ingredient	Ex 1F**	Ex 1G	Ex 1H
water	586.67	586.67	890.4
maltodextrin	71	71	0
Castor oil	0	0	0.13
HPMC (1910, 5mPas)	0	0	32.4
PEG 400	5	5	0
Hydroxy-ethylcellulose*	24	24	0
Total coating solution	686.67	686.67	722.9
Wt % solids in coating solution	15%	15%	4.5%

* Available from Aqualon, under the tradename, "Natrosol 250L"

** all values expressed in terms of parts by weight unless otherwise noted

Example 2.) Preparation of Subcoated Tablets

Compressed tablets were prepared in accordance with the procedure set forth in Example 1 of United States Patent No. 5,658,589 ("589 Patent"), which was incorporated by reference herein.

The dispersion of Example 1 was then applied onto the compressed tablets via spraying in accordance with the procedure set forth in the examples of the '589 Patent . As shown in Table D below, the dried subcoated tablets possessed an average 2% to 4% weight gain relative to the weight of the subcoating-free tablets.

This process was repeated with additional compressed tablets, but with the substitution of each, respective subcoating dispersion produced in Example 1A to 1H for that of Example 1. The percentage weight gain of the dried subcoated tablets are set forth below in Table D:

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Table D: % Weight Gain of Dried Subcoated Tablets

Example Number	% Weight Gain
1A	2
1B	2
1C	4
1D	2
1E	4
1F	2
1G	4
1H	4

Example 3) Preparation of HPMC Coated Tablets

Aqueous HPMC dipping solutions containing the ingredients set forth in Table E were prepared:

Table E: Composition of HPMC Dipping Solutions

Ingredient	Ex 3A (g)	Ex 3B (g)	Ex 3C (g)	Ex 3D (%)	Ex 3E (%)	Ex 3F (%)
HPMC E5	32.5	0	32.5	10	11	14
Water	200	200	200	89.89	88.879	85.85
HPMC (2910, 15mPa)	0	20	0		0	0
Xanthan gum	0	0	0	0.11	0.121	0.15
PEG 400	0	0	8	0	0	0
% (wt.) solids in dipping solution	14	9	17	10.11	11.121	14.15

* all values expressed in terms of weight (g) unless otherwise noted

Example 3A: Preparation Of Dipping Solution of Example 3A: HPMC was dispersed into 200 ml of deionized water at a temperature of 70 °C. After adding about 1 wt % FD&C blue dye thereto, the solution was mixed until homogeneous. The solution was then cooled to a temperature of about 22 °C.

Example 3B: Preparation of Dipping Solution of Example 3B: The procedure of Example 3A was repeated, but with substitution of HPMC (2910, 15mPa) for the HPMC E5.

Example 3C: Preparation Of Dipping Solution of Example 3C: HPMC was dispersed into 200 ml of deionized water at a temperature of 70 °C. After adding the PEG 400 thereto, the solution was mixed until homogeneous. The solution was then cooled to a temperature of about 22 °C.

Example 3D: Preparation Of Dipping Solution of Example 3D: HPMC and xanthan gum were added to purified water at a temperature of 80 °C until the powder was dispersed. After discontinuing the heat, the solution was divided into two parts. 4.35 wt. % of a yellow color dispersion available from Colorcon, Inc. under the tradename, "Opatint Yellow DD-2115" was added to the first part and mixed at a low speed until dispersed. 5.8% of a green color dispersion available from Colorcon, Inc. under the tradename, "Opatint Green DD-11000" was added to the second part and mixed at a low speed until dispersed. The two dispersed solutions were then stored under ambient conditions for about 12 hours.

Example 3E: Preparation Of Dipping Solution of Example 3E: The procedure of Example 3D was repeated, but using the components of Example 3E.

Example 3F: Preparation Of Dipping Solution of Example 3F: The procedure of Example 3D was repeated, but using the components of Example 3F.

Example 3G: Preparation of Hand-Dipped Dip Coated Tablets: The subcoated tablets prepared in accordance with Example 2 using the subcoating produced in Example 1H were hand-dipped into the dipping solutions of Example 3A for a dwell time of 1 second, removed from the dipping solution, then dried under ambient conditions.

This procedure was repeated, but with substitution of the dipping solutions of Examples 3B and 3C, respectively, for the dipping solution of Example 3A.

An observation of the resulting coatings showed the following:

Tablets Coated with Coating of Ex. 3A: The coatings were smooth, hard, and shiny, and had no bubbles or cracking. However, the coatings were non-uniform and thin, with land areas not well-covered. Upon exposure to ambient conditions for a six month period, no cracks were seen in the coatings.

Tablets Coated with Coating of Ex. 3B: The coating were shiny, with few bubbles and no cracking. The coatings were more uniform and rough relative to those of Example 3A. The coatings were also somewhat tacky and thin, with land areas not well-covered. Upon exposure to ambient conditions for a six month period, no cracks were seen in the coatings.

Tablets Coated with Coating of Ex. 3C: The coatings were shiny with few bubbles and no cracking. The coatings were more uniform and rough relative to those of Example 3A. The coatings were also somewhat tacky and thin, with land areas not well-covered. Upon exposure to ambient conditions for a six month period, no cracks were seen in the coatings.

Example 3H: Preparation of Production Scale Dipped Tablets: Additional subcoated tablets prepared in accordance with Example 2 using the subcoating produced in Example 1H were coated with the resulting dipping solution of Examples 3D using a commercial grade gel-

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dipping machine in accordance with the procedure described in United States Patent No. 4,820,524, which is incorporated by reference herein.

This procedure was repeated, but with substitution of the dipping solutions of Examples 3E and 3F, respectively, for the dipping solution of Example 3D.

The average percentage weight gain of the dried dipped coatings were as set forth in Table F:

Table F: Weight Gain of Dried Dip Coating

<u>Example</u>	<u>% Wt. Gain of Dried Coating*</u>
Ex. 3D	0.75 – 2.26
Ex. 3E	1.9 – 3.52
Ex. 3F	3.2 – 5.8

* Relative to weight of dried subcoating and core

This example showed that the addition of xanthan gum to the HPMC dipping solution provided a viscosity enhancement to the dip coating, and thus an increased weight gain of the dip coating on the tablets.

Example 3I: Preparation of Dipping Solution of Example 3I

The procedure of Example 3D was repeated, but using the components of Example 3I, as set forth in Table M:

Table M: Composition of HPMC Dipping Solutions

<u>Ingredient</u>	<u>Ex 3I *(g)</u>	<u>Ex 3J (g)</u>
HPMC E5	14	12
Water	85.89	87.88
HPMC (2910, 15mPa)	0	0
Xanthan gum	0.11	0.12
PEG 400	0	0
% (wt.) solids in dipping solution	14.11	12.12

* all values expressed in terms of weight (g) unless otherwise noted

Example 3J: Preparation of Dipping Solution of Example 3J

The procedure of Example 3D was repeated, but using the components of Example 3J, as set forth in Table M above.

Example 4) Preparation of Pre-gelatinized Starch-Containing Dip Coating Solutions

Dipping solutions comprised of the components set forth in Table G were prepared by dispersing 75 g of the modified waxy maize starch into 200 ml of water under ambient conditions with mbdng:

Table G: Pre-gelatinized starch-containing Dipping solutions

Component/Other	Example 4A*	Example 4B
Modified waxy maize starch (Purity® Gum 59)	75	125
water	200	200
Total weight of solution	275	325
Wt % solids in dipping solution	27	39

* all values expressed in terms of weight (g) unless otherwise noted

Dipping solutions comprised of the components set forth in Table H below were prepared by dispersing all of the components into 200 ml of water under ambient conditions with mbdng until the resulting solution was clear.

Table H: Pre-gelatinized starch-containing Dipping solutions With Silmethicone of Example 4C

Component	Tradename	Supplier	Amount used *
Modified waxy maize starch	Purity ® Gum 59	National Starch & Chemical Co.	125
Silmethicone	Antifoam®		2
Colloidal silicone dioxide	Aerosil ® A200		6
Glycerin	—	—	63.5
Sucrose	—	—	38
colorant	Opatint®		6.9
water	—	—	200
Total solids			241.4
TOTAL solution (w/ 55% solids)			441.1

* all values expressed in terms of weight (mg) unless otherwise noted

Each side of the subcoated tablets prepared in accordance with Example 2 using the subcoating produced in Example 1H were hand-dipped into the dipping solution of Example 4A for a dwell time of about 1 second, pulled up, then dried under ambient conditions.

This procedure was repeated, but with substitution of the dipping solution of Example 4B for the dipping solution of Example 4A and with about a 3 day period between the completion of production of the dipping solution and the commencement of dip coating process.

This procedure was further repeated, but with substitution of the dipping solutions of Example 4C for the dipping solution of Example 4A and with about a 12 hour period between the completion of production of the dipping solution and the commencement of dip coating process.

An observation of the resulting coatings showed the following:

Tablets Coated With Dipping Solution of Ex. 4A: The coatings were very shiny, hard, smooth, even, and not tacky or cracked. However, the coatings were too thin, and land areas were not covered. No cracking after exposure to ambient conditions for a period of 6 months.

Tablets Coated With Dipping Solution of Ex. 4B: The coatings were smooth and shiny. Initially the land areas were covered; however, the coatings cracked after exposure to ambient conditions for a period of 6 months.

Tablets Coated With Dipping Solution of Ex. 4C: The coatings possessed excellent shine and cover, and were smooth with no cracks. No cracking after exposure to ambient conditions for a period of 2 months.

Example 5) Preparation of Pre-Gelatinized Starch-Containing Dip Coating Solutions

The procedure set forth in Example 4C is repeated, but without the inclusion of simethicone. Prior to coating the substrate, the solution is exposed to a vacuum pressure of 5 inches Hg in order to remove substantially all of the visible bubbles from the solution. The resulting coating possesses excellent shine and cover, and is smooth with no cracks.

Example 6) Effect of Simethicone on Coating Weight Gain

The following dip coating solutions set forth in Table I were prepared to illustrate the effect of simethicone as a weight gain enhancer. Amounts are percent based on the total weight of coating solution.

Table I Dip Coating Solutions

Ingredient	6A	6B	6C	6D	6E
HPMC 2810, 5mPa	12	12	12	12	12
Xanthan Gum	1	1	1	1	1
Simethicone	0	0.035	0.07	0.14	0.25
Yellow color dispersion***	8	8	8	8	8
Water	81	80.965	80.93	80.86	80.75

*** Yellow color dispersion was "Opatin"® No. DD2125 obtained from Colorcon, Inc.

Dipping solutions A through E, above, were prepared in the following manner: Purified water was heated to about 35°C. HPMC and xanthan gum were added while mixing using a laboratory

scale electric mixer (Janke and Kunkel, IKA Labortechnik, Staufen, Germany) with propeller blade at approximately 1000 rpm until the powders appeared uniformly dispersed. Heating was discontinued, and the resulting dispersion was allowed to stand overnight at room temperature. Simethicone and yellow color dispersion were then added with mixing at approximately 500 rpm.

Subcoated cores, prepared according to the method of example 1A, were pre-weighed, then dipped in solutions A, B, C, D, and E, above for a dwell time of about 2 seconds, pulled up, then dried at ambient conditions (about 22 °C). The cores were dipped simultaneously in sets of 7. Three separate sets of seven cores were dipped in each solution A through E. The average weight gain was determined from the triplicate sets of dipped cores from each coating solution.

Resulting weight gains were as follows in Table J:

Table J – Average Weight Gain

Dipping Solution	6A	6B	6C	6D	6E
Average weight gain from dip coat (mg/tablet)	13.3	20.8	22.3	23.7	19.1

Example 7) Surface Gloss Measurement of Coated Tablets

Tablets made according to the preceding examples were tested for surface gloss using an instrument available from TriCor Systems Inc. (Elgin, IL) under the tradename, "Tri-Cor Model 805A/808H Surface Analysis System" and generally in accordance with the procedure described in "TriCor Systems WGLOSS 3.4 Model 805A/808H Surface Analysis System Reference Manual" (1998), which is incorporated by reference herein, except as modified below.

This instrument utilized a CCD camera detector, employed a flat diffuse light source, compared tablet samples to a reference standard, and determined average gloss values at a 60 degree incident angle. During its operation, the instrument generated a grey-scale image, wherein the occurrence of brighter pixels indicated the presence of more gloss at that given location.

The instrument also incorporated software that utilized a grouping method to quantify gloss, i.e., pixels with similar brightness were grouped together for averaging purposes.

The "percent full scale" or "percent ideal" setting (also referred to as the "percent sample group" setting), was specified by the user to designate the portion of the brightest pixels above the threshold that will be considered as one group and averaged within that group. "Threshold", as used herein, is defined as the maximum gloss value that will not be included in the average gloss value calculation. Thus, the background, or the non-glossy areas of a sample were excluded from the average gloss value calculations. The method disclosed in K. Fegley and C. Vesey, "The Effect of Tablet Shape on the Perception of High Gloss Film Coating Systems", which is available at www.colortcon.com as of 18 March, 2002 and incorporated by reference herein, was used in order to minimize the effects resulting from different tablet shapes, and thus report a metric that was comparable across the industry. (Selected the 50% sample group setting as the setting which best approximated analogous data from tablet surface roughness measurements.).

After initially calibrating the instrument using a calibration reference plate (190-228; 294 degree standard; no mask, rotation 0, depth 0), a standard surface gloss measurement was then created using gel-coated caplets available from McNEIL-PPC, Inc. under the tradename, "Extra Strength Tylenol Gelcaps." The average gloss value for a sample of 112 of such gel-coated caplets was then determined, while employing the 25 mm full view mask (190-280), and configuring the instrument to the following settings:

- Rotation: 0
- Depth: 0.25 inches
- Gloss Threshold: 95
- % Full Scale: 50%
- Index of Refraction: 1.57

The average surface gloss value for the reference standard was determined to be 269, using the 50% Ideal (50% full scale) setting.

Samples of coated tablets prepared according to the preceding examples were then tested in accordance with the same procedure. The surface gloss values at the 50% Ideal setting that were obtained are summarized in Table K below.

Table K: Gloss values of coated tablets

Example No.	3D	3I	3J	4C	6B
Type of coating	dipped	dipped	dipped	poured film	dipped
No. of tablets tested	48	48	51	plate	3
Gloss Value(% Ideal at 50)	234	247	229	259	221

Additional samples of other, commercially available gel coated tablets were also tested in accordance with the same procedure and compared to the same standard. The results are summarized in Table L below.

Table L: Gloss values of commercially available coated tablets

Product	Motrin IB * Caplet (white)	Excedrin* * Aspirin free Caplets (red)	Excedrin ** Migraine Geltab (green side)	Excedrin ** Migraine Geltab (white side)	Extra Strength Tylenol Geltabs * (yellow side)	Extra Strength Tylenol Geltabs * (red side)
Type of coating	sprayed film	sprayed film	gelatin enrobed	gelatin enrobed	dipped	dipped
No. of tablets tested	41	40	10	10	112	112
Gloss Value(% Ideal at 50)	125	119	270	264	268	268

* Available from McNEIL-PPC, Inc.

** Available from Bristol-Myers, Squibb, Inc.

5 This Example showed that the tablets coated with the compositions of the present
Invention possessed a high surface gloss value that either was comparable to or exceeded that
possessed by commercially -available gelatin coated tablets. In contrast, typical sprayed films
possessed a substantially lower surface gloss, e.g. 119 to 125 in this Example.

10 **Example 8: Preparation of Coated tablets**

Example 8A: Preparation of Tablets Spray Coated With Opadry® II Subcoating

122.8 kg (18% w/w) of a prepared blend containing HPMC 2910-8cP, maltodextrin,
HPMC2910-3cP, HPMC2910-50cP, and PEG-400 (commercially available from Colorcon Inc.,
15 West Point, PA as "Opadry® II") was added with mixing into 559.7 kg (82% w/w) of 35°C purified
water in a conventional pressure pot, and mixed with an air-driven propeller-type Lightnin mixer at
a speed of 500 rpm. After the powder was completely added, the dispersion was mixed at 500
rpm for 2 hours, then allowed to stand without mixing at ambient conditions for 12 hours.

20 The resulting film coating dispersion was then applied onto compressed acetaminophen
tablets, which were prepared in accordance with the procedure set forth in Example 1 of US Patent
No. 5,658,589 ("589 Patent"), which is incorporated by reference herein, via spraying in
accordance with the procedure set forth in the examples of the '589 patent. The resulting spray-
coated tablets possessed a 4% weight gain relative to the weight of the uncoated tablet cores.

25 **Example 8B: Preparation of Tablets Spray Coated with HPMC / Castor Oil Subcoating**

88.4 kg (9% w/w) of hydroxypropyl methylcellulose 2910, 5mPa and 0.347 kg (0.04% w/w)
of castor Oil were mixed into 583.8 kg (91% w/w) of purified water at 35°C in a tank with mixer

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(Lee Industries) at a speed of 1750 rpm. After the powder was completely added, the mixer speed was increased to 3500 rpm for 15 minutes. The mixer speed was then reduced to 1750 rpm while the pressure was reduced to 15 inches of water for 2 hours to deaerate the dispersion.

The resulting film coating dispersion was then applied onto the compressed acetaminophen tablets of Example 8A via spraying in accordance with the procedure set forth above in Example 8A. The resulting spray coated tablets possessed a 4% weight gain relative to the weight of the uncoated tablet cores.

Example 8C: Preparation of Tablets Dip Coated with HPMC/Castor Oil dipping solutions

A dipping solution comprised of the components set forth in Table M below was produced:

Table M: HPMC/Castor Oil Clear Dipping Solutions

Example	A&B	C&D	E&F
HPMC 2910 5mPa	9%	13%	13%
Castor Oil	0.04%	0.06%	0.05%
Purified Water	90.96%	86.95%	86.95%

Purified water was heated to 80° C, then added to a Lee jacketed mix tank while mixing at a speed of 1750 rpm. After HPMC 2910, 5mPa and castor oil were added thereto with mixing, the mixer speed was increased to 3500 rpm for 15 minutes. The mixer speed was then reduced to 1750 rpm while the temperature of the dispersion was reduced to 35 °C and the pressure was reduced to 15 inches water for deaeration. After mixing the dispersion for 2 hours, the resulting dispersion remained under constant pressure conditions for an additional 3 hours without mixing.

The colorant of Example 8C-a was then added to 96 kg of the resulting clear dipping solutions with mixing at a 1750 rpm speed in the amounts set forth in Table N below :

Table N: HPMC/Castor Oil Colored Dipping Solutions

<u>Example</u>	<u>8C-a</u>	<u>8C-b</u>	<u>8C-c</u>	<u>8C-d</u>	<u>8C-e</u>	<u>8C-f</u>
Colorant	Opatint (DD-1781)	Opatint (DD-2125)	Opatint (DD-1781)	Opatint (DD-2125)	Opatint (DD-10516)	Opatint (DD-18000)
Amount of colorant (kg)	2.700	2.570	2.700	2.570	4.072	2.175
Color	red	yellow	red	yellow	blue	white
Visc/Temp	490 cps @40C	518 cps @40C	612cps @30C	457cps @30C	361cps @40C	319cps @40C
Dipping Temp	40C	40C	30C	30C	40C	40C
Weight Gain in dipping (mg/tablet)	16*	16*	26**	26**	20***	20***
Gloss	229	229	249	228	238	233

* Indicates total weight gain for a tablet having an 8Ca coating on one half and an 8Cb coating on the other

** Indicates total weight gain for a tablet having an 8Cc coating on one half and an 8Cd coating on the other

*** Indicates total weight gain for a tablet having an 8Ce coating on one half and an 8Cf coating on the other

This procedure was independently repeated for each of the colorants set forth above in Table N.

Subcoated tablets, which were prepared in accordance with the procedure set forth above in Example 8A, were dip-coated with the dip-coating solution prepared in accordance with Example 8C-a and 8C-b using a commercial grade gel-dipping machine and in accordance with the procedure described in United States Patent No. 4,820,524, which is incorporated by reference herein, using the dipping solution temperatures reported in the table above. This procedure was independently repeated on subcoated tablets, which were prepared in accordance with the procedure set forth above in Example 8B, for each of the colored dipping solutions 8C-c through 8C-f in Table N above.

A visual comparison of the dip-coated tablets prepared according to examples 8C-a and 8C-b with those prepared in accordance with Examples 8C-c through 8C-f revealed that the former did not possess complete coating coverage around the edges of the tablets. By contrast, the dip-coated tablets prepared according to examples 8C-c through 8C-f possessed a superior good coating coverage around the tablet edges. This indicated that a weight gain of 16 mg per gelcap (such as that produced by the 9% HPMC formula of examples 8C-a and 8C-b) was insufficient for the HPMC/Castor Oil dipping formula, while a weight gain of 20 to 26 mg per gelcap/gelcap (such as that produced by the 13% HPMC formula of examples 8C-c through 8C-f) provided good coverage.

In addition, a visual comparison of the HPMC/Castor Oil dip-coated tablets of Examples 8C-c through 8C-f and the HPMC/Xanthan Gum dip-coated tablets of Examples 3I and 3J

indicated that the former possessed superior gloss and surface smoothness. The superior gloss and smoothness were likely attributed to the inclusion of castor oil in the dip coating.

**Example 9: Preparation of Tablets Dip Coated
with HPMC/Maltodextrin/PEG dipping solutions**

143.3 kg (21% w/w) of the Opadry® II blend of Example 8A was added into 539.2 kg (79% w/w) of 35°C purified water while mixing at a speed of 3500 rpm for 15 minutes. The mixer speed was then decreased to 1750 rpm, and the tank evacuated to 30 PSIA to deaerate the solution for 5 hours. 2.70 kg of Colorant (Opatint® Red DD-1781, from Colorcon Inc.) was then added to 98 kg of the clear dipping solution while mixing at a speed of 1750 rpm. 2.570 kg of Colorant (Opatint® Yellow DD-2125, from Colorcon Inc.) was then added to a second 98 kg portion of the clear dipping solution while mixing at a speed of 1750 rpm until dispersed.

Subcoated tablets, which were prepared in accordance with the procedure and materials set forth above in Example 8B, were dip-coated with the dip-coating solution prepared in accordance with this Example using a commercial grade gel-dipping machine and in accordance with the procedure described in United States Patent No. 4,820,524, which is incorporated by reference herein, using a dipping solution temperature of 30°C. The viscosity of the dipping solutions was 807 cPs at 30°C for the yellow solution, and 677 cPs at 30°C for the red solution. An average weight gain of about 27 mg/gelcap was obtained.

Seventy-two (72) dipped gel caps produced in accordance with this Example were tested for surface gloss in accordance with the procedure set forth in Example 7. The average surface gloss for these dipped gelcaps was 256 gloss units.

**Example 10: Preparation of Tablets Dip
Coated with HPMC/Carrageenan dipping solutions**

88.4 kg (13% w/w) of HPMC 2910-5 mPs, 0.347 kg of Castor Oil (0.05% w/w), and 0.68 kg (0.1% w/w) of kappa Carrageenan-911 were added into a tank containing 590 kg (87% w/w) of 80°C purified water while mixing at a speed of 1750 rpm. After the addition was complete, the mixer speed was increased to 3500 rpm for 15 minutes. The mixer speed was then decreased to 1750 rpm, and the tank evacuated to 15 inches of water to deaerate the solution for 2 hours. Mixing was then stopped, and the dispersion was allowed to stand at constant pressure for an additional 3 hours. 2.175 kg of Colorant (Opatint® White DD-18000, from Colorcon Inc.) was then added to 98 kg of the clear dipping solution while mixing at a speed of 1750 rpm. 4.072 kg of Colorant (Opatint® Blue DD-10516, from Colorcon Inc.) was then added to a second 98 kg portion of the clear dipping solution while mixing at a speed of 1750 rpm until dispersed.

Subcoated tablets, which were prepared in accordance with the procedure and materials set forth above in Example 8B, were dip-coated with the dip-coating solution prepared in accordance with this Example using a commercial grade gel-dipping machine and in accordance

with the procedure described in United States Patent No. 4,820,524, which is incorporated by reference herein, using a dipping solution temperature of 40°C. An average weight gain of about 20 mg/gelcap was obtained.

- 5 Eighty-eight (88) dipped gel caps produced in accordance with this Example were tested for surface gloss in accordance with the procedure set forth in Example 7. The average surface gloss for these dipped gelcaps was 232 gloss units.

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We claim:

1. A water soluble composition for dip-coating a substrate comprised of:

a) hydroxypropylmethyl cellulose; and

b) a thickener selected from the group consisting of xanthan gum, carrageenan, and mixtures thereof,

wherein the composition possesses a surface gloss of at least 150 when applied via dip coating to a substrate.

2. The composition of claim 1, wherein the composition is comprised of, based upon the total dry weight of the composition,

a) from about 95 percent to less than about 100 percent of hydroxypropylmethyl cellulose; and

b) from about 0.5 percent to about 5 percent of a thickener selected from the group consisting of xanthan gum, carrageenan, and mixtures thereof.

3. The composition of claim 1, wherein the composition is comprised of, based upon the total dry weight of the composition,

a) from about 95 percent to about 99.5 percent of hydroxypropylmethyl cellulose; and

b) from about 0.5 percent to about 5 percent of xanthan gum.

4. The composition of claim 2 further comprising, based upon the total dry weight of the composition, up to about 40% plasticizers.

5. The composition of claim 4 wherein the plasticizers are selected from the group consisting of polyethylene glycol, glycerin, sorbitol, triethyl citrate, tributyl citrate, dibutyl sebacate, vegetable oils, surfactants, propylene glycol, mono acetate of glycerol, diacetate of glycerol, triacetate of glycerol, natural gums, and mixtures thereof.

6. The composition of claim 4, wherein the plasticizers are selected from the group consisting of glycerin, polyethylene glycol, propylene glycol, castor oil, and mixtures thereof.

7. The composition of claim 2 further comprising, based upon the total dry weight of the composition, up to about 14% of a coloring agent.

8. The composition of claim 7 wherein the coloring agent is selected from the group consisting of azo dyes, quinophthalone dyes, triphenylmethane dyes, xanthene dyes, indigold dyes, iron oxides, iron hydroxides, titanium dioxide, natural dyes, and mixtures thereof.

9. A dosage form for delivering an active agent, the form comprising an outer coating, said outer coating comprising the composition of claim 2.

10. A pharmaceutical dosage form comprising an outer coating of the composition of claim 2.

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11. A pharmaceutical dosage form comprising a core, a subcoating substantially covering said core, and an outer coating substantially covering said subcoating, wherein the outer coating is comprised of the composition of claim 2.

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12. The coated dosage form of claim 11 wherein the subcoating comprises materials selected from the group consisting of cellulose ethers, plasticizers, polycarbohydrates, pigments, opacifiers, and mixtures thereof.

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13. The coated dosage form of claim 11 wherein the subcoating comprises materials selected from the group consisting of hydroxypropylmethylcellulose, castor oil, polyethylene glycol, polysorbate 80, maltodextrin, and mixtures thereof.

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14. The dosage form of claim 11 wherein the subcoating is comprised of, based upon the total dry weight of the subcoating,

a) from about 2 percent to about 8 percent of a water-soluble cellulose ether selected from the group consisting of hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, and mixtures thereof.

b) from about 0.1 percent to about 1 percent castor oil.

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15. The dosage form of claim 11 wherein the subcoating is comprised of, based upon the total dry weight of the subcoating,

a) from about 4 percent to about 8 percent hydroxypropylmethylcellulose; and

b) from about 0.1 percent to about 1 percent castor oil.

30

16. The dosage form of claim 15 wherein the hydroxypropylmethylcellulose has a viscosity of about 5000 cps in an aqueous solution containing 2 weight percent hydroxypropylmethylcellulose.

35

17. The dosage form of claim 11 wherein the subcoating is comprised of, based upon the total dry weight of the subcoating,

a) from about 20 percent to about 50 percent hydroxypropylmethylcellulose;

b) from about 45 percent to about 75 percent maltodextrin;

c) from about 1 percent to about 10 percent PEG 400.

40

18. The coated dosage form of claim 11, wherein the coating is comprised of, based upon the total dry weight of the subcoating,

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- a) from about 25 percent to about 40 percent hydroxyethylcellulose;
- b) from about 50 percent to about 70 percent maltodextrin;
- c) from about 5 percent to about 10 percent PEG 400.

5 19. A tablet coated with the film forming composition according to claim 2.

20. The coated dosage form of claim 11, further comprising an effective amount of a pharmaceutical active ingredient, wherein said dosage form meets USP dissolution requirements for immediate release forms of said pharmaceutical active ingredient.

10

21. An aqueous dispersion of the composition of claim 2 for the manufacture of dip-coated tablets.

15

22. The aqueous dispersion of claim 21 comprised of, based upon the total weight of the aqueous dispersion,

- a) from about 10 percent to about 14 percent of hydroxypropylmethylcellulose; and
- b) from about 0.1 percent to about 0.14 percent of xanthan gum.

20

23. The composition of claim 1 which is substantially free of gelatin.

24. Use of the aqueous dispersion of claim 21 for the manufacture of dip coated tablets.

25

25. A pharmaceutical dosage form comprising a core and a coating, said coating substantially covering said core and having a surface gloss of at least 150; wherein said coating comprises the composition of claim 1.

26. The composition of claim 2 further comprising a weight enhancer selected from the group consisting of simethicone, polysorbate 80, and mixtures thereof.

30

27. A simulated capsule-like medicament comprising:

- a. a core having a first end and a second end,
- b. a first coating layer having a first color provided on said first end of said core;
- c. a second coating layer having a second color on said second end of said core, said first color is different from said second color;

35

wherein at least one of said first coating layer and second coating layer comprises the composition of claim 1.

40

28. The medicament of claim 27 wherein at least one of said first coating layer and said second coating layer is comprised of a coating composition, said coating composition comprised of, based upon the total dry weight of the coating composition,

- a) from about 95 percent to less than about 100 percent of hydroxypropylmethyl cellulose; and
- b) from about 0.5 percent to about 5 percent of xanthan gum.

5 29. The medicament of claim 28 further comprising a subcoating layer substantially covering said core, said subcoating layer provided between said core and said first coating layer and said second coating layer.

10 30. The medicament of claim 29 wherein the subcoating comprises materials selected from the group consisting of cellulose ethers, plasticizers, polycarbohydrates, pigments, opacifiers, and mixtures thereof.

31. A water soluble composition for dip-coating a substrate comprised of:

- 15 a) hydroxypropylmethyl cellulose; and
- b) castor oil,

wherein the composition possesses a surface gloss of at least 150 when applied via dip coating to a substrate.

20 32. A pharmaceutical dosage form comprising a core and a coating, said coating substantially covering said core; wherein said coating comprises the composition of claim 31.

33. Use of the composition of claim 31 for the manufacture of dip coated tablets.

25 34. A water soluble composition for dip-coating a substrate comprised of:

- a) hydroxypropylmethyl cellulose; and
- b) maltodextrin,

wherein the composition possesses a surface gloss of at least 150 when applied via dip coating to a substrate.

30 35. The composition of claim 34 further comprising polyethylene glycol.

35 36. A pharmaceutical dosage form comprising a core and a coating, said coating substantially covering said core; wherein said coating comprises the composition of claim 34.

37. Use of the composition of claim 34 for the manufacture of dip coated tablets.

40 38. The water soluble composition of claim 1, wherein the composition is comprised of, based upon the total dry weight of the composition:

a) greater than about 95 percent and less than about 99.5 percent of hydroxypropylmethyl cellulose; and

b) greater than about 0.5 percent and less than about 5 percent of carrageenan, wherein the composition possesses a surface gloss of at least 150 when applied via dip coating to a substrate.

5

39. A pharmaceutical dosage form comprising a core and a coating, said coating substantially covering said core; wherein said coating comprises the composition of claim 38.

10

40. Use of the composition of claim 38 for the manufacture of dip coated tablets.

202140.86622101

ABSTRACT OF THE INVENTION

Water soluble, gelatin-free dip coatings for pharmaceutical solid dosage forms such as tablets comprising HPMC and xanthan gum, carrageenan, and mixtures thereof, or HPMC and castor oil or maltodextrin.

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PTO/SB/01 (10-03)
Approved for use through 10/31/2032, OMB 0581-0032
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DECLARATION AND POWER OF ATTORNEY FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63) ☐ Declaration Submitted with Initial Filing ☒ Declaration Submitted after Initial Filing (Surcharge (37 CFR 1.18(e)) required)	Attorney Docket Number	MCP-303
	First Named Inventor	Cynthia Gulian et al.
	COMPLETE IF KNOWN	
	Application Number	
	Filing Date	12 April 2002
	Group Art Unit	
	Examiner Name	

As a below named inventor, I hereby declare that:

My residence, mailing address, and citizenship are as stated below next to my name.
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

DIP COATING COMPOSITIONS CONTAINING CELLULOSE ETHERS
(Title of the invention)

the specification of which

☐ is attached hereto

OR

☒ is identified by Attorney Docket No. MCP-303, which appeared on the specification as filed on 12 April 2002.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.55, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT International filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT International application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or any PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES NO
			☐ ☐ ☐ ☐	☐ ☐ ☐ ☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

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DECLARATION - Utility or Design Patent Application		
I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.		
Application Number(s)	Filing Date (MM/DD/YYYY)	☐ Additional provisional application numbers are listed on a supplemental priority date sheet PTO/SB/Q28 attached hereto.
60/291,127 60/325,726	15 May 2001 28 September 2001	
I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application.		
Application Serial No.	Filing Date	Status
		Patented Patented Patented
I hereby appoint:		
☒ Practitioners at Customer Number 000027777		Place Customer Number Bar Code Label Here
AND		
☐ Practitioner(s) named below: Name _____ Registration Number _____		
as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.		
Address all telephone calls to Michele G. Mangini at telephone number (732) 524-2810.		
Direct all correspondence to: Customer Number 000027777 OR ☐ Correspondence address below		
Name:		
Address:		
Address:		
City:	State:	ZIP
Country	Telephone:	Fax:

101229 B-041202

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.			
NAME OF SOLE OR FIRST INVENTOR:		☐ A petition has been filed for this unsigned inventor	
Given Name (first and middle (if any)) Cyntha		Family Name or Surname Gulan	
Inventor's Signature		Date	
Residence: City Lansdale	State PA	Country U.S.A.	Citizenship U.S.A.
Mailing Address 117 Crestwood Drive			
City Lansdale	State PA	ZIP 19446	Country U.S.A.
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.			
NAME OF SECOND INVENTOR:		☐ A petition has been filed for this unsigned inventor	
Given Name (first and middle (if any)) Walter G.		Family Name or Surname Gowan, Jr.	
Inventor's Signature		Date	
Residence: City Woodstock	State GA	Country U.S.A.	Citizenship U.S.A.
Mailing Address 808 Lovinggood Trail			
City Woodstock	State GA	ZIP 30186	Country U.S.A.
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.			
NAME OF THIRD INVENTOR:		☐ A petition has been filed for this unsigned inventor	
Given Name (first and middle (if any)) Kishor B.		Family Name or Surname Parekh	
Inventor's Signature		Date	
Residence: City Horsham	State PA	Country U.S.A.	Citizenship U.S.A.
Mailing Address 33 Greenwoods Drive			
City Horsham	State PA	ZIP 19044	Country U.S.A.

10122 99-041202

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.			
NAME OF FOURTH INVENTOR:		☐ A petition has been filed for this unsigned inventor	
Given Name (first and middle (if any)) Joseph M.		Family Name or Surname Morris	
Inventor's Signature		Date	
Residence: City Coatsville	State PA	Country U.S.A.	Citizenship U.S.A.
Mailing Address 180 Lafayette Road			
City Coatsville	State PA	ZIP 19320	Country U.S.A.
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.			
NAME OF FIFTH INVENTOR:		☐ A petition has been filed for this unsigned inventor	
Given Name (first and middle (if any)) Thomas J.		Family Name or Surname Morley	
Inventor's Signature		Date	
Residence: City North Wales	State PA	Country U.S.A.	Citizenship U.S.A.
Mailing Address 111 Green Tree Tavern Road			
City North Wales	State PA	ZIP 19454	Country U.S.A.
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.			
NAME OF SIXTH INVENTOR:		☐ A petition has been filed for this unsigned inventor	
Given Name (first and middle (if any)) Dennis C.		Family Name or Surname Weand	
Inventor's Signature		Date	
Residence: City Coopersburg	State PA	Country U.S.A.	Citizenship U.S.A.
Mailing Address 2850 Possum Hollow Road			
City Coopersburg	State PA	ZIP 18036	Country U.S.A.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.			
NAME OF SEVENTH INVENTOR:		☐ A petition has been filed for this unsigned inventor	
Given Name (first and middle (if any)) Gerard P.		Family Name or Surname McNally	
Inventor's Signature		Date	
Residence: City Berwyn	State PA	Country U.S.A.	Citizenship U.S.A.
Mailing Address 177 Coldstream Drive			
City Berwyn	State PA	ZIP 19312	Country U.S.A.
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.			
NAME OF EIGHTH INVENTOR:		☐ A petition has been filed for this unsigned inventor	
Given Name (first and middle (if any))		Family Name or Surname	
Inventor's Signature		Date	
Residence: City	State	Country	Citizenship
Mailing Address			
City	State	ZIP	Country
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.			
NAME OF NINTH INVENTOR:		☐ A petition has been filed for this unsigned inventor	
Given Name (first and middle (if any))		Family Name or Surname	
Inventor's Signature		Date	
Residence: City	State	Country	Citizenship
Mailing Address			
City	State	ZIP	Country

101229 9.041202

LOS ESTADOS UNIDOS DE AMÉRICA

A todos aquellos a quienes las presentes llegaren:

DEPARTAMENTO DE COMERICO DE LOS ESTADOS UNIDOS

Oficina de Patentes y Marcas de los Estados Unidos

Mayo 13, 2002

**ESTA ES PARA CERTIFICAR QUE ANEXA A LA PRESENTE ESTÁ
UNA COPIA FIEL TOMADA DE LOS ARCHIVOS DE LA OFICINA DE
PATENTES Y MARCAS DE LOS ESTADOS UNIDOS DE LOS
DOCUMENTOS DE LA SOLICITUD DE PATENTE ABAJO IDENTIFICADA
QUE SATISFACE LOS REQUISITOS PARA OTORGAR UNA FECHA DE
PRESENTACIÓN BAJO EL 35 USC 111.**

SOLICITUD NÚMERO: 60/325,726

FECHA DE PRESENTACIÓN: 28 de Septiembre de 2001.

Por autoridad del

COMISIONADO DE PATENTES Y MARCAS

M.K. HAWKINS

Oficial de Certificaciones

HOJA DE PORTADA DE SOLICITUD PROVISIONAL

Esta es una petición para presentar una SOLICITUD PROVISIONAL bajo el CFR 37 1.53 (c).

			EXTRACTO NÚMERO	MCP-282
INVENTOR(ES)SOLICITANTE(S)				
APELLIDO	NOMBRE DE PILA	INICIAL INTERMEDIA	RESIDENCIA (CIUDAD Y,O ESTADO O PAIS EXTRANJERO)	
GULIAN SZYMCZAK	Cynthia Christopher	M. E.	117 Crestwood Drive, Lansdale, PA 19446 79 Colts Gait Road, Mariton, NJ 08053	
TÍTULO DE LA INVENCIÓN (280 letras máximo)				
TABLETAS SUMERGIDAS EN MATERIALES LIBRES DE GELATINA				
DIRECCIÓN DE CORREO				
Dirigir toda la correspondencia a:				
☒ Número de Cliente 00027777				
☐ Firma de Nombre Particular				
PARTES INCLUIDAS DE LA SOLICITUD (verificar todas las que sean pertinentes)				
☒ Especificación	Número de Páginas	18	☐ Hoja de datos de la solicitud	
☒ Reivindicaciones	Número de Reivindicaciones	0	☐ CD(s), Número	
☐ Dibujo(s)	Número de Láminas	0	☒ Otros (especificar)	Certificado de correo Expreso
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☐ Se incluye una orden de cheque o de dinero para cubrir los derechos de presentación Provisional			Importe de derechos de presentación provisional (\$)	\$150.00
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La invención fue hecha por una agencia del Gobierno de los Estados Unidos o bajo un contrato con una agencia del Gobierno de los Estados Unidos.



No



Sí, el nombre de la agencia del Gobierno de los Estados Unidos y el número de contrato con el Gobierno son:

Respetuosamente presentado,

FIRMA: _____

REGISTRO No. 36,806.

NOMBRE ESCRITO EN MÁQUINA

O IMPRESO

Michele G. Mangini

FECHA: Sept. 28 de 2001

TELÉFONO

(732) 524-2810

PRESENTACIÓN DE SOLICITUD PROVISIONAL ÚNICAMENTE

EXTRACTO No. MCP-282

EN LA OFICINA DE MARCAS Y PATENTES DE LOS ESTADOS UNIDOS

Solicitante: Cynthia M. Gulian et al.

Para: TABLETAS SUMERGIDAS EN MATERIALES LIBRES DE GELATINA

Certificado de Correo Expreso

Número de envío por "Correo Expreso" : EL710606195US

Fecha de Depósito: 28 de septiembre de 2001

Por este medio certifico que esta solicitud provisional completa (que incluye 18 páginas de especificación) y una Hoja de Cubierta de Solicitud Provisional de una página, está siendo depositada con el Servicio Postal de los Estados Unidos "Oficina Postal de Correo de Entrega Inmediata al destinatario" servicio bajo 37 CFR 1.10 en la fecha indicada anteriormente y está dirigida al Comisionado de Patentes, Washington, D.C. 20231.

Karen Hall- Morgan

(Nombre escrito a máquina o impreso de la persona que envía por correo el documento o los derechos)

(Firma ilegible)

(Firma de la persona que envía por correo el documento o los derechos)

TABLETAS SUMERGIDAS EN MATERIALES LIBRES DE GELATINA

REFERENCIA RECÍPROCA A SOLICITUD RELACIONADA

Esta solicitud reclama el beneficio de la solicitud estadounidense
5 Número 60/291.127 presentada el 15 de mayo de 2001, la cual es
incorporada aquí en su totalidad por vía de referencia.

CAMPO DE LA INVENCION

Esta invención se relaciona con composiciones novedosas, solubles
10 en agua, libres de gelatina, para cubrir substratos por inmersión, tales como
tabletas y cápsulas, y con métodos para producir tales tabletas y cápsulas.
Esta invención se relaciona adicionalmente con un método para incrementar
la ganancia de peso de una película soluble en agua, libre de gelatina, que
forma recubrimiento sobre una tableta o cápsula recubierta por inmersión.

15

ANTECEDENTES DE LA INVENCION

Durante la mayor parte de este siglo, las cápsulas de gelatina dura
fueron una forma popular de dosificación para drogas de prescripción y
drogas de suministro sobre el mostrador (OTC). La capacidad de combinar
20 mitades de cápsulas que tienen diferentes colores proporcionó a los
fabricantes un medio único de distinguir diferentes productos farmacéuticos.
Muchos pacientes prefirieron cápsulas respecto a las tabletas,
percibiéndolas como más fáciles de ingerir. Esta preferencia del consumidor
impulsó a los fabricantes de productos farmacéuticos a comercializar ciertos

productos en la forma de cápsulas, aún cuando ellos se encontraran también disponibles en forma de tableta.

En general, cápsulas vacías de gelatina dura son manufacturadas
5 utilizando equipo automatizado. Este equipo utiliza filas de clavijas de acero inoxidable, montadas sobre barras o placas, las cuales son sumergidas dentro de una solución de gelatina mantenida a una temperatura y fluidez uniformes. Las clavijas son luego retiradas desde la solución de gelatina, se hacen girar, y luego se insertan dentro de hornos de secamiento, a través de
10 los cuales se forza una fuerte ráfaga de aire filtrado con humedad controlada. Una mitad de cápsula sin acabar es formada de esta manera sobre cada clavija durante el secamiento. Cada mitad de cápsula es luego desmontada, recortada hasta longitud uniforme, llenada y unida a una mitad casante apropiada.

15

Una alternativa para productos de cápsula son "caplets", que son tabletas sólidas, oblongas, que frecuentemente están recubiertas con diferentes polímeros tales como ésteres de celulosa para mejorar su aspecto estético, estabilidad, e ingeribilidad. Típicamente, tales polímeros son
20 aplicados a las tabletas ya sea desde solución en solventes orgánicos, o desde dispersión acuosa mediante rocío. No obstante, tales tabletas recubiertas por rocío carecen de la superficie lustrosa y de la elegancia de las cápsulas de gelatina dura. Adicionalmente, no es comercialmente factible recubrir por rocío una tableta con un recubrimiento de color diferente en
25 cada extremo.

Otra alternativa para productos de cápsula son las "gelcaps", las cuales son formas de dosificación elegantes, lustrosas, preferidas por el consumidor que son preparadas sumergiendo cada mitad de una tableta alargada en dos colores diferentes de solución de gelatina. Véase las
5 patentes estadounidenses Nos.: 4.820.524; 5.538.125; 5.685.589; 5.770.225; 5.198.227; y 5.296.233, las cuales son todas incorporadas aquí por vía de referencia. Una forma de dosificación similar, comercialmente disponible como una "geltab", es preparada sumergiendo cada mitad de una tableta redonda, convexa, dentro de solución de gelatina de colores
10 diferentes, tal como se describe en las Patentes Estadounidenses Nos. 5.228.916; 5.436.026 y 5.679.406, las cuales son todas incorporadas aquí por vía de referencia. Tal como aquí se usa tales "gelcaps" y "geltabs" estarán incluidas dentro del término más amplio, "tabletas".

15 No obstante, el uso de gelatina como un material farmacéutico de recubrimiento presenta ciertas desventajas y limitaciones, las cuales incluyen el potencial para velocidad de disolución disminuida después de almacenamiento prolongado debido a la formación de enlaces transversales de la gelatina, potencial para contaminación microbial de la solución de
20 gelatina durante el procesamiento, y prolongados tiempos de elaboración por razón de exigencias extensivas de secamiento. Adicionalmente, los costos relativos a energía asociados con los recubrimientos de gelatina tienden a ser elevados puesto que el material de gelatina es aplicado típicamente a los substratos a una temperatura elevada de por lo menos aproximadamente
25 40°C, con el fin de mantener fluidez de la gelatina, mientras los substratos

son mantenidos aproximadamente a 50°C con el fin de reducir al mínimo el desarrollo microbial.

Se han hecho diferentes intentos para producir cápsulas de conchas
5 duras sin gelatina. Por ejemplo, la WO 00/18835 expone la combinación de
éteres de almidón o almidón oxidado e hidrocoloides para uso para preparar
envolturas de cápsulas duras mediante procesamiento convencional de
moldeo por inmersión. Véase también la patente estadounidense No.
4.001.211 (cápsulas preparadas mediante recubrimiento por inmersión de
10 clavija con composiciones de éter de metilcelulosa termogelificada). No
obstante, debido a inquietudes de apisonamiento potencial, las cápsulas de
gelatina dura ya no constituyen un sistema preferido de suministro para el
consumidor (sobre el mostrador) de productos farmacéuticos, suplementos
de dieta, u otros productos similares. Adicionalmente, las propiedades de
15 una composición ideal dentro de la cual se han de sumergir clavijas de
acero, luego secarse para formar vainas de cápsulas duras sobre las
mismas no son necesariamente iguales tal como aquellas para sumergir
tabletas para formar un recubrimiento sobre las mismas. Por ejemplo,
propiedades físicas pertinentes tales como viscosidades, ganancia de peso,
20 espesor de película, resistencia a la tracción, elasticidad, y contenido de
humedad diferirán entre composiciones para formación de cápsulas duras y
para recubrir tabletas. Véase, por ejemplo, la Patente Estadounidense No.
1.787.777 (Difieren las condiciones de temperaturas óptimas del sustrato y
de la solución de recubrimiento, los tiempos de permanencia en la solución,
25 y las condiciones de secamiento).

Una desventaja asociada con la inmersión de tabletas o de cápsulas dentro de un sistema de recubrimiento sin gelatina consiste en que los recubrimientos resultantes frecuentemente carecen de resistencia a la tensión adecuada de plasticidad, dureza, y de espesor. Además, la inclusión de plastificantes dentro de tales sistemas de recubrimiento sin gelatina frecuentemente producen tabletas que tienen recubrimientos blandos, pastosos, sin una dureza suficiente para mantener su forma o uniformidad durante el manejo. Además, muchas composiciones sin gelatina no se adhieren al sustrato de la tableta en una cantidad suficiente para cubrir de manera uniforme la tableta después de una sola inmersión. Además, muchas composiciones sin gelatina carecen de las propiedades reológicas suficientes necesarias para mantener dispersión uniforme de color a través de todo el proceso de inmersión y secamiento. Aunque se han hecho intentos para mejorar las propiedades reológicas de estas composiciones mediante, por ejemplo, acción de incrementar su contenido de sólidos, con el fin de aumentar la viscosidad. No obstante, tales composiciones frecuentemente originaron desventajosamente estética indeseable de recubrimiento, tal como rugosidad superficial, lustre disminuido, y espesor de recubrimiento no uniforme.

20

Es deseable encontrar un material de recubrimiento por inmersión, que no solamente produzca una forma de dosificación similar elegante, brillante, de alto lustre, preferida por el consumidor, similar a la de las formas recubiertas con gelatina, pero la cual carezca de las limitaciones de la gelatina, particularmente las observadas anteriormente.

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Es conveniente adicionalmente encontrar tal material de inmersión que produzca una ganancia de peso incrementada del recubrimiento secado por inmersión con el fin de proveer un recubrimiento estéticamente agradable que cubra suficientemente la superficie del sustrato.

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DESCRIPCIÓN DETALLADA DE LA INVENCION

Tal como aquí se usa, el término "cápsulas" se refiere a compartimentos duros de envoltura, que encierran un ingrediente dosificable. El término "Tabletas", tal como aquí se usa, se refiere a formas de dosificación sólidas comprimidas o moldeadas de cualquier tamaño o forma. El término "Capletas", tal como aquí se emplea, se refiere a tabletas sólidas, de forma oblonga. "Gelcaps" se refiere a capletas sólidas que tienen un recubrimiento gelatinoso lustroso y el término "geltabs" se refiere a tabletas sólidas que tienen lados planos, caras opuestas convexas, y un recubrimiento gelatinoso lustroso. "Dureza" tal como aquí se usa en conexión con películas o recubrimientos indica la resistencia de la película/recubrimiento a la deformación por impacto. "Soluble en agua", tal como aquí se usa en conexión con materiales no poliméricos, significará desde escasamente solubles hasta muy solubles, es decir, se requieren no más de 100 partes de agua para disolver 1 parte de soluto no polimérico, soluble en agua. Véase Remington, "The Science and Practice of Pharmacy", páginas 208-209 (2000). "Soluble en agua", tal como aquí se emplea en conexión con materiales poliméricos, significará que el polímero se dilata en agua y puede ser dispersado al nivel molecular para formar una dispersión homogénea o "solución" coloidal.

Dimeticona es un material farmacéutico suficientemente conocido formado por polímeros de siloxano lineales que contienen unidades repetitivas de la fórmula $\{-(CH_2)_2SiO\}_n$ estabilizados con unidades bloqueadoras de extremo de trimetilsiloxi de la fórmula $\{(CH_3)_3SiO-\}$.

- 5 Simeticona es una mezcla de dimeticona y dióxido de silicio. Para las finalidades de esta invención, los dos materiales pueden ser utilizados de manera intercambiable.

- La primera modalidad de esta invención está dirigida a composiciones
- 10 formadoras de película solubles en agua, substancialmente libres de gelatina para tabletas de recubrimiento por inmersión o a la manufactura de cápsulas mediante un proceso de moldeo por inmersión. Una composición comprende, está compuesta de, y/o consiste esencialmente de un formador de película tal como un éter de celulosa, por ejemplo,
- 15 hidroxipropilmetilcelulosa; un espesador, tal como un hidrocoloide, por ejemplo, goma de xantano. En otra modalidad, la composición comprende, está formada por, y/o consiste esencialmente de un formador de película tal como un almidón modificado seleccionado entre almidón de maíz céreo, dextrina de tapioca y sus derivados y mezclas de los mismos; un espesador
- 20 seleccionado entre sucrosa, dextrosa, fructosa, maltodextrina, polidextrosa y derivados y mezclas de los mismos; y un plastificante, por ejemplo, polietilenglicol, propilenglicol, aceites vegetales tales como aceite de castor, glicerina, y sus mezclas. Tal como aquí se usa, la expresión "substancialmente libre de gelatina" significará menos que aproximadamente

1 por ciento, por ejemplo, menos de aproximadamente 0,5 por ciento, de gelatina en la composición.

Cualquier formador de película conocido en la técnica es adecuado para uso en la composición formadora de película de la presente invención. Ejemplos de formadores adecuados de película incluyen, pero no están limitados a estos, polivinil alcohol (PVA), almidón hidroxipropílico, almidón hidroxietílico, pululán, almidón metileílico, almidón carboximetílico, metilcelulosa, hidroxipropilcelulosa (HPC), hidroxietilmetilcelulosa (HEMC), hidroxipropilmetilcelulosa (HPMC), hidroxibutilmetilcelulosa (HBMC), hidroxietilcelulosa (HEEC), hidroxietilhidroxipropilmetilcelulosa (HEMPMC), almidones pregelatinizados y polímeros y derivados y mezclas de los mismos.

Un compuesto de hidroxipropilmetilcelulosa adecuado es "HPMC 2910", el cual es un éter de celulosa que tiene un grado de sustitución de aproximadamente 1,9 y una sustitución molar de hidroxipropilo de 0,23, y que contiene, con base en el peso total del compuesto, desde aproximadamente 29% hasta alrededor de 30% de metoxilo y desde aproximadamente 7% hasta alrededor de 12% de grupos de hidroxilpropilo. El HPMC-2910 se encuentra comercialmente disponible de la Dow Chemical Company bajo el nombre comercial, "Metocel E". El "Metocel E5", que es una calidad de HPMC-2910 adecuado para uso en la presente invención, tienen una viscosidad de aproximadamente 4 a 6 cps (4 a 6 milipascal-segundos) a 20°C en una solución acuosa al 2% según se determina

mediante un viscosímetro Ubbelohde. De manera similar, el "Metocel E6", que es otra calidad de HPMC-2910 adecuado para uso en la presente invención, tiene una viscosidad de aproximadamente 5 a 7 cps (5 a 7 milipascal-segundos) a 20°C en una solución acuosa al 2% según se
5 determina mediante un viscosímetro Ubbelohde. El "Metocel E15", que es otra categoría de HPMC-2910 adecuada para uso en la presente invención, tiene una viscosidad aproximadamente de 15000 cps (15 milipascal-segundos) a 20°C en una solución acuosa al 2%, según se determinó mediante un viscosímetro Ubbelohde. Tal como se utiliza en la presente,
10 "grado de sustitución" significará el número promedio de grupos sustituyentes unidos a un anillo de anhidroglucosa, y "solución molar de hidroxipropilo" significará el número de moles de hidroxipropilo por mol de anhidroglucosa.

15 Tal como aquí se emplea, el término "almidones modificados", incluye almidones que han sido modificados mediante formación de enlaces transversales, modificados químicamente para estabilidad mejorada o modificados físicamente para lograr propiedades mejoradas de solubilidad. Tal como aquí se emplea, "almidones pregelatinizados" o "almidones hechos
20 instantáneos" incluye almidones que han sido modificados mediante formación de enlaces transversales, modificados químicamente para estabilidad mejorada, o modificados físicamente para lograr propiedades mejoradas de solubilidad. Tal como aquí se emplea, "almidones pregelatinizados" o "almidones hechos instantáneos" se refiere a almidones
25 modificados que han sido prehumedecidos, luego secados, para mejorar su

solubilidad en agua fría. Almidones modificados adecuados se encuentran comercialmente disponibles de varios proveedores tales como, por ejemplo, A.E. Staley Manufacturing Company y National Starch & Chemical Company. Un almidón modificado adecuado incluye los almidones derivados de maíz
5 céreo pre-gelatinizado que se encuentran comercialmente disponibles de National Starch & Chemical Company bajo los nombres comerciales, "Purity Gum" y "Filmset", y derivados, copolímeros, y sus mezclas. Tales almidones grasos de maíz contienen típicamente, con base en el peso total del almidón, desde aproximadamente 0 por ciento hasta alrededor de 18 por ciento de
10 amilosa y desde aproximadamente 100 por ciento hasta alrededor de 88 por ciento de amilopectina.

Dextrinas de tapioca adecuadas incluyen las que se encuentran disponibles de National Starch & Chemical Company bajo el nombre
15 comercial "Crystal Gum" o "K-4484", y sus derivados tales como almidón alimenticio modificado derivado de tapioca, que se encuentra disponible de National Starch & Chemical bajo el nombre comercial "Purity Gum 40", y copolímeros y sus mezclas.

20 Cualquier espesador conocido en la técnica es adecuado para uso en la composición formadora de película de la presente invención. Ejemplos de tales espesadores incluyen, pero no están limitados a hidrocoloides tales como alginatos, agar, goma guar, algarroba, carrágeno, tara, goma arábica, tragacanto, pectina, xantano, gelano, maltodextrina, galactomanano,
25 pustulano, laminarín, escleroglucano, goma arábica, inulina, pectina, fuelan,

ramsan, zooglan, metilán, quitina, ciclodextrina, quitosán, y derivados y mezclas de los mismos. Espesadores adicionales adecuados incluyen sucrosa, dextrosa, fructosa, maltodextrina, polidextrosa, y materiales similares, y sus derivados y combinaciones de los mismos.

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Gomas de xantano adecuadas incluyen aquellas disponibles de C.P. Kelco Company bajo el nombre comercial "Keltrol 1000", "Xantrol 180", o "K9B310".

10 Cualquier plastificante conocido en la industria farmacéutica es adecuado para uso en la presente invención, y puede incluir pero sin limitación, polietilenglicol; glicerina; sorbitol, citrato de trietilo; citrato de tributilo; cebacato de dibutilo; aceites vegetales tales como aceite de castor; agentes activos de superficie tales como polisorbato, sulfatos laurílicos de sodio, y sulfosuccinatos dioctílicos de sodio; propilén glicol; monoacetato de
15 glicerol; diacetato de glicerol; triacetato de glicerol; gomas naturales y sus mezclas. En soluciones que contienen un formador de película de éter de celulosa, un plastificante opcional puede estar presente en una cantidad, basada en el peso total de la solución, desde aproximadamente 0 por ciento,
20 hasta alrededor de 40 por ciento.

En una modalidad, la composición formadora de película para substratos de recubrimiento por inmersión contiene, con base al peso total de sólidos secos de la composición, desde aproximadamente 95 por ciento,
25 hasta menos de aproximadamente 100 por ciento, por ejemplo, desde

aproximadamente 95 por ciento hasta alrededor de 99,5 por ciento, de un formador de película tal como un éter de celulosa, por ejemplo, hidroxipropilmetilcelulosa; y desde aproximadamente 0,5 por ciento hasta alrededor de 5 por ciento de un espesador tal como un hidrocoloide, por ejemplo, goma de xantano.

En otra modalidad, la composición formadora de película para sustratos de recubrimiento por inmersión contiene, con base en el peso total de sólidos secos de la composición, desde aproximadamente 40 por ciento hasta alrededor de 60 por ciento, por ejemplo, desde aproximadamente 50 por ciento hasta alrededor de 55 por ciento, de un almidón modificado, por ejemplo, un almidón de maíz céreo, una dextrina de tapioca, y/o mezclas y derivados de las mismas; desde aproximadamente 15 por ciento hasta alrededor de 30 por ciento, por ejemplo, desde alrededor de 20 por ciento hasta cerca de 25 por ciento de un plastificante, por ejemplo, glicerina, polietilén glicol, propilén glicol, aceite de castor, y sus mezclas; y desde aproximadamente 5 por ciento hasta alrededor de 25 por ciento, por ejemplo, desde aproximadamente 10 por ciento hasta alrededor de 20 por ciento, de un espesador, por ejemplo, sucrosa, dextrosa, fructosa, maltodextrina, polidextrosa, y sus mezclas.

Estas composiciones formadoras de película están típicamente en la forma de una dispersión para facilidad de sustratos de recubrimiento por inmersión en las mismas. Tales dispersiones contienen un solvente en una cantidad, basada en el peso total de la composición, que varía

aproximadamente desde 30 por ciento hasta cerca de 97 por ciento, por ejemplo, desde aproximadamente 80 por ciento hasta cerca de 92 por ciento ó desde cerca de 40 por ciento hasta alrededor de 75 por ciento. Ejemplos de solventes adecuados incluyen, pero no están limitados, a agua; alcoholes
5 tales como metanol, etanol, e isopropanol; solventes orgánicos tales como cloruro de metileno, acetona, y solvente similares; y mezclas de los mismos. En una modalidad, el solvente es agua. La dispersión resultante formadora de película posee típicamente un nivel de sólidos de, con base en el peso total de la dispersión formadora de película, desde aproximadamente 3 por
10 ciento hasta alrededor de 70 por ciento, por ejemplo, desde alrededor de 8 por ciento hasta aproximadamente 20 por ciento, o desde alrededor de 25 por ciento hasta alrededor de 60 por ciento.

En una modalidad, la composición formadora de película para
15 substratos de recubrimiento por inmersión contiene, con base en el peso total en húmedo de la composición de dispersión por inmersión, desde alrededor de 5 por ciento hasta cerca de 20 por ciento, por ejemplo, desde aproximadamente 8 por ciento, hasta alrededor de 15 por ciento, o desde cerca de 10 por ciento hasta aproximadamente 14 por ciento de un formador
20 de película tal como hidroxipropilmetilcelulosa, y desde cerca de 0,05 por ciento hasta alrededor de 0,2 por ciento, por ejemplo desde aproximadamente 0,08 por ciento hasta más o menos 0,16 por ciento o desde aproximadamente 0,1 por ciento hasta alrededor de 0,14 por ciento de un espesador tal como goma de xantano.

En otra modalidad, la composición formadora de película para substratos de recubrimiento por inmersión, contiene, con base en el peso total en húmedo de la composición de dispersión por inmersión, desde aproximadamente 20 por ciento hasta alrededor de 35 por ciento, por ejemplo, desde cerca de 25 por ciento hasta alrededor de 30 por ciento, de un formador de película tal como almidón de maíz céreo, dextrina de tapioca, y/o derivados y mezclas de los mismos; desde aproximadamente 5 por ciento hasta alrededor de 20 por ciento, por ejemplo, desde aproximadamente 10 por ciento hasta alrededor de 15 por ciento de un plastificante tal como glicerina, polietilén glicol, propilén glicol, aceite de castor, y sus mezclas; y desde aproximadamente 5 por ciento hasta alrededor de 15 por ciento de un plastificante seleccionado entre sucrosa, fructosa, dextrosa, maltodextrina, polidextrosa, y sus mezclas.

Opcionalmente, la composición para inmersión puede comprender adicionalmente otros ingredientes tales como, basados en el peso total de la solución de inmersión, desde aproximadamente 0 por ciento hasta alrededor de 2 por ciento de preservativos tales como metilparabeno y propilparabeno, desde aproximadamente 0 por ciento hasta alrededor de 14 por ciento de agentes opacificantes tales como dióxido de titanio y/o desde aproximadamente 0 por ciento hasta alrededor de 14 por ciento de colorantes. Véase *Remington's Practice of Pharmacy*, Martin & Cook, 17th ed., pp 1625-30, que se incorpora aquí por vía de referencia.

En la presente invención se puede utilizar cualquier agente colorante adecuado para uso en aplicaciones farmacéuticas y puede incluir, pero no estar limitado, colorantes azo, colorantes de quinoftalona, colorantes de trifenilmetano, colorantes de xanteno, colorantes indigoides, óxidos de hierro, hidróxidos de hierro, dióxido de titanio, colorantes naturales, y sus mezclas. Más específicamente, los colorantes adecuados incluyen pero sin limitación, azul V visible, verde brillante ácido BS, rojo 2G, azorubina, ponceau 4R, amaranto, D&C rojo 33, D+C rojo 22, D+C rojo 26, D+C rojo 28, D+C amarillo 10, FD+C amarillo 5, FD+C amarillo 6, FD+C rojo 3, FD+C rojo 40, FD+C azul 1, FD+C azul 2, FD+C verde 3, negro brillante BN, negro carbón, óxido de hierro negro, óxido de hierro rojo, óxido de hierro amarillo, dióxido de titanio, riboflavina, carotenos, antihocianinas, tumeric, extracto de cochinilla, clorofilina, cantaxantina, caramelo, betanina, y sus mezclas.

En una modalidad, cada extremo de la tableta o cápsula puede ser recubierto con recubrimiento por inmersión de colores diferentes para proveer una apariencia distintiva para productos de especialidad. Véase en la patente estadounidense No. 4.820.524, la cual es incorporada aquí por vía de referencia.

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En una modalidad, la forma de dosificación farmacéutica está formada por a) un núcleo que contiene un ingrediente activo; b) una capa opcional de primer recubrimiento formada por un subrecubrimiento que cubre substancialmente el núcleo; y c) una segunda capa de recubrimiento sobre la superficie de la primera capa de recubrimiento, estando formada la

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segunda capa de recubrimiento por la composición de recubrimiento por inmersión de la presente invención. Tal como aquí se utiliza, la expresión "cubre substancialmente" significará que al menos aproximadamente el 95 por ciento del área superficial del núcleo está cubierta por el subrecubrimiento.

En una modalidad alternativa, un primr ingrediente activo puede estar contenido en la primera capa de recubrimiento, y el núcleo puede contener un segundo ingrediente activo y/o una cantidad adicional del primer ingrediente activo. Todavía, en otra modalidad, el ingrediente activo puede estar contenido en la primera capa de recubrimiento, y el núcleo puede estar substancialmente libre, es decir, menos de aproximadamente 1 por ciento, por ejemplo, menos de aproximadamente 0,1 por ciento, de ingrediente activo.

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El uso de subrecubrimientos es suficientemente conocido en la técnica y es expuesto, por ejemplo, en la Patente Estadounidense No. 3.185.626, la cual se incorpora aquí por vía de referencia. Cualquier composición adecuada para recubrir con película una tableta puede ser utilizada como un subrecubrimiento de acuerdo con la presente invención. Ejemplos de subrecubrimientos adecuados son expuestos en las Patentes Estadounidenses Nos. 4.683.256, 4.543.370, 4.643.894, 4.828.841, 4.725.441, 4.802.924, 5.630.871, y 6.274.162, las cuales son todas incorporadas aquí por vía de referencia. Subrecubrimientos adicionales adecuados incluyen uno o más de los siguientes ingredientes: éteres de

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celulosa tales como hidroxipropilmetil celulosa, hidroxipropilcelulosa, e hidroxietilcelulosa; polícarbohidratos tales como goma de xantano, almidón, y maltodextrina; plastificantes que incluyen, por ejemplo, glicerina, polietilén glicol, propilén glicol, sebacato dibutílico, citrato trietilico, aceites vegetales
5 tales como aceite de castor, agentes activos de superficie tales como polisorbato-80, sulfato laurílico de sodio y sulfosuccinato de dioctil-sodio; polícarbohidratos, pigmentos, y opacificantes.

En una modalidad, el subrecubrimiento puede estar formado por , con
10 base en el peso total del subrecubrimiento, desde aproximadamente 2 por ciento hasta alrededor de 8 por ciento, por ejemplo, desde cerca de 4 por ciento hasta más o menos 6 por ciento de un éter de celulosa soluble en agua, y desde aproximadamente 0,1 hasta alrededor de 1 por ciento, de aceite de castor, según se expone en detalle en la Patente Estadounidense
15 No. 5.658.589, la cual se incorpora aquí por vía de referencia. En otra modalidad, el subrecubrimiento puede estar formado por, sobre la base del peso total del subrecubrimiento, desde aproximadamente 20 por ciento hasta alrededor de 50 por ciento, por ejemplo, desde cerca de 25 por ciento hasta más o menos 40 por ciento de HPMC; desde aproximadamente 45 por
20 ciento hasta alrededor de 75 por ciento, por ejemplo, desde cerca de 50 por ciento hasta más o menos 70 por ciento de maltodextrina; y desde aproximadamente 1 por ciento hasta alrededor de 10 por ciento, por ejemplo, desde cerca de 5 por ciento hasta alrededor de 10 por ciento de PEG 400.

El subrecubrimiento seco típicamente está presente en una cantidad, con relación al peso seco del núcleo, desde aproximadamente 0 por ciento hasta alrededor de 5 por ciento. La capa de recubrimiento secado por inmersión típicamente está presente en una cantidad, con base al peso seco del núcleo y el recubrimiento opcional, desde aproximadamente 1,5 por ciento hasta alrededor de 10 por ciento.

El espesor promedio de la capa de recubrimiento, por inmersión secada típicamente es desde aproximadamente 40 hasta alrededor de 400 micrones. No obstante, un experto en la materia apreciaría con facilidad sin experimentación indebida, que el espesor del recubrimiento por inmersión puede variar con el fin de proveer una forma de dosificación más uniforme, más fácil de ingerir, o para lograr un perfil de disolución deseado. Además, el espesor de los recubrimientos de película obtenidos por inmersión pueden variar en localizaciones diferentes sobre el substrato dependiendo de su forma. Por ejemplo, el espesor del recubrimiento en un borde o esquina de un substrato puede ser tanto como cincuenta por ciento hasta setenta por ciento menos que el espesor del recubrimiento en el centro de una cara principal del substrato. Esta diferencia puede ser reducida al mínimo, por ejemplo, mediante el uso de un subrecubrimiento más grueso, o mediante el uso de composiciones de inmersión que originen incrementos de peso más elevados sobre el substrato.

En modalidades en donde se desea un recubrimiento por inmersión más grueso, hemos encontrado que una cantidad efectiva de un

intensificador de incremento de peso seleccionado entre el grupo formado por simeticona, polisorbato 80 y sus mezclas, puede ser agregada a una composición formadora de película comprendida, compuesta por, y/o que esencialmente consiste en un formador de película y un espesador opcional tal como un hidrocoloide. El intensificador de ganancia de peso es usado en una cantidad suficiente para incrementar la ganancia de peso de la solución de recubrimiento, por ejemplo, al menos por aproximadamente 10%, por lo menos aproximadamente 20%, o por al menos aproximadamente 30% sobre un sustrato al secarse. El incremento de ganancia de peso por ciento es determinado con base en la diferencia entre el peso total del sustrato recubierto con la composición de recubrimiento que incluye el incrementador de ganancia de peso, y el peso total de un sustrato equivalente recubierto, el cual ha sido recubierto bajo condiciones similares de procesamiento con una composición de recubrimiento que no incluye una cantidad efectiva de incrementador de ganancia de peso.

En una modalidad, el formador de película es un éter de celulosa tal como HPMC, y el espesador es un hidrocoloide tal como goma de xantano y el incrementador de ganancia de peso es simeticona.

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Una composición adecuada formadora de película capaz de lograr ganancia incrementada de peso de recubrimiento por inmersión sobre un sustrato puede contener, con base en el peso seco total de la composición formadora de película, desde aproximadamente 40 por ciento hasta alrededor de 99,9 por ciento, por ejemplo, desde aproximadamente 85 por

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ciento hasta alrededor de 99,5 por ciento, o desde aproximadamente 40 por ciento hasta cerca de 60 por ciento de un formador de película; desde aproximadamente 0 por ciento hasta alrededor de 60 por ciento, por ejemplo, desde aproximadamente 0 por ciento hasta más o menos 10 por ciento, o desde cerca de 10 por ciento hasta aproximadamente 25 por ciento de un espesador, y desde cerca de 0,01 por ciento hasta alrededor de 0,25 por ciento, por ejemplo, desde cerca de 0,03 por ciento hasta alrededor de 0,15 por ciento de un intensificador de ganancia de peso. Cuando las características estéticas de la tableta final son de interés particular, se recomienda no utilizar más de aproximadamente 0,25 por ciento de un incrementador de ganancia de peso. Como se indicó anteriormente, la cantidad de espesador adecuada para uso en la composición variará según, por ejemplo, el espesador particular seleccionado y las propiedades deseadas del recubrimiento. Por ejemplo, cuando goma de xantano es el espesador de selección, la cantidad de espesador de goma de xantano puede variar, con base en el peso seco total de la composición formadora de película, desde aproximadamente 0,5 por ciento hasta alrededor de 5 por ciento.

Las composiciones formadoras de película de la presente invención pueden ser preparadas combinando el formador de película, el espesador, y cualesquier ingredientes opcionales tales como plastificantes, preservativos, colorantes, opacificantes, el incrementador de ganancia de peso, u otros ingredientes con el solvente utilizando un mezclador de alto esfuerzo cortante, hasta obtener estado homogéneo bajo condiciones del ambiente.

En modalidades en donde se utiliza un derivado de almidón de maíz céreo como un formador de película, la mezcla puede ser calentada hasta una temperatura de aproximadamente 60°C hasta alrededor de 90°C para obtener dispersión más rápida de los ingredientes. Alternativamente, el
5 formador de película y el espesador pueden ser mezclados previamente como polvos secos, seguido por la adición de la mezcla del polvo resultante al agua e incrementador de ganancia de peso opcional con alta velocidad de mezclado. Con el fin de retirar substancialmente todas las burbujas desde la mezcla resultante, la presión puede ser entonces disminuida hasta
10 aproximadamente 5 pulgadas de Hg al tiempo que se reduce la velocidad de mezclado con el fin de evitar originar un vórtice en ese lugar. Cualesquier otros ingredientes opcionales adicionales pueden ser añadidos entonces al mismo con operación de mezcla constante.

15 Substratos pueden ser sumergidos dentro de tales soluciones de la presente invención utilizando el mismo equipo e intervalo de condiciones de proceso como las utilizadas para la producción de tabletas recubiertas con gelatina, moldeadas por inmersión. Detalles de tal equipo y condiciones de procesamiento son conocidos en la técnica y son expuestos, por ejemplo, en
20 la patente estadounidense No. 4.820.524, la cual se incorpora aquí por vía de referencia. De manera ventajosa, puesto que las soluciones de recubrimiento de la presente invención son fluidas a temperatura ambiente y son menos susceptibles a desarrollo microbial que composiciones de gelatina, el proceso de recubrimiento por inmersión puede tener lugar bajo
25 condiciones ambientales de temperatura y presión.

Las tabletas recubiertas por inmersión con las composiciones de la presente invención pueden contener uno o más agentes activos. El término "agente activo" es usado aquí en un sentido amplio y puede abarcar cualquier material que pueda ser llevado por o atrapado en el sistema. Por ejemplo, el agente activo puede ser un producto farmacéutico, nutracéutico, vitamina, suplemento de dieta, nutriente, hierba, producto alimenticio, producto colorante, nutricional, mineral, de suplemento, o agente favorecedor o agente similar y combinaciones de los mismos.

Los agentes activos útiles en la presente invención pueden ser seleccionados entre las clases de estos en las siguientes categorías terapéuticas: inhibidores sobresalientes; alcaloides; antiácidos; analgésicos; agentes anabólicos; drogas anti-anginales; agentes antialérgicos; agentes de anti-arritmia; antiasmáticos; antibióticos; anticolsterolémicos; anticolvulsivos; anticoagulantes; antidepresivos; preparaciones antidiarréicas; antieméticos; antihistaminas; antihipertensivos; anti-infecciosos; antiinflamatorios; agentes antilípidos; antimánicos; agentes anti-migraña; antinauseantes; antipsicóticos; agentes antiapoplejía; preparaciones antitiroideas; drogas anabólicas; agentes antiobesidad; anti-parasíticos; antipsicóticos; antipiréticos; antiespasmódicos; antitrombóticos; agentes antitumores; antitusivos; agentes antiúlceras; agentes antiuricémicos; agentes ansiolíticos; estimulantes del apetito; supresores del apetito; agentes beta-bloqueadores; broncodilatadores; agentes cardiovasculares, dilatadores cerebrales; agentes quelantes; antagonistas de colecistequinina; agentes quimioterapéuticos; activadores del conocimiento; contraceptivos;

dilatadores coronarios; supresores de la tos; descongestionantes; desodorantes; agentes dermatológicos; agentes para la diabetes; diuréticos; emolientes; enzimas; drogas eritropoyéticas; expectorantes; agentes de fertilidad; fungicidas; agentes gastrointestinales; reguladores del crecimiento; 5 agentes de reemplazo de hormonas; agentes hiperglicémicos; agentes hipoglicémicos; resinas de intercambio iónico; laxantes; tratamientos de migraña; suplementos minerales; mucolíticos; narcóticos; neurolépticos; drogas neuromusculares; antiinflamatorios no esteroides (NSAIDs); aditivos nutricionales; vasodilatadores periféricos; polipéptidos; prostaglandinas; 10 psicotrópicos; inhibidores de la renina; estimulantes respiratorios, sedantes; esteroides; estimulantes; simpatolíticos; preparaciones tiroideas; tranquilizadores; relajantes uterinos; preparaciones vaginales; vasoconstrictores; vasodilatadores; agentes de vértigo; vitaminas; agentes curativos de heridas; y otros.

15

Agentes activos que pueden ser utilizados en la invención incluyen, pero no están limitados a los mismos: acetaminofem; ácido acético; ácido acetilsalicílico, incluyendo sus formas buffer; acrivastina; albuterol y su sulfato; alcohol; fosfatasa alcalina; alantoina; aloe; acetato, carbonato, 20 clorohidrato e hidróxido de aluminio; alprozolam; aminoácidos; ácido aminobenzóico; amoxicilina; ampicilina; amsacrina; amsalog; anetol; ácido ascórbico; aspartame; astemizol; atenolol; azatidina y su maleato; bacitracin; bálsamo del Perú; BCNU (carmustina); dipropionato de beclometasona; benzocaína; ácido benzoico; benzofenonas; peróxido de benzoilo; 25 benzquinamida y su hidrocloreto; betanecol; bioestaño; bisacodil;

subsalicilato de bismuto; acetato de bornilo; bromofeniramina y su maleato; buspirona; cafeína; calamina; carbonato, casinato e hidróxido de cálcio; alcanfor; captopril; cáscara sagrada; aceite de castor; cefaclor; cefadroxilo; cefalexin; centrizina y su hidrocloreto; cetirizina; alcohólico cetílico; cloruro de
5 cetilpiridinio; minerales quelados; cloramfenicol; hidrocloreto de clorociclizina; gluconato de clorhexidina; cloroxilenol; cloropentostatina; clorofeniramina y sus maleatos y tanatos; cloropromazina; resina de colestiramina; bitartrato de colina; proteína estimulante condrogénica; cimetidina; hidrocloreto de cinamedrina; citalopram; ácido cítrico;
10 claritromicina; clemastina y su fumarato; clonidina; clorfibrato; manteca de cacao; aceite de hígado de bacalao; codeína y su fumarato y fosfato; acetato de cortisona; ciprofloxacina HCl; cianocobalamina; hidrocloreto de ciclizina; ciproheptadina; dantron; maleato de dexbromofeniramina; dextrometorfán y sus hidroháluros; diazepam; dibucalína; dicloralfenazona; diclofen y sus sales
15 de metal alcalino; diclofenaco de sodio; digoxina; dihidroergotamina y sus hidrogenatos/mesilatos; diltiazem; dimeticona; dioxibenzona; difenhidramina y su citrato; difenhidramina y su hidrocloreto; divalproex y sus sales de metal alcalino; docusato de calcio, de potasio y de sodio; hidrato de doxiciclina; succinato de doxilamina, dronabinol; efaroxan; enalapril; enoxacina;
20 ergotamina y su tartrato; eritromicina; estropipato; estradiol de etinilo; efedrina; bitartrato de epinefrina; eritropoyetina; eucaliptol; famotidina; fenoprofeno y sus sales metálicas; fumarato, gluconato y sulfato ferroso; fexofenadina; fluoxetina; ácido fólico; fosfenitoína; 5-fluorouracilo (5-FU); fluoxetina; flurbiprofeno; furosemida; gabapentano; gentamicina; gemfibrozil;
25 glipizida; glicerina; estearato de glicerilo; granisetron; griseofulvina; hormona

sulfato de polimicin B; cloruro y nitrato de potasio; prazepam; hidrocloreto de procainamida; procaterol; prometazina y su hidrocloreto; propoxifeno y su hidrocloreto y napsilato; pramiracetin; pramoxina y su sal de hidrocloreto; proclorperazina y su maleato; propanol y su hidrocloreto; prometacina y su hidrocloreto; propanolol; pseudoefedrina y sus sulfatos e hidrocloretos; piridoxina; pirolamina y sus hidrocloretos y tanatos; quinapril; gluconato y sulfato de quinidina; quínestrol; ralitolina; ranitadina; resorcinol; riboflavina; ácido salicílico; escopolamina; aceite de sésamo; aceite de hígado de tiburón; simeticona; bicarbonato, citrato, y fluoruro de sodio; monofluorofosfato de sodio; sucralpato; sulfanetoxazol; sulfasalazina; azufre; sumatriptan y su succinato; tacrina y su hidrocloreto; teofilina; terfenadina; tietilperazina y su maleato; timolol y su maleato; tioperidona; tramadol; trimetrexato; triazolam; tretinoína; hidrocloreto de tetraciclina; tolmetin; tolnaftato; triclosan; trimetoxebenzamida y su hidrocloreto; tripelenamina y su hidrocloreto; hidrocloreto de triplidina; ácido undecilénico; vancomicina; verapamil HCl; fosfato de vidaribina; vitaminas A, B, C, D, B₁, B₂, B₆, B₁₂, E, y K; avellana de bruja; hidrocloreto de xilometazolina; zinc; sulfato de zinc; undecilenato de zinc. Agentes activos pueden incluir adicionalmente, pero no están limitados a ácidos de alimentos; metales e hidróxidos minerales insolubles; carbonatos, óxidos, policarbofilos, y sus sales; adsorbatos de drogas activas sobre una base de trisilicato de magnesio y sobre una base de silicato de magnesio y aluminio, y sus mezclas. Mezclas y sales farmacéuticamente aceptables de estos y de otros compuestos activos pueden ser utilizadas.

Hemos encontrado inesperadamente que los recubrimiento formados sumergiendo substrato dentro de las composiciones de la presente invención poseen propiedades excelentes comparables con las que tienen los recubrimientos de gelatina, por ejemplo, resistencia al resquebrajamiento, dureza, consistencia, uniformidad de color, tersura, y lustre. Además, tabletas recubiertas por inmersión con las composiciones de la presente invención, son superiores a tabletas recubiertas por inmersión con recubrimientos convencionales a base de gelatina en varias maneras importantes. En primer lugar, las tabletas recubiertas por inmersión con las composiciones de la presente invención retienen de manera ventajosa características aceptables de disolución durante la vida en estantería y el período de almacenamiento en condiciones de temperatura y humedad elevadas. Las composiciones a base de éter de celulosa de acuerdo con la presente invención también son ventajosamente más resistentes a desarrollo microbial, lo cual por este medio hizo posible una vida en estantería o vida de uso más prolongada de la solución de inmersión así como también una reducción en costo de manufactura. Además, las dispersiones de inmersión espesadas con azúcar de acuerdo con la presente invención benéficamente emplean un contenido de agua más bajo con relación al de las dispersiones que contienen gelatina, las cuales por este medio hacen posible un tiempo de ciclo de secado más corto. Aunque el contenido de agua de las otras dispersiones de inmersión de la presente invención es más elevado del que típicamente se encuentra en soluciones de inmersión a base de gelatina, las composiciones basadas en éter de celulosa de la presente invención, sorprendentemente requirieron un tiempo más corto de ciclo de secamiento

con relación de aquél para las composiciones que contiene gelatina. Los recubrimientos secos comprendidos de las composiciones de la presente invención, también sorprendentemente y de manera ventajosa contenían menor número de burbujas de aire con relación a la cantidad presente en composiciones de inmersión secas, a base de gelatina. A diferencia del procesamiento con composiciones que contienen gelatina, substratos opcionalmente pueden ser sumergidos en las soluciones de la presente invención a temperatura ambiente, lo cual es económicamente más benéfico. Además, las composiciones de recubrimiento por inmersión de la presente invención poseen un grado más elevado de lustre con relación a recubrimientos similares aplicados por medio de métodos de recubrimiento por rocío conocidos en la técnica. Véase, la Patente Estadounidense No. 6.274.162 (Sistema de formación de imagen para determinaciones de lustre).

15

Hemos encontrado inesperadamente de manera adicional que la adición de una cantidad efectiva de incrementador de ganancia en peso para una composición formadora de película compuesta por formador de película e hidrocoloide no solamente incrementó de manera significativa el peso seco resultante del recubrimiento por inmersión sobre un substrato, sino que también mejoró la uniformidad de color del recubrimiento.

20

La invención aquí expuesta ilustrativamente puede ser practicada de manera adecuada en ausencia de cualquier componente, ingrediente, o etapa que no esté específicamente expuesto en la presente. Varios ejemplos

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se exponen adelante para ilustrar adicionalmente la naturaleza de la invención y la manera de realizarla. No obstante, la invención no debe ser considerada como limitada a los detalles de los mismos.

5 EJEMPLOS

Ejemplo 1). Preparación de dispersiones de subrecubrimiento

Una dispersión acuosa que contiene los ingredientes expuestos en la Tabla A fue preparada combinando todos los ingredientes en un vaso de laboratorio, bajo condiciones ambientales.

10 Tabla A: Composición de subrecubrimiento de dispersión acuosa.

<u>Ingrediente</u>	<u>Parte*</u>
HPMC (2910, 5mPs) de Dow Chemical Company bajo el nombre comercial "Metocel E-5"	20
Aceite de castor	1
Agua	241,5
Solución total de recubrimiento	262,5
Porcentaje de sólidos en la solución de recubrimiento	8%

*expresado en términos de partes en peso a menos que se indique otra cosa.

Dispersiones acuosas adicionales que contienen los ingredientes en la Tabla B fueron similarmente preparadas:

Tabla B: Composiciones de subrecubrimiento de dispersión acuosa

Ingrediente	Ei 1 A**	Ei 1B	Ei 1C	Ei 1D	Ei 1E
HPMC 2910, 5 mPs	20	40	40	28	28
Aceite de castor	1	0	0	0	0
Agua	212,3	566,67	566,67	566,67	566,67
Maltodextrina	0	53	53	67	67
PEG 400	0	7	7	5	5
Hidroxietilcelulosa*	0	0	0	0	0
Solución de recubrimiento total	233,3	666,67	666,67	666,67	666,67
Porcentaje en peso de sólidos en la solución de recubrimiento	9%	15%	15%	15%	15%

* Disponible de Aqualon, bajo el nombre comercial "Natrosol 250L"

**Todos los valores son expresados en términos de partes en peso a menos que se indique otra cosa.

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Dispersiones acuosas adicionales que contienen los ingredientes expuestos en la Tabla C fueron preparados de manera similar:

10

Tabla C: Composiciones de subrecubrimiento de dispersión acuosa

Ingrediente	Ei 1F**	Ei 1G	Ei 1H
Agua	566,67	566,67	690,4
Maltodextrina	71	71	0
Aceite de castor	0	0	0,13
HPMC (1910, 5 mPas)	0	0	32,4
PEG 400	5	5	0
Hidroxietilcelulosa*	24	24	0
Total de solución de recubrimiento	666,67	666,67	722,9
Porcentaje en peso de sólidos en la solución de recubrimiento	15%	15%	4,5%

* Disponible de Aqualon, bajo el nombre comercial "Natrosol 250L"

**Todos los valores son expresados en términos de partes en peso a menos que se indique otra cosa.

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Ejemplo 2). Preparación de tabletas subrecubiertas

Se prepararon tabletas comprimidas de acuerdo con el procedimiento expuesto en el Ejemplo 1 de la Patente Estadounidense No. 5.658.589 ("Patente '589"), la cual fue incorporada aquí por vía de referencia.

10

La dispersión del Ejemplo 1 fue luego aplicada encima de tabletas comprimidas mediante pulverización en conformidad con el procedimiento expuesto en los ejemplos de la patente No. 5.658.589. Como se muestra en la Tabla D que se indica adelante, las tabletas subrecubiertas secas poseían

un promedio de 2 por ciento a 4 por ciento de ganancia de peso con relación al peso de las tabletas libres de subrecubrimiento.

Este proceso fue repetido con tabletas comprimidas adicionales, pero con la sustitución de cada una, dispersión respectiva de subrecubrimiento producida en el Ejemplo 1 A a 1H, para la del Ejemplo 1. La ganancia en peso por ciento de las tabletas subrecubiertas secas se expone adelante en la Tabla D:

10 Tabla D: Ganancia de peso por ciento de tabletas subrecubiertas secas

<u>Ejemplo Número</u>	<u>% Ganancia en peso</u>
1 A	2
1B	2
1C	4
1D	2
1E	4
1F	2
1G	4
1H	4

Ejemplo 3). Preparación de tabletas recubiertas de HPMC

Fueron preparadas las soluciones acuosas de inmersión de HPMC que contenían los ingredientes expuestos en la Tabla E:

Tabla E: Composición de soluciones de inmersión de HPMC

Ingrediente	Ei 3 A * (g)	Ei 3B (g)	Ei 3C (g)	Ei 3D (%)	Ei 3E (%)	Ei 3F (%)
HPMC E5	32,5	0	32,5	10	11	14
Agua	200	200	200	89,89	88,879	85,85
HPMC (2910,15 mPs)	0	20	0		0	0
Goma de xantano	0	0	0	0,11	0,121	0,15
PEG 400	0	0	8	0	0	0
Solución total de inmersión	232,5	220	232,5	100	100	100
Porcentaje en peso de sólidos en la solución de inmersión	14	9	17	10,11	11,121	14,15

*Todos los valores son expresados en términos de peso (g) a menos que se indique otra cosa.

5

Ejemplo 3 A: Preparación de solución de inmersión del Ejemplo 3 A:

Se dispersó HPMC dentro de 200 ml de agua desionizada a una temperatura de 70°C. Después de agregar aproximadamente 1 por ciento en peso de de colorante FD&C azul a la misma, la solución fue mezclada hasta condición

10 homogénea. La solución fue enfriada entonces hasta una temperatura de aproximadamente 22°C.

Ejemplo 3 B: Preparación de solución de inmersión del ejemplo 3B:

Se repitió el procedimiento del Ejemplo 3 A, pero con sustitución de HPMC (2910, 15mPs) para la HPMC E5.

5 **Ejemplo 3C: Preparación de solución de inmersión del Ejemplo de 3C:**

Fue dispersada HPMC dentro de 200 cc de agua desionizada a una temperatura de 70°C. Después de adicionar a la misma PEG 400 la solución fue mezclada hasta condición homogénea. La solución fue enfriada entonces hasta una temperatura de aproximadamente 22°C.

10

Ejemplo 3 D: Preparación de solución de inmersión del Ejemplo 3 D:

HPMC y goma de xantano fueron agregados a agua purificada a una temperatura de 80°C hasta que se dispersó el polvo. Después de descontinuar el calor, la solución fue dividida en dos partes. 4,35 por ciento en peso de una dispersión de color amarillo disponible de Colorcon, Inc. bajo el nombre comercial, "Opatint Yellow DD-2115" fue añadido a la primera parte y mezclado a una baja velocidad hasta dispersarse. 5,8 por ciento de una dispersión de color verde disponible de Colorcon, Inc. bajo el nombre comercial "Opatint Green DD-11000" fue agregada a la segunda parte y
15 mezclada a una baja velocidad hasta dispersarse. Las dos soluciones dispersadas fueron entonces almacenadas bajo condiciones ambiente durante aproximadamente 12 horas.
20

Ejemplo 3 E: Preparación de solución de inmersión del Ejemplo 3 E:

Se repitió el procedimiento del Ejemplo 3D, pero utilizando los componentes del Ejemplo 3E.

- 5 **Ejemplo 3F: Preparación de solución de inmersión del Ejemplo 3F:** Se repitió el procedimiento del Ejemplo 3D, pero utilizando los componentes del Ejemplo 3F.

- 10 **Ejemplo 3G: Preparación de tabletas recubiertas de inmersión de manos-sumergidas:** Las tabletas subrecubiertas preparadas de acuerdo con el Ejemplo 2 utilizando el subrecubrimiento producido en el Ejemplo 1H fueron sumergidas manualmente dentro de las soluciones de inmersión del Ejemplo 3 A durante un tiempo de permanencia de 1 segundo, fueron retiradas desde la solución de inmersión, luego secadas bajo condiciones
15 ambientales.

Este procedimiento fue repetido, pero con sustitución de las soluciones de inmersión de los Ejemplos 3 B y 3C, respectivamente, para la solución de inmersión del Ejemplo 3 A.

20

Una observación de los recubrimientos resultantes mostró lo siguiente:

- 25 **Tabletas recubiertas con recubrimiento del Ej. 3A:** Los recubrimientos eran uniformes, duros, y brillantes, y no tenían burbujas ni grietas. No obstante, los recubrimientos no eran uniformes

y delgados, con áreas planas no bien cubiertas. Por exposición a condiciones ambientales durante un período de seis meses, no se observaron grietas en los recubrimientos.

5 Tabletas recubiertas con recubrimiento del Ej. 3B: El recubrimiento era brillante, con pocas burbujas y ninguna grieta. Los recubrimientos eran más uniformes y ásperos con relación a los del Ejemplo 3 A. Los recubrimientos eran también algo pegajosos y delgados, con áreas planas no bien cubiertas. Por exposición a

10 condiciones ambientales durante un período de seis meses, no se observó ninguna grieta en los recubrimientos.

Tabletas recubiertas con recubrimiento del Ej. 3C: Los recubrimientos eran brillantes con pocas burbujas y sin grietas. Los

15 recubrimientos eran más uniformes y ásperos con relación a los del Ejemplo 3 A. Los recubrimientos eran también algo pegajosos y delgados, con áreas planas no bien cubiertas. Por exposición a condiciones ambientales durante un período de 6 meses, no se observaron grietas en los recubrimientos.

20

Ejemplo 3 H: Preparación de tabletas por inmersión en escala de producción: Tablet

 as adicionales subrecubiertas preparadas de acuerdo con el Ejemplo 2 utilizando el subrecubrimiento producido en el Ejemplo 1 H fueron recubiertas con la solución de inmersión resultante de los Ejemplos

25 3D utilizando una máquina de inmersión en gel de calidad comercial de

acuerdo con el procedimiento descrito en la Patente Estadounidense No. 4.820.524, la cual se incorpora aquí por vía de referencia.

Este procedimiento fue repetido pero con sustitución de las soluciones de inmersión de los Ejemplos 3E y 3F, respectivamente, por la solución de inmersión del Ejemplo 3D.

El porcentaje promedio de ganancia de peso de los recubrimientos secados por inmersión fueron según se expone en la Tabla F:

10

Tabla F: Ganancia de peso de recubrimiento por inmersión seco

<u>Ejemplo</u>	<u>Porcentaje de ganancia en peso de recubrimiento seco*</u>
Ej. 3D	0,75-2,26
Ej. 3E	1,9-3,52
Ej. 3F	3,2-5,8

* Relativa al peso del subrecubrimiento y núcleo secos.

Este ejemplo demostró que la adición de goma de xantano a la solución de inmersión de HPMC proporcionó una mejora de viscosidad al recubrimiento de inmersión, y de esta manera una ganancia de peso incrementado del recubrimiento por inmersión sobre las tabletas.

20

Ejemplo 4). Preparación de almidón pre-gelatinizado que contiene soluciones de recubrimiento por inmersión

Las soluciones de inmersión formadas por los componentes
5 expuestos en la Tabla G fueron preparadas dispersando 75 g del almidón de maíz céreo modificado en 200 ml de agua bajo condiciones ambiente, con operación de mezcla:

Tabla G:Almidón pre-gelatinizado que contiene soluciones de inmersión

<u>Componente/Otro</u>	<u>Ejemplo 4 A*</u>	<u>Ejemplo 4B</u>
Almidón de maíz céreo modificado (Purity® Gum 59)	75	125
Agua	200	200
Peso total de solución	275	325
Porcentaje en peso de sólidos en solución de inmersión	27	39

10 *Todos los valores se expresan en términos de peso (g) a menos que se observe otra cosa

Soluciones de inmersión formadas por los componentes expuestos en
la Tabla H siguiente fueron preparados dispersando todos los componentes
15 en 200 ml de agua bajo condiciones ambiente con operación de mezcla hasta que la solución resultante fue clara.

Tabla H: Almidón pre-gelatinizado que contiene soluciones de inmersión con simeticona del Ejemplo 4 C:

<u>Componente</u>	<u>Nombre comercial</u>	<u>Proveedor</u>	<u>Cantidad utilizada*</u>
Almidón de maíz céreo modificado	Purity ® Gum 59	National Starch & Chemical Co.	125
Simeticona	Antifoam ®		2
Dióxido de silicona coloidal	Aerosil® A200		6
Glicerina	—	—	63,5
Sucrosa	—	—	38
Colorante	Opatint®		6,9
Agua	—	—	200
Sólidos totales			241,4
Solución total (peso/ 55% de sólidos)			441,1

*Todos los valores se expresan en términos de peso (mg) a menos que se indique otra cosa

5

Cada lado de las tabletas subrecubiertas preparadas en conformidad con el Ejemplo 2 utilizando el subrecubrimiento producido en el Ejemplo 1H fueron sumergidas manualmente dentro de la solución de inmersión del Ejemplo 4A durante un tiempo de permanencia de aproximadamente 1 segundo, detenido, luego secado bajo condiciones ambientales.

10

Este procedimiento fue repetido, pero con sustitución de la solución de inmersión del Ejemplo 4B por la solución de inmersión del Ejemplo 4A y aproximadamente con un período de tres días entre la terminación de la producción de la solución de inmersión y la iniciación del proceso de recubrimiento por inmersión.

15

Este procedimiento fue repetido adicionalmente, pero con sustitución de las soluciones de inmersión del Ejemplo 4C por la solución de inmersión del Ejemplo 4A y aproximadamente con un período de 12 horas entre la terminación de la producción de la solución de inmersión y la iniciación del
5 proceso de recubrimiento por inmersión.

Una observación de los recubrimientos resultantes mostró lo siguiente:

Tabletas recubiertas con solución de inmersión del Ej. 4A: Los
10 recubrimientos fueron muy lustrosos, duros, pulidos, uniformes, y no pastosos o agrietados. No obstante, los recubrimientos fueron muy delgados, y las áreas planas no fueron recubiertas. Ningún agrietamiento después de exposición a condiciones ambientales durante un período de seis meses.

15

Tabletas recubiertas con la solución de inmersión del Ej. 4B:
Los recubrimientos fueron pulidos y lustrosos. Inicialmente las áreas planas estaban cubiertas; no obstante, los recubrimientos se agrietaron después de exposición a condiciones ambientales durante
20 un período de seis meses.

25

Tabletas recubiertas con solución de inmersión del Ej. 4C: Los recubrimientos poseían excelente lustre y cobertura, y eran pulidos sin grietas. Ningún agrietamiento después de exposición a condiciones ambientales durante un período de dos meses.

Ejemplo 5) Preparación de almidón pre-gelatinizado, que contiene soluciones de recubrimiento por inmersión

Se repitió el procedimiento expuesto en el Ejemplo 4C, pero sin la inclusión de simeticona. Antes de recubrir el sustrato, la solución es
5 expuesta a una presión de vacío de 5 pulgadas de Hg con el fin de retirar sustancialmente todas las burbujas visibles desde la solución. El recubrimiento resultante posee lustre y cubierta excelentes, y es uniforme y sin grietas.

10 **Ejemplo 6). Efecto de simeticona sobre la ganancia de peso del recubrimiento**

Las siguientes soluciones de recubrimiento por inmersión fueron preparadas para ilustrar el efecto de simeticona como un mejorador de la ganancia de peso. Las cantidades se dan en porcentaje basado en el peso
15 total de la solución de recubrimiento.

Ingrediente	6A	6B	6C	6D	6E
HPMC 2910, 5mPs	12	12	12	12	12
Goma de xantano	1	1	1	1	1
Simeticona	0	0,035	0,07	0,14	0,25
Dispersión de color amarillo***	6	6	6	6	6
Agua	81	80,695	80,93	80,86	80,75

*** Dispersión de color amarillo fue "Opatint®" No. DD2125 obtenido de Colorcon, Inc.

Soluciones de inmersión A a E, anteriores, fueron preparadas en la siguiente manera: Agua purificada fue calentada hasta aproximadamente

35°C. Se añadieron HPMC y goma de xantano mientras se mezclaba utilizando un mezclador eléctrico de escala de laboratorio (Janke and Kunkel, IKA Labortechnik, Staufen, Alemania) con paleta propulsora aproximadamente a 1000 rpm hasta que aparecieron los polvos
5 uniformemente dispersados. Se interrumpió el calentamiento, y la dispersión resultante se dejó reposar durante la noche a temperatura ambiente. Luego se agregaron dispersión de simeticona y color amarillo mezclando aproximadamente a 500 rpm.

10 Núcleos subrecubiertos, preparados de acuerdo con el método del Ejemplo 1A, fueron pesados previamente, luego sumergidos en las soluciones A, B, C, D y E, anteriores, durante un tiempo de permanencia de aproximadamente 2 segundos, levantados, luego secados en condiciones ambiente (aproximadamente 22°C). Los núcleos fueron sumergidos
15 simultáneamente en grupos de 7. Tres grupos separados de siete núcleos fueron sumergidos en cada solución A hasta E. La ganancia de peso promedio fue determinada a partir de los grupos triplicados de núcleos sumergidos desde cada solución de recubrimiento.

20 Las ganancias de peso resultantes fueron como sigue:

Solución de inmersión	6 A	6B	6C	6D	6E
Ganancia en peso promedio del recubrimiento de inmersión (mg/tableta)	13,3	20,8	22,3	23,7	19,1

PA 013311



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

May 13, 2002

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/325,726

FILING DATE: September 28, 2001



**By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS**

M. K. Hawkins

**M. K. HAWKINS
Certifying Officer**

10-01-01

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A/PROV

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53 (c).

DOCKET NUMBER			MCP-282
INVENTOR(s) / APPLICANT(s)			
LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
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TITLE OF THE INVENTION (250 characters max)			
TABLETS DIPPED IN NON-GELATIN MATERIALS			
CORRESPONDENCE ADDRESS			
Direct all correspondence to:			
☒ Customer Number 000027777			
OR			
☐ Firm or Individual Name:			
ENCLOSED APPLICATION PARTS (check all that apply)			
☒ Specification	Number of Pages	18	☐ Application Data Sheet
☒ Claims	Number of Claims	2	☐ CD(s), Number
☐ Drawing(s)	Number of Sheets	0	☒ Other (specify) Express Mail Certificate
METHOD OF PAYMENT (check one)			
☐ A check or money order is enclosed to cover the Provisional filing fees.		Provisional Filing Fee Amount (\$)	\$ 150.00
☒ The Commissioner is hereby authorized to charge filing fees and credit any overpayment to Deposit Account No. 10-0750			

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

SIGNATURE: Michele Mangini

REGISTRATION NO. 38,808

TYPED or PRINTED NAME Michele G. Mangini

DATE: 28 Sept 2001

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PROVISIONAL APPLICATION FILING ONLY

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DOCKET NO. MCP-282

IN THE UNITED STATES
PATENT AND TRADEMARK OFFICE

Applicant: Cynthia M. Gulian et al.

For : TABLETS DIPPED IN NON-GELATIN MATERIALS

Express Mail Certificate

"Express Mail" mailing number: EL710606195US

Date of Deposit: September 28, 2001

I hereby certify that this complete provisional application (including specification 16 pages) and one page Provisional Application Cover Sheet, is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

50325-092801

Karen Hall-Morgan
(Typed or printed name of person mailing paper or fee)

Karen Hall Morgan
(Signature of person mailing paper or fee)

TABLETS DIPPED IN NON-GELATIN MATERIALS

CROSS-REFERENCE TO RELATED APPLICATION

This Application claims the benefit of United States Application Number 60/291,127 filed on 16 May 2001, which is incorporated by reference in its entirety herein.

FIELD OF THE INVENTION

This invention relates to novel, water soluble, gelatin-free compositions for dip coating substrates, such as tablets and capsules, and methods for producing such tablets and capsules. This invention further relates to a method for increasing the weight gain of a water soluble, gelatin-free, film forming coating on a dip-coated tablet or caplet.

BACKGROUND OF THE INVENTION

During most of this century, hard gelatin capsules were a popular dosage form for prescription and over-the-counter (OTC) drugs. The ability to combine capsule halves having different colors provided manufacturers with a unique means of distinguishing various pharmaceutical products. Many patients preferred capsules over tablets, perceiving them as being easier to swallow. This consumer preference prompted pharmaceutical manufacturers to market certain products in capsule form even when they were also available in tablet form.

Generally, empty hard gelatin capsules are manufactured using automated equipment. This equipment employs rows of stainless steel pins, mounted on bars or plates, which are dipped into a gelatin solution maintained at a uniform temperature and fluidity. The pins are then withdrawn from the gelatin solution, rotated, and then inserted into drying kilns through which a strong blast of filtered air with controlled humidity is forced. A crude capsule half is thus formed over each pin during drying. Each capsule half is then stripped, trimmed to uniform length, filled and joined to an appropriate mating half.

An alternative to capsule products are caplets, which are solid, oblong tablets that are often coated with various polymers such as cellulose ethers to improve their aesthetics, stability, and swallowability. Typically, such polymers are applied to the tablets either from solution in organic solvents, or from aqueous dispersion via spraying. However, such spray-coated tablets lack the shiny surface and elegance of the hard gelatin capsules. Additionally, it is not commercially feasible to spray-coat a tablet with a different color coating on each end.

Another alternative to capsule products are "gelcaps," which are elegant, shiny, consumer-preferred dosage forms that are prepared by dipping each half of an elongated tablet in two different colors of gelatin solution. See United States Patent Nos.: 4,620,624; 5,538,125; 5,685,589; 5,770,225; 5,198,227; and 5,296,233, which are all incorporated by reference herein. A similar dosage form, commercially available as a "geltab," is prepared by dipping each half of a round, convex tablet into different colors of gelatin solution, as described in United States Patent

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No. 5,228,918, US5,436,028 and US6,879,408, which are all incorporated by reference herein. As used herein, such "gelcaps" and "getabs" shall be included within the broader term, "tablets."

However, the use of gelatin as a pharmaceutical coating material presents certain disadvantages and limitations, including the potential for decreased dissolution rate after extended storage due to cross-linking of the gelatin, potential for microbial contamination of the gelatin solution during processing, and long processing times due to extensive drying requirements. Further, the energy-related costs associated with gelatin coatings tend to be high since the gelatin material is typically applied to the substrates at an elevated temperature of at least about 40°C in order to maintain fluidity of the gelatin, while the substrates are maintained at about 50°C in order to minimize microbial growth.

Various attempts have been made to produce gelatin-free hard shell capsules. For example, WO 00/18835 discloses the combination of starch ethers or oxidized starch and hydrocolloids for use in preparing hard capsule shells via conventional dip molding processing. See also U.S. Pat. No. 4,001,211 (capsules prepared via pin dip coating with thermogelled methylcellulose ether compositions). However, due to potential tampering concerns, hard gelatin capsules are no longer a preferred delivery system for consumer (over-the-counter) pharmaceuticals, dietary supplements, or other such products. Additionally, the properties of an ideal composition into which steel pins are to be dipped then dried to form hard capsule shells thereon are not necessarily the same as those for dipping tablets to form a coating thereon. For example, relevant physical properties such as viscosity, weight-gain, film thickness, tensile strength, elasticity, and moisture content will differ between compositions for hard capsule formation and for coating tablets. See e.g., U.S. Pat. No. 1,787,777 (Optimal temperatures of the substrate and coating solution, residence times in the solution, and drying conditions differ.)

One disadvantage associated with dipping tablets or capsules into a non-gelatin coating system is that the resulting coatings often lack adequate tensile strength, plasticity, hardness, and thickness. Moreover, the inclusion of plasticizers into such non-gelatin coating systems often results in tablets having soft, tacky coatings without a hardness sufficient to maintain their shape or smoothness during handling. In addition, many non-gelatin compositions do not adhere to the tablet substrate in an amount sufficient to uniformly cover the tablet after a single dipping. Further, many non-gelatin compositions lack the sufficient rheological properties necessary to maintain uniform color dispersion throughout the dipping and drying process. Although attempts have been made to improve the rheological properties of these compositions by, for example, increasing their solids content in order to increase viscosity. However, such compositions often disadvantageously resulted in undesirable coating aesthetics such as surface roughness, decreased gloss, and non-uniform coating thickness.

It is desirable to find a dip coating material, which not only produces a similar elegant, shiny, high gloss, consumer-preferred dosage form similar to that of gelatin-coated forms, but which is absent the limitations of gelatin, particularly those noted above.

It is further desirable to find such a dipping material that produces an increased weight gain of the dried dip coating in order to provide an aesthetically pleasing coating that sufficiently covers the substrate surface.

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DETAILED DESCRIPTION OF THE INVENTION

As used herein, "capsules" refer to hard shell compartments that enclose a doseable ingredient. "Tablets," as used herein, refer to compressed or molded solid dosage forms of any shape or size. "Caplets," as used herein, refer to solid, oblong-shaped tablets. "Gelcaps" refer to solid caplets having a glossy gelatinous coating, and "gellabs" refer to solid tablets having flat sides, convex opposing faces, and a glossy gelatinous coating. "Hardness" as used herein in connection with films or coatings indicates the resistance of the film/coating to deformation upon impact. "Water soluble," as used herein in connection with non-polymeric materials, shall mean from sparingly soluble to very soluble, i.e., not more than 100 parts water required to dissolve 1 part of the non-polymeric, water soluble solute. See Remington, "The Science and Practice of Pharmacy," pages 208 - 209 (2000). "Water soluble," as used herein in connection with polymeric materials, shall mean that the polymer swells in water and can be dispersed at the molecular level to form a homogeneous dispersion or colloidal "solution."

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Dimethicone is a well known pharmaceutical material consisting of linear siloxane polymers containing repeating units of the formula $-(CH_3)_2SiO-$, stabilized with trimethylsiloxy and blocking units of the formula $[(CH_3)_3SiO-]$. Simethicone is the mixture of dimethicone and silicon dioxide. For the purposes of this invention, the two materials may be used interchangeably.

The first embodiment of this invention is directed to water soluble, substantially gelatin-free, film forming compositions for dip coating tablets or manufacturing capsules via a dip molding process. One composition comprises, consists of, and/or consists essentially of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose; and a thickener, such as a hydrocolloid, e.g., xanthan gum. In another embodiment, the composition comprises, consists of, and/or consists essentially of a film former such as a modified starch selected from waxy maize starch, tapioca dextrin, and derivatives and mixtures thereof; a thickener selected from sucrose, dextrose, fructose, maltodextrin, polydextrose, and derivatives and mixtures thereof; and a plasticizer, e.g., polyethylene glycol, propylene glycol, vegetable oils such as castor oil, glycerin, and mixtures thereof. As used herein, "substantially gelatin-free" shall mean less than about 1 percent, e.g. less than about 0.5 percent, of gelatin in the composition.

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Any film former known in the art is suitable for use in film forming composition of the present invention. Examples of suitable film formers include, but are not limited to, polyvinylalcohol (PVA), hydroxypropyl starch, hydroxyethyl starch, pullulan, methylcellulose, carboxymethyl starch, methylcellulose, hydroxypropylcellulose (HPC), hydroxyethylmethylcellulose (HEMC), hydroxypropylmethylcellulose (HPMC), hydroxybutylmethylcellulose (HBMC), hydroxyethylethylcellulose (HEEC), hydroxyethylhydroxypropylmethyl cellulose (HEMPMC), pre-gelatinized starches, and polymers and derivatives and mixtures thereof.

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One suitable hydroxypropylmethylcellulose compound is "HPMC 2910", which is a cellulose ether having a degree of substitution of about 1.9 and a hydroxypropyl molar substitution of 0.23, and containing, based upon the total weight of the compound, from about 29% to about 30% methoxyl and from about 7% to about 12% hydroxypropyl groups. HPMC 2910 is commercially available from the Dow Chemical Company under the tradename, "Methocel E." "Methocel E5," which is one grade of HPMC-2910 suitable for use in the present invention, has a viscosity of about 4 to 6 cps (4 to 6 millipascal-seconds) at 20 °C in a 2% aqueous solution as determined by a Ubbelohde viscometer. Similarly, "Methocel E6," which is another grade of HPMC-2910 suitable for use in the present invention, has a viscosity of about 5 to 7 cps (5 to 7 millipascal-seconds) at 20 °C in a 2% aqueous solution as determined by a Ubbelohde viscometer. "Methocel E15," which is another grade of HPMC-2910 suitable for use in the present invention, has a viscosity of about 15000 cps (15 millipascal-seconds) at 20 °C in a 2% aqueous solution as determined by a Ubbelohde viscometer. As used herein, "degree of substitution" shall mean the average number of substituent groups attached to a anhydroglucose ring, and "hydroxypropyl molar substitution" shall mean the number of moles of hydroxypropyl per mole anhydroglucose.

As used herein, "modified starches" include starches that have been modified by crosslinking, chemically modified for improved stability, or physically modified for improved solubility properties. As used herein, "pre-gelatinized starches" or "instantized starches" refers to modified starches that have been pre-wetted, then dried to enhance their cold-water solubility. Suitable modified starches are commercially available from several suppliers such as, for example, A.E. Staley Manufacturing Company, and National Starch & Chemical Company. One suitable modified starch includes the pre-gelatinized waxy maize derivative starches that are commercially available from National Starch & Chemical Company under the tradenames, "Purify Gum" and "FilmSet", and derivatives, copolymers, and mixtures thereof. Such waxy maize starches typically contain, based upon the total weight of the starch, from about 0 percent to about 18 percent of amylose and from about 100 percent to about 88 percent of amylopectin.

Suitable tapioca dextrins include those available from National Starch & Chemical Company under the tradename, "Crystal Gum" or "K-4484," and derivatives thereof such as modified food starch derived from tapioca, which is available from National Starch and Chemical under the tradename, "Purify Gum 40," and copolymers and mixtures thereof.

Any thickener known in the art is suitable for use in the film forming composition of the present invention. Examples of such thickeners include but are not limited to hydrocolloids such as alginates, agar, guar gum, locust bean, carrageenan, tara, gum arabic, tragacanth, pectin, xanthan, gellan, maltodextrin, galactomannan, pustulan, laminarin, scleroglucan, gum arabic, inulin, pectin, whey, rhaman, zooglan, methyl, chitin, cyclodextrin, chitosan, and derivatives and mixtures thereof. Additional suitable thickeners include sucrose, dextrose, fructose, maltodextrin, polydextrose, and the like, and derivatives and combinations thereof.

Suitable xanthan gums include those available from C.P. Kelco Company under the tradename, "Keltrol 1000," "Kantrol 180," or "K9B310."

Any plasticizer known in the pharmaceutical art is suitable for use in the present invention, and may include, but not be limited to polyethylene glycol; glycerin; sorbitol; triethyl citrate; tributyl citrate; dibutyl sebacate; vegetable oils such as castor oil; surfactants such as polysorbates, sodium lauryl sulfates, and dioctyl-sodium sulfosuccinates; propylene glycol; mono acetate of
 5 glycerol; diacetate of glycerol; triacetate of glycerol; natural gums and mixtures thereof. In solutions containing a cellulose ether film former, an optional plasticizer may be present in an amount, based upon the total weight of the solution, from about 0 percent to about 40 percent.

In one embodiment, the film forming composition for dip coating substrates contains, based upon the total dry solids weight of the composition, from about 95 percent to less than
 10 about 100 percent, e.g. from about 95 percent to about 99.5 percent, of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose; and from about 0.5 percent to about 5 percent of a thickener such as a hydrocolloid, e.g., xanthan gum.

In another embodiment, the film forming composition for dip coating substrates contains, based upon the total dry solids weight of the composition, from about 40 percent to about 80
 15 percent, e.g. from about 50 percent to about 65 percent, of a modified starch, e.g. a waxy maize starch, a tapioca dextrin, and/or mixtures and derivatives thereof; from about 15 percent to about 30 percent, e.g., from about 20 percent to about 25 percent of a plasticizer, e.g., glycerin, polyethylene glycol, propylene glycol, castor oil, and mixtures thereof; and from about 5 percent to about 25 percent, e.g., from about 10 percent to about 20 percent, of a thickener, e.g., sucrose,
 20 dextrose, fructose, maltodextrin, polydextrose, and mixtures thereof.

These film forming compositions are typically in the form of a dispersion for ease of dip coating substrates therein. Such dispersions contain a solvent in an amount, based upon the total weight of the dispersion, from about 30 percent to about 97 percent, for example, from about 80 percent to about 92 percent or from about 40 percent to about 75 percent. Examples of suitable solvents include, but are not limited to water; alcohols such as methanol, ethanol, and isopropanol; organic solvents such as methylene chloride, acetone, and the like; and mixtures thereof. In one
 25 embodiment, the solvent is water. The resulting film forming dispersion typically possesses a solids level of, based upon the total weight of the film forming dispersion, from about 3 percent to about 70 percent, for example, from about 8 percent to about 20 percent or from about 25 percent to about 60 percent.
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In one embodiment, the film forming composition for dip coating substrates contains, based upon the total wet weight of the dipping dispersion composition, from about 5 percent to about 20 percent, e.g. from about 8 percent to about 15 percent or from about 10 percent to about 14 percent, of a film former such as hydroxypropylmethylcellulose and from about 0.05
 35 percent to about 0.2 percent, e.g. from about 0.08 percent to about 0.16 percent or from about 0.1 percent to about 0.14 percent, of a thickener such as xanthan gum.

In another embodiment, the film forming composition for dip coating substrates contains, based upon the total wet weight of the dipping dispersion composition, from about 20 percent to about 35 percent, e.g. from about 25 percent to about 30 percent, of a film former such as waxy
 40 maize starch, tapioca dextrin, and/or derivatives and mixtures thereof; from about 5 percent to

about 20 percent, e.g., from about 10 percent to about 15 percent of a plasticizer such as glycerin, polyethylene glycol, propylene glycol, castor oil, and mixtures thereof; and from about 5 percent to about 15 percent of a plasticizer selected from sucrose, fructose, dextrose, maltodextrin, polydextrose, and mixtures thereof.

5 Optionally, the composition for dipping may further comprise other ingredients such as, based upon the total weight of the dipping solution, from about 0 percent to about 2 percent preservatives such as methylparaben and propylparaben, from about 0 percent to about 14 percent opacifying agents such as titanium dioxide, and/or from about 0 percent to about 14 percent colorants. See *Remington's Practice of Pharmacy*, Martin & Cook, 17th ed., pp. 1625 - 30, 10 which is herein incorporated by reference.

Any coloring agent suitable for use in pharmaceutical applications may be used in the present invention and may include, but not be limited to azo dyes, quinophthalone dyes, triphenylmethane dyes, xanthene dyes, indigoid dyes, iron oxides, iron hydroxides, titanium dioxide, natural dyes, and mixtures thereof. More specifically, suitable colorants include, but are 15 not limited to patent blue V, acid brilliant green BS, red 2G, azorubine, ponceau 4R, amaranth, D&C red 33, D+C red 22, D+C red 28, D+C red 28, D+C yellow 10, FD+C yellow 5, FD+C yellow 6, FD+C red 3, FD+C red 40, FD+C blue 1, FD+C blue 2, FD+C green 3, brilliant black BN, carbon black, iron oxide black, iron oxide red, iron oxide yellow, titanium dioxide, riboflavin, carotenes, antihocyanines, turmeric, cochineal extract, chlorophyllin, canthaxanthin, caramel, betanin, and 20 mixtures thereof.

In one embodiment, each end of the tablet or capsule may be coated with dip coatings of different colors to provide a distinctive appearance for specialty products. See United States Patent No. 4,820,524, which is incorporated by reference herein.

25 In one embodiment, the pharmaceutical dosage form is comprised of a) a core containing an active ingredient; b) an optional first coating layer comprised of a subcoating that substantially covers the core; and c) a second coating layer on the surface of the first coating layer, the second coating layer comprised of the dip coating composition of the present invention. As used herein, "substantially covers" shall mean at least about 95 percent of the surface area of the core is covered by the subcoating.

30 In an alternate embodiment, a first active ingredient may be contained in the first coating layer, and the core may contain a second active ingredient and/or an additional amount of the first active ingredient. In yet another embodiment, the active ingredient may be contained in the first coating layer, and the core may be substantially free, i.e., less than about 1 percent, e.g. less than about 0.1 percent, of active ingredient.

35 The use of subcoatings is well known in the art and disclosed in, for example, United States Patent Nos. 3,185,826, which is incorporated by reference herein. Any composition suitable for film-coating a tablet may be used as a subcoating according to the present invention. Examples of suitable subcoatings are disclosed in United States Patent Nos. 4,683,266, 4,543,370, 4,643,894, 4,828,841, 4,725,441, 4,802,924, 5,830,871, and 6,274,162, which are all 40 incorporated by reference herein. Additional suitable subcoatings include one or more of the

following ingredients: cellulose ethers such as hydroxypropylmethylcellulose, hydroxypropylcellulose, and hydroxyethylcellulose; polycarbohydrates such as xanthan gum, starch, and maltodextrin; plasticizers including for example, glycerin, polyethylene glycol, propylene glycol, dibutyl sebacate, triethyl citrate, vegetable oils such as castor oil, surfactants such as polysorbate-80, sodium lauryl sulfate and dioctyl-sodium sulfosuccinate; polycarbohydrates, pigments, and opacifiers.

In one embodiment, the subcoating may be comprised of, based upon the total weight of the subcoating, from about 2 percent to about 8 percent, e.g. from about 4 percent to about 6 percent of a water-soluble cellulose ether and from about 0.1 percent to about 1 percent, castor oil, as disclosed in detail in United States Patent No. 5,858, 589, which is incorporated by reference herein. In another embodiment, the subcoating may be comprised of, based upon the total weight of the subcoating, from about 20 percent to about 50 percent, e.g., from about 25 percent to about 40 percent of HPMC; from about 48 percent to about 75 percent, e.g., from about 50 percent to about 70 percent of maltodextrin; and from about 1 percent to about 10 percent, e.g., from about 5 percent to about 10 percent of PEG 400.

The dried subcoating typically is present in an amount, based upon the dry weight of the core, from about 0 percent to about 5 percent. The dried dip coating layer typically is present in an amount, based upon the dry weight of the core and the optional subcoating, from about 1.5 percent to about 10 percent.

The average thickness of the dried dip coating layer typically is from about 40 to about 400 microns. However, one skilled in the art would readily appreciate without undue experimentation that the dip coating thickness may be varied in order to provide a smoother, easier to swallow, dosage form or to achieve a desired dissolution profile. Moreover, the thickness of dipped film coatings may vary at different locations on the substrate depending upon its shape. For example, the thickness of the coating at an edge or corner of a substrate may be as much as 50 percent to 70 percent less than the thickness of the coating at the center of a major face of the substrate. This difference can be minimized by, for example, use of a thicker subcoating, or use of dipping compositions that result in higher weight gains on the substrate.

In embodiments wherein a thicker dip coating is desired, we have found that an effective amount of a weight gain enhancer selected from the group consisting of simethicone, polysorbate 80 and mixtures thereof, may be added to a film forming composition comprised, consisting of, and/or consisting essentially of a film former and an optional thickener such as a hydrocolloid. The weight gain enhancer is used in an amount sufficient to increase the weight gain of the coating solution, e.g. by at least about 10 percent, by at least about 20%, or by at least about 30 % on a substrate when dried. The percent weight gain increase is determined based upon the difference between the total weight of the coated substrate with the coating composition including the weight gain enhancer, and the total weight of an coated equivalent substrate, which has been coated under similar processing conditions with a coating composition that does not include an effective amount of weight gain enhancer.

In one embodiment, the film former is a cellulose ether such as HPMC, and the thickener is a hydrocolloid such as xanthan gum and the weight gain enhancer is simethicone.

A suitable film forming composition capable of achieving increased weight gain of dip coating on a substrate may contain, based upon the total dry weight of the film forming composition, from about 40 percent to about 99.9 percent, e.g. from about 85 percent to about 99.5 percent, or from about 40 percent to about 60 percent of a film former; from about 0 percent to about 60 percent, e.g. from about 0 percent to about 10 percent or from about 10 percent to about 25 percent of a thickener; and from about 0.01 percent to about 0.25 percent, e.g. from about 0.03 percent to about 0.15 percent of a weight gain enhancer. When aesthetics of the final tablet are of particular concern, it is recommended to not use greater than about 0.25 percent of a weight gain enhancer. As shown above, the amount of thickener suitable for use in the composition will vary depending upon, for example, the particular thickener selected and the desired properties of the coating. For example, when xanthan gum is the thickener of choice, the amount of xanthan gum thickener may range, based upon the total dry weight of the film forming composition, from about 0.5 percent to about 5 percent.

The film forming compositions of the present invention may be prepared by combining the film former, the thickener, and any optional ingredients such as plasticizers, preservatives, colorants, opacifiers, the weight gain enhancer, or other ingredients with the solvent using a high shear mixer until homogeneous under ambient conditions. In embodiments wherein a waxy maize starch derivative is used as a film former, the mixture may be heated to a temperature of about 60 °C to about 90 °C for faster dispersion of the ingredients. Alternatively, the film former and thickener may be preblended as dry powders, followed by addition of the resulting powder blend to the water and optional weight gain enhancer with high speed mixing. In order to remove substantially all of the bubbles from the resulting mixture, the pressure may then be decreased to about 5 inches Hg while reducing the mixing speed in order to avoid creating a vortex therein. Any other additional optional ingredients may then be added thereto at constant mixing.

Substrates may be dipped into such solutions of the present invention using the same equipment and range of process conditions as used for the production of dip molded, gelatin-coated tablets. Details of such equipment and processing conditions are well-known in the art and are disclosed at, for example, United States Patent No. 4,820,524, which is incorporated by reference herein. Advantageously, because the coating solutions of the present invention are fluid at room temperature and are less susceptible to microbial growth than gelatin compositions, the dip coating process may occur under ambient temperature and pressure conditions.

The tablets dip coated with the composition of the present invention may contain one or more active agents. The term "active agent" is used herein in a broad sense and may encompass any material that can be carried by or entrained in the system. For example, the active agent can be a pharmaceutical, nutraceutical, vitamin, dietary supplement, nutrient, herb, foodstuff, dyestuff, nutritional, mineral, supplement, or favoring agent or the like and combinations thereof.

The active agents useful herein can be selected from classes from those in the following therapeutic categories: ace-inhibitors; alkaloids; antacids; analgesics; anabolic agents; anti-anginal

drugs; anti-allergy agents; anti-arrhythmia agents; antiepileptics; antibiotics; anticholesterolemics; anticonvulsants; anticoagulants; antidepressants; antidiarrheal preparations; anti-emetics; antihistamines; antihypertensives; anti-infectives; anti-inflammatories; antilipid agents; antimanics; anti-migraine agents; antinauseants; antipsychotics; antistroke agents; antithyroid preparations; anabolic drugs; antitubercular agents; antiparasitics; antipsychotics; antipyretics; antispasmodics; antithrombotics; antitumor agents; antitussives; antulcer agents; anti-uricemic agents; arthralgic agents; appetite stimulants; appetite suppressants; beta-blocking agents; bronchodilators; cardiovascular agents; cerebral dilators; chelating agents; cholecystalkin antagonists; chemotherapeutic agents; cognition activators; contraceptives; coronary dilators; cough suppressants; decongestants; deodorants; dermatological agents; diabetes agents; diuretics; emollients; enzymes; erythropoietic drugs; expectorants; fertility agents; fungicides; gastrointestinal agents; growth regulators; hormone replacement agents; hyperglycemic agents; hypoglycemic agents; ion-exchange resins; laxatives; migraine treatments; mineral supplements; mucolytics; narcotics; neuroleptics; neuromuscular drugs; non-steroidal anti-inflammatories (NSAIDs); nutritional additives; peripheral vasodilators; polypeptides; prostaglandins; psychotropics; renin inhibitors; respiratory stimulants; sedatives; steroids; stimulants; sympatholytics; thyroid preparations; tranquilizers; uterine relaxants; vaginal preparations; vasoconstrictors; vasodilators; vertigo agents; vitamins; wound healing agents; and others.

Active agents that may be used in the invention include, but are not limited to:

acetaminophen; acetic acid; acetylsalicylic acid, including its buffered forms; acrivastine; albuterol and its sulfate; alcohol; alkaline phosphatase; allantoin; aloe; aluminum acetate, carbonate, chloride and hydroxide; alprostadil; amino acids; aminobenzoic acid; amoxicillin; ampicillin; amesacrine; amesalog; anethole; ascorbic acid; aspartame; astemizole; atenolol; azatidine and its maleate; bacitracin; balsam peru; BCNU (carmustine); beclomethasone dipropionate; benzocaine; benzoic acid; benzophenones; benzoyl peroxide; benzquinamide and its hydrochloride; bethanechol; biotin; blebistatin; blinatumomab; bismuth subsalicylate; bornyl acetate; brompheniramine and its maleate; buspirone; caffeine; calamine; calcium carbonate, caseinate and hydroxide; camphor; captopril; cascara sagrada; castor oil; cefaclor; cefadroxil; cephalosporins; cetirizine and its hydrochloride; cetirizine; cetyl alcohol; cetylpyridinium chloride; chelated minerals; chloramphenicol; chlorcyclizine hydrochloride; chlorhexidine gluconate; chloroxylenol; chloropentoxifylline; chlorpheniramine and its maleates and tartrates; chlorpromazine; cholestyramine resin; choline bitartrate; chondrogenic stimulating protein; cimetidine; cinnamidine hydrochloride; citalopram; citric acid; clarithromycin; clemastine and its fumarate; clonidine; cloribate; cocoa butter; cod liver oil; codeine and its fumarate and phosphate; cortisone acetate; ciprofloxacin HCl; cyanocobalamin; cyclizine hydrochloride; cyproheptadine; dantrolene; dexbrompheniramine maleate; dextromethorphan and its hydrohalides; diazepam; dibucaine; dichloralphenazone; diclofenac and its alkali metal salts; diclofenac sodium; digoxin; dihydroergotamine and its hydrogenates/mesylates; diltiazem; dimethicone; dioxibenzene; diphenhydramine and its citrate; diphenhydramine and its hydrochloride; divalproex and its alkali metal salts; docosate calcium, potassium, and sodium; doxycycline hydrate; doxylamine succinate;

5 drosabinol; efavirenz; enalapril; enoxacin; ergotamine and its tartrate; erythromycin; estropipate;
ethinyl estradiol; ephedrine; epinephrine bitartrate; erythropoietin; eucalyptol; famotidine;
fenoprofen and its metal salts; ferrous fumarate, gluconate and sulfate; fexofenadine; fluoxetine;
folic acid; fosphenytoin; 5-fluorouracil (5-FU); fluoxetine; flurbiprofen; furosemide; gabapentin;
10 gentamicin; gemfibrozil; glipizide; glycerine; glyceryl stearate; granisetron; griseofulvin; growth
hormone; guaifenesin; hexylresorcinol; hydrochlorothiazide; hydrocodone and its tartrate;
hydrocortisone and its acetate; 8-hydroxyquinoline sulfate; hydroxyzine and its pamoate and
hydrochloride salts; ibuprofen; indomethacin; inositol; insulin; iodine; ipecac; iron; isosorbide and
its mono- and dinitrates; isodexam; ketamine; kaolin; ketoprofen; lactic acid; lanolin; lecithin;
15 leuprolide acetate; lidocaine and its hydrochloride salt; lisinopril; liothric; loperamide; loratadine;
lovastatin; luteinizing hormone; LHRH (luteinizing hormone replacement hormone); magnesium
carbonate, hydroxide, salicylate, and trisilicate; meclizine; mefenamic acid; meclofenamic acid;
meclofenamate sodium; medroxyprogesterone acetate; methenamine mandelate; menthol;
meprobamate hydrochloride; metaproterenol sulfate; methacopolamine and its nitrates; methaergide
and its maleate; methyl nicotinate; methyl salicylate; methyl cellulose; methazolidine;
20 metoclopramide and its halides/hydrates; metronidazole; metoprolol tartrate; miconazole nitrate;
mineral oil; minoxidil; morphine; naproxen and its alkali metal sodium salts; nifedipine; neomycin
sulfate; niacin; niacinamide; nicotine; nicotinamide; nimesulide; nitroglycerine; nonoxonyl-9;
norethindrone and its acetate; nystatin; octoxynol; octoxynol-9; octyl dimethyl PABA; octyl
methoxycinnamate; omega-3 polyunsaturated fatty acids; omeprazole; ondaneestron and its
hydrochloride; oxolinic acid; oxybenzone; oxtriphylline; para-aminobenzoic acid (PABA); padimate-
O; paramethadione; pentastatin; peppermint oil; pentaerythritol tetranitrate; pentobarbital sodium;
perphenazine; phenazine sulfate; phenindamine and its tartrate; pheniramine maleate;
phenobarbital; phenol; phenolphthalein; phenylephrine and its tannates and hydrochlorides;
25 phenylpropanolamine; phenytoin; plimeno; piroxicam and its salts; polymixin B sulfate; potassium
chloride and nitrate; prazepam; procainamide hydrochloride; procaterol; promethazine and its
hydrochloride; propoxyphene and its hydrochloride and napsylate; pramiracetin; pramoxine and its
hydrochloride salt; prochlorperazine and its maleate; propanolol and its hydrochloride;
promethazine and its hydrochloride; propanolol; pseudoephedrine and its sulfates and
hydrochlorides; pyridoxine; pyrolamine and its hydrochlorides and tannates; quinapril; quinidine
gluconate and sulfate; quinine; ranitidine; resorcinol; riboflavin; salicylic acid;
30 scopolamine; sesame oil; shark liver oil; simethicone; sodium bicarbonate, citrate, and fluoride;
sodium monofluorophosphate; sucralose; sulfanethoxazole; sulfasalazine; sulfur; sumatriptan and
its succinate; tacrine and its hydrochloride; theophylline; terfenadine; thiothipiperazine and its
maleate; timolol and its maleate; thioperidone; tramadol; trimetazone; triazolam; tretinoin;
35 tetracycline hydrochloride; tolmetin; tolnaftate; triclosan; trimethobenzamide and its hydrochloride;
tripelennamine and its hydrochloride; triprolidine hydrochloride; undecylenic acid; vancomycin;
verapamil HCl; vidarabine phosphate; vitamins A, B, C, D, B₁, B₂, B₆, B₁₂, E, and K; witch hazel;
xylometazoline hydrochloride; zinc; zinc sulfate; zinc undecylenate. Active agents may further
40 include, but are not limited to food acids; insoluble metal and mineral hydroxides, carbonates,

oxides, polycarbophils, and salts thereof; adsorbates of active drugs on a magnesium trisilicate base and on a magnesium aluminum silicate base, and mixtures thereof. Mixtures and pharmaceutically acceptable salts of these and other actives can be used.

We have unexpectedly found that the coatings formed by dipping substrates into the compositions of the present invention possess excellent properties comparable to those possessed by gelatin coatings, e.g. crack resistance, hardness, thickness, color uniformity, smoothness, and gloss. Additionally, tablets dip coated with the compositions of the present invention are superior to tablets dip coated with conventional gelatin-based coatings in several important ways. First, tablets dip coated with the compositions of the present invention advantageously retain acceptable dissolution characteristics for the desired shelf-life and storage period at elevated temperature and humidity conditions. The cellulose-ether based compositions according to the present invention are also advantageously more resistant to microbial growth, which thereby enables a longer shelf-life or use-life of the dipping solution as well as a reduction in manufacturing cost. In addition, the sugar-thickened dipping dispersions according to the present invention beneficially employ a lower water content relative to that of gelatin-containing dispersions, which thereby enables a shorter drying cycle time. Although the water content of the dipping dispersions of the present invention is higher than that typically found in gelatin-based dipping solutions, the cellulose-ether based compositions of the present invention surprisingly required a shorter drying cycle time relative to that for gelatin-containing compositions. The dried coatings comprised of the compositions of the present invention also surprisingly and advantageously contained fewer air bubbles relative to the amount present in dried, gelatin based dipping compositions. Unlike processing with gelatin-containing compositions, substrates may optionally be dipped in the solutions of the present invention at room temperature, which is economically more beneficial. In addition, the dip coated compositions of the present invention possess a higher degree of glossiness relative to similar coatings applied via spray coating method known in the art. See United States Patent No. 6,274,162 (imaging system for gloss measurements).

We have further unexpectedly found that the addition of an effective amount of weight gain enhancer to a film forming composition comprised of film former and hydrocolloid not only significantly increased the resulting dry weight of the dip coating on a substrate, but it also improved the color uniformity of the coating.

The invention illustratively disclosed herein suitably may be practiced in the absence of any component, ingredient, or step which is not specifically disclosed herein. Several examples are set forth below to further illustrate the nature of the invention and the manner of carrying it out. However, the invention should not be considered as being limited to the details thereof.

EXAMPLES

Example 1.) Preparation of Subcoating Dispersions

An aqueous dispersion containing the ingredients set forth in Table A was prepared by combining all of the ingredients in a beaker under ambient conditions.

Table A: Aqueous Dispersion Subcoating Composition

Ingredient	Part*
HPMC (2910, 5 mPa) from Dow Chemical Company under the tradename, "Methocel E-5"	20
Castor oil	1
Water	241.5
Total Coating Solution	262.5
% solids in coating solution	8%

* expressed in terms of part by weight unless otherwise noted

Additional aqueous dispersions containing the ingredients in Table B were similarly prepared:

Table B: Aqueous Dispersion Subcoating Compositions

Ingredient	Ex 1A**	Ex 1B	Ex 1C	Ex 1D	Ex 1E
HPMC 2910, 5 mPa	20	40	40	28	28
Castor oil	1	0	0	0	0
water	212.3	568.67	568.67	568.67	668.67
maltodextrin	0	53	53	67	67
PEG 400	0	7	7	5	5
Hydroxy-ethylcellulose*	0	0	0	0	0
Total coating solution	233.3	668.67	668.67	668.67	668.67
Wt % solids in coating solution	9%	15%	15	15	15

* Available from Aquelon, under the tradename, "Natrezol 250L"

** all values expressed in terms of parts by weight unless otherwise noted

Additional aqueous dispersions containing the ingredients in Table C were similarly prepared:

Table C: Aqueous Dispersion Subcoating Compositions

Ingredient	Ex 1F**	Ex 1G	Ex 1H
water	568.67	568.67	690.4
maltodextrin	71	71	0
Castor oil	0	0	0.13
HPMC (1910, 5mPas)	0	0	32.4
PEG 400	5	5	0

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Hydroxy-ethylcellulose*	24	24	0
Total coating solution	888.87	888.87	722.9
Wt % solids in coating solution	15%	15%	4.5%

* Available from Aqualon, under the tradename, "Natrosol 250L."

** all values expressed in terms of parts by weight unless otherwise noted

Example 2.) Preparation of Subcoated Tablets

Compressed tablets were prepared in accordance with the procedure set forth in Example 1 of United States Patent No. 5,858,589 ("589 Patent"), which was incorporated by reference herein.

The dispersion of Example 1 was then applied onto the compressed tablets via spraying in accordance with the procedure set forth in the examples of the '589 Patent. As shown in Table D below, the dried subcoated tablets possessed an average 2% to 4% weight gain relative to the weight of the subcoating-free tablets.

This process was repeated with additional compressed tablets, but with the substitution of each, respective subcoating dispersion produced in Example 1A to 1H for that of Example 1. The percentage weight gain of the dried subcoated tablets are set forth below in Table D:

Table D: % Weight Gain of Dried Subcoated Tablets

Example Number	% Weight Gain
1A	2
1B	2
1C	4
1D	2
1E	4
1F	2
1G	4
1H	4

Example 3) Preparation of HPMC Coated Tablets

Aqueous HPMC dipping solutions containing the ingredients set forth in Table E were prepared:

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Table E: Composition of HPMC Dipping Solutions

Ingredient	Ex 3A (g)	Ex 3B (g)	Ex 3C (g)	Ex 3D (%)	Ex 3E (%)	Ex 3F (%)
HPMC E5	32.5	0	32.5	10	11	14
Water	200	200	200	89.89	88.879	85.85
HPMC (2910, 15mPa)	0	20	0		0	0
Xanthan gum	0	0	0	0.11	0.121	0.15
PEG 400	0	0	8	0	0	0
Total dipping solution	232.5	220	232.5	100	100	100
% (wt.) solids in dipping solution	14	9	17	10.11	11.121	14.15

* all values expressed in terms of weight (g) unless otherwise noted

5 **Example 3A: Preparation Of Dipping Solution of Example 3A:** HPMC was dispersed into 200 ml of deionized water at a temperature of 70 °C. After adding about 1 wt % FD&C blue dye thereto, the solution was mixed until homogeneous. The solution was then cooled to a temperature of about 22 °C.

10 **Example 3B: Preparation of Dipping Solution of Example 3B:** The procedure of Example 3A was repeated, but with substitution of HPMC (2910, 15mPa) for the HPMC E5.

15 **Example 3C: Preparation Of Dipping Solution of Example 3C:** HPMC was dispersed into 200 ml of deionized water at a temperature of 70 °C. After adding the PEG 400 thereto, the solution was mixed until homogeneous. The solution was then cooled to a temperature of about 22 °C.

20 **Example 3D: Preparation Of Dipping Solution of Example 3D:** HPMC and xanthan gum were added to purified water at a temperature of 80 °C until the powder was dispersed. After discontinuing the heat, the solution was divided into two parts. 4.35 wt. % of a yellow color dispersion available from Colorcon, Inc. under the tradename, "Opatint Yellow DD-2115" was added to the first part and mixed at a low speed until dispersed. 5.6% of a green color dispersion available from Colorcon, Inc. under the tradename, "Opatint Green DD-11000" was added to the second part and mixed at a low speed until dispersed. The two dispersed solutions were then stored under ambient conditions for about 12 hours.

Example 3E: Preparation Of Dipping Solution of Example 3E: The procedure of Example 3D was repeated, but using the components of Example 3E.

Example 3F: Preparation Of Dipping Solution of Example 3F: The procedure of Example 3D was repeated, but using the components of Example 3F.

Example 3G: Preparation of Hand-Dipped Dip Coated Tablets: The subcoated tablets prepared in accordance with Example 2 using the subcoating produced in Example 1H were hand-dipped into the dipping solutions of Example 3A for a dwell time of 1 second, removed from the dipping solution, then dried under ambient conditions.

This procedure was repeated, but with substitution of the dipping solutions of Examples 3B and 3C, respectively, for the dipping solution of Example 3A.

An observation of the resulting coatings showed the following:

Tablets Coated with Coating of Ex. 3A: The coatings were smooth, hard, and shiny, and had no bubbles or cracking. However, the coatings were non-uniform and thin, with land areas not well-covered. Upon exposure to ambient conditions for a six month period, no cracks were seen in the coatings.

Tablets Coated with Coating of Ex. 3B: The coating were shiny, with few bubbles and no cracking. The coatings were more uniform and rough relative to those of Example 3A. The coatings were also somewhat tacky and thin, with land areas not well-covered. Upon exposure to ambient conditions for a six month period, no cracks were seen in the coatings.

Tablets Coated with Coating of Ex. 3C: The coatings were shiny with few bubbles and no cracking. The coatings were more uniform and rough relative to those of Example 3A. The coatings were also somewhat tacky and thin, with land areas not well-covered. Upon exposure to ambient conditions for a six month period, no cracks were seen in the coatings.

Example 3H: Preparation of Production Scale Dipped Tablets: Additional subcoated tablets prepared in accordance with Example 2 using the subcoating produced in Example 1H were coated with the resulting dipping solution of Examples 3D using a commercial grade gel-dipping machine in accordance with the procedure described in United States Patent No. 4,820,624, which is incorporated by reference herein.

This procedure was repeated, but with substitution of the dipping solutions of Examples 3E and 3F, respectively, for the dipping solution of Example 3D.

The average percentage weight gain of the dried dipped coatings were as set forth in Table F:

Table F: Weight Gain of Dried Dip Coating

<u>Example</u>	<u>% Wt. Gain of Dried Coating*</u>
Ex. 3D	0.75 - 2.28
Ex. 3E	1.9 - 3.52
Ex. 3F	3.2 - 5.8

* Relative to weight of dried subcoating and core

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This example showed that the addition of xanthan gum to the HPMC dipping solution provided a viscosity enhancement to the dip coating, and thus an increased weight gain of the dip coating on the tablets.

Example 4) Pre-gelatinized Starch-Containing Dip Coating Solutions

Dipping solutions comprised of the components set forth in Table G were prepared by dispersing 75 g of the modified waxy maize starch into 200 ml of water under ambient conditions with mixing:

Table G: Pre-gelatinized starch-containing Dipping solutions

<u>Component/Other</u>	<u>Example 4A*</u>	<u>Example 4B</u>
Modified waxy maize starch (Purify® Gum 50)	75	125
water	200	200
Total weight of solution	275	325
Wt % solids in dipping solution	27	39

* all values expressed in terms of weight (g) unless otherwise noted

Dipping solutions comprised of the components set forth in Table H below were prepared by dispersing all of the components into 200 ml of water under ambient conditions with mixing until the resulting solution was clear.

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Table H: Pre-gelatinized starch-containing Dipping solutions With Simethicone of Example 4C

Component	Trade name	Supplier	Amount used *
Modified waxy maize starch	Purity ® Gum 59	National Starch & Chemical Co.	125
Simethicone	Antifoam®		2
Colloidal silicone dioxide	Aerosil ® A200		6
Glycerin	—	—	63.5
Sucrose	—	—	38
colorant	Opalint®		6.9
water	—	—	200
Total solids			241.4
TOTAL solution (w/ 55% solids)			441.1

* all values expressed in terms of weight (mg) unless otherwise noted

Each side of the subcoated tablets prepared in accordance with Example 2 using the subcoating produced in Example 1H were hand-dipped into the dipping solution of Example 4A for a dwell time of about 1 second, pulled up, then dried under ambient conditions.

This procedure was repeated, but with substitution of the dipping solution of Example 4B for the dipping solution of Example 4A and with about a 3 day period between the completion of production of the dipping solution and the commencement of dip coating process.

This procedure was further repeated, but with substitution of the dipping solutions of Example 4C for the dipping solution of Example 4A and with about a 12 hour period between the completion of production of the dipping solution and the commencement of dip coating process.

An observation of the resulting coatings showed the following:

Tablets Coated With Dipping Solution of Ex. 4A: The coatings were very shiny, hard, smooth, even, and not tacky or cracked. However, the coatings were too thin, and land areas were not covered. No cracking after exposure to ambient conditions for a period of 6 months.

Tablets Coated With Dipping Solution of Ex. 4B: The coatings were smooth and shiny. Initially the land areas were covered; however, the coatings cracked after exposure to ambient conditions for a period of 6 months.

Tablets Coated With Dipping Solution of Ex. 4C: The coatings possessed excellent shine and cover, and were smooth with no cracks. No cracking after exposure to ambient conditions for a period of 2 months.

Example 5) Preparation of Pre-Gelatinized Starch-Containing Dip Coating Solutions

The procedure set forth in Example 4C is repeated, but without the inclusion of simethicone. Prior to coating the substrate, the solution is exposed to a vacuum pressure of 5 inches Hg in order to remove substantially all of the visible bubbles from the solution. The resulting coating possesses excellent shine and cover, and is smooth with no cracks.

Example 6) Effect of Simethicone on Coating Weight Gain

The following dip coating solutions were prepared to illustrate the effect of simethicone as a weight gain enhancer. Amounts are percent based on the total weight of coating solution.

Ingredient	8A	8B	8C	8D	8E
HPMC 2910, 5mPa	12	12	12	12	12
Xanthan Gum	1	1	1	1	1
Simethicone	0	0.035	0.07	0.14	0.25
Yellow color dispersion***	8	8	8	8	8
Water	81	80.965	80.93	80.88	80.75

*** Yellow color dispersion was "Opasint"® No. DD2125 obtained from Colorcon, Inc.

Dipping solutions A through E, above, were prepared in the following manner. Purified water was heated to about 35°C. HPMC and xanthan gum were added while mixing using a laboratory scale electric mixer (Jenke and Kunkel, IKA Labora-technik, Staufen, Germany) with propeller blade at approximately 1000 rpm until the powders appeared uniformly dispersed. Heating was discontinued, and the resulting dispersion was allowed to stand overnight at room temperature. Simethicone and yellow color dispersion were then added with mixing at approximately 500 rpm.

Subcoated cores, prepared according to the method of example 1A, were pre-weighed, then dipped in solutions A, B, C, D, and E, above for a dwell time of about 2 seconds, pulled up, then dried at ambient conditions (about 22°C). The cores were dipped simultaneously in sets of 7.

Three separate sets of seven cores were dipped in each solution A through E. The average weight gain was determined from the triplicate sets of dipped cores from each coating solution.

Resulting weight gains were as follows:

Dipping Solution	8A	8B	8C	8D	8E
Average weight gain from dip coat (mg/tablet)	13.3	20.8	22.3	23.7	19.1

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**ESTADOS UNIDOS DE AMERICA
A TODOS AQUELLOS A QUIENES EL PRESENTE LLEGUE:**

**DEPARTAMENTO DE COMERCIO DE LOS ESTADOS
UNIDOS
Oficina de Patentes y Marcas de los Estados Unidos**

Mayo 13, 2002

La presente es para certificar que el anexo es una copia fiel de los registros de la Oficina de Patentes y Marcas de los Estados Unidos, de los documentos de la solicitud de patente identificada más adelante, que cumplieron con los requerimientos para concederse una fecha de presentación de acuerdo con 35 USC 111.

Número de Solicitud: 60/291,127

Fecha de Presentación: Mayo 15, 2001

**Por la autoridad del
Comisionado de Patentes y Marca**

**(fdo) M.K HAWKINS
Oficial Certificador
Sello oficial de la Oficina de Patentes y Marcas de los
Estados Unidos de América**

HOJA DE PORTADA DE SOLICITUD PROVISIONAL

Esta es una petición para presentar una SOLICITUD PROVISIONAL bajo el CFR 37 1.53 (c).

			EXTRACTO NÚMERO	MCP-0278
INVENTOR(ES)/SOLICITANTE(S)				
APELLIDO	NOMBRE DE PILA	INICIAL INTERMEDIA	RESIDENCIA (CIUDAD Y/O ESTADO O PAIS EXTRANJERO)	
Gulian	Cynthia	M.	117 Crestwood Dr., Lansdale, PA 19446	
TÍTULO DE LA INVENCION (280 letras máximo)				
TABLETAS SUMERGIDAS EN MATERIALES LIBRES DE GELATINA				
DIRECCIÓN DE CORREO				
Dirigir toda la correspondencia a:				
☒ Número de Cliente 00027777				
☐ O ☐ Firma de Nombre Particular				
PARTES INCLUIDAS DE LA SOLICITUD (verificar todas las que sean pertinentes)				
☐ Especificación	Número de Páginas	22	☐ Hoja de datos de la solicitud	
☐ Revindicaciones	Número de Reindicaciones	-	☐ CD(s), Número	
☐ Dibujo(s)	Número de Láminas	-	☐ Otros (especificar)	
MÉTODO DE PAGO (marcar uno)				
☐	Se incluye una orden de cheque o de dinero Para cubrir los derechos de presentación Provisional		Importe de derechos de presentación provisional (\$)	\$150.00
☒	El comisionado está autorizado por este medio a cargar los derechos de presentación y acreditar cualquier pago en exceso a la Cuenta de Depósito No. 10-0750			

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La invención fue hecha por una agencia del Gobierno de los Estados Unidos o bajo un contrato con una agencia del Gobierno de los Estados Unidos.



No



Sí, el nombre de la agencia del Gobierno de los Estados Unidos y el número de contrato con el Gobierno son:

Respetuosamente presentado,

FIRMA: _____

REGISTRO No. 35,231.

NOMBRE ESCRITO EN MÁQUINA

O IMPRESO

Sharon H. Hegedus

FECHA: 5/15/01

TELÉFONO

(732) 524-2242

PRESENTACIÓN DE SOLICITUD PROVISIONAL ÚNICAMENTE

EXTRACTO No. MCP-0278

EN LA OFICINA DE MARCAS Y PATENTES DE LOS ESTADOS UNIDOS

Solicitante: Cynthia M. Gulian.

Para: Tabletillas Sumergidas En Materiales Libres De Gelatina

Certificado de Correo Expreso

Número de envío por "Correo Expreso" : EL457887408US

Fecha de Depósito: 15 de mayo de 2001

Por este medio certifico que esta solicitud Provisional completa, que incluye páginas de especificación, está siendo depositada con el Servicio Postal de los Estados Unidos "Oficina Postal de Correo de Entrega Inmediata al destinatario" servicio bajo 37 CFR 1.10 en la fecha indicada anteriormente y está dirigida al Comisionado de Patentes, Washington, D.C. 20231.

Martin Rizzi

(Nombre escrito a máquina o impreso de la persona que envía por correo el documento o los derechos)

(Firma ilegible)

(Firma de la persona que envía por correo el documento o los derechos)

TABLETAS SUMERGIDAS EN MATERIALES LIBRES DE GELATINA

Una forma de dosificación similar a cápsula elegante, lustrosa, preferida por el consumidor, comercialmente disponible como una "gelcap" se prepara sumergiendo cada mitad de una tableta alargada en dos colores diferentes de solución de gelatina según se describe en las patentes US 4.820.524, US5.538.125, US5.685.589, US5.770.225, US5.198.227 y US5.296.233. Una forma de dosificación similar, comercialmente disponible como una "geltab", es preparada sumergiendo cada mitad de una tableta redonda, convexa dentro de solución de gelatina de colores diferentes, según se describe en las patentes Estadounidenses US5.228.916, US5.436.026 y US5.679.406.

Antes del desarrollo de la tecnología de inmersión, las tabletas eran generalmente recubiertas con diferentes polímeros para mejorar su aspecto estético, estabilidad, y facilidad de ingestión. Los polímeros eran aplicados ya sea desde solución en solventes orgánicos, o desde una dispersión acuosa por rocío. Las tabletas recubiertas mediante este método carecían de superficie lustrosa y de elegancia de la gelcap y la geltab. Adicionalmente, no es posible recubrir por rocío una tableta con un recubrimiento de color diferente sobre cada extremo.

El uso de gelatina como un material de recubrimiento farmacéutico presenta ciertas desventajas y limitaciones, que incluyen el potencial para velocidad de disolución disminuida después de almacenamiento prolongado

debido a la formación de enlaces transversales (que originan insolubilización) de la gelatina, potencial para contaminación microbiana, y tiempos de procesamiento prolongados debido a exigencias de secamiento amplio. Adicionalmente, inquietud reciente con respecto a encefalitis
5 espongiforme bovina (BSE, "enfermedad de las vacas locas") determina que la gelatina sea menos conveniente para uso en productos farmacéuticos.

En conveniente encontrar un material para inmersión que produzca una forma de dosificación semejante a cápsula, que sea elegante, lustrosa,
10 preferida por el consumidor, pero en la cual estén ausentes las limitaciones inherentes a la gelatina, particularmente aquellas señaladas anteriormente.

Se hicieron tabletas recubiertas utilizando los siguientes tipos de materiales en el hundidor de núcleos en escala de laboratorio solo o en
15 combinación de uno con otro, así como también con espesadores, plastificantes, y agentes antifomadores de espuma:

1. Polímeros Altos en Sólidos – Eudragit, Surerelease, Aquacoat
2. Celulósicos – HPMC, HEC, CMC
- 20 3. Almidones Alimenticios Modificados – Goma de Pureza 59
4. Polímeros de glucosa – Maltodextrinas
5. Misceláneos – Opadry II, PVP K29/32.

Véase la Tabla 1 para detalles completos de las formulaciones,
25 resultados de inmersión, y observaciones.

La Tabla 1 contiene también alguna información sobre estabilidad limitada para los núcleos sumergidos. Los dos mejores sistemas fueron inicialmente 14% HMPC E5 y Goma de Pureza 59/Sucrosa/Glicerina.

5 Desde este amplio sistema de examen, se hizo experimentación adicional con HPMC E5 puesto que este era el mejor candidato para reemplazo de la gelatina. Las ventajas de usar HPMC mejor que gelatina consistieron en que este podría ser:

- 10 1. Sumergido a RT, disminuyendo así los defectos de burbujeo;
2. Hecho y desaireado con facilidad;
3. Ventajoso para uso en la planta por razón del potencial para menos problemas relacionados con la máquina asociados con humedad y calor provenientes de cubetas de inmersión, y más
- 15 4. bajo consumo de energía;
4. No tan susceptible a contaminación microbial;
5. Se seca rápido hasta un recubrimiento cristalino, duro, no pegajoso;
6. Sumergido en núcleos subrecubiertos o no recubiertos
- 20 7. reducidos;
7. Estable a 40°C/75% RH y 50°C;
8. Funciona sin ningún control de temperatura o de viscosidad en las cubetas de inmersión.

La desventaja principal de la HPMC E5 consistía en costos de materia prima más elevados después de la gelatina. La goma de xantano (XG) era utilizada en combinación con HPMC E5 para disminuir la cantidad de HPMC E5 requerida en el recubrimiento y para mejorar la apariencia del recubrimiento.

Dos grupos de ensayos utilizando el material de HPMC E5 fueron conducidos en equipo de goteo. En los primeros ensayos, se utilizaron tres tipos de núcleos subrecubiertos con dos tipos de material de inmersión HPMC E5/XG. Los núcleos fueron sumergidos a temperatura ambiente con muy pocos defectos de burbujas y funcionaron bien en la máquina. La cuestión con todos los núcleos sumergidos radicó en excesivamente escasa ganancia de peso (5-15 mg) y una apariencia muy delgada.

En el siguiente grupo de ensayos, se hicieron materiales de inmersión de HPMC E5/XG a más elevado porcentaje de sólidos que en los primeros ensayo para incrementar la ganancia de peso del material de inmersión sobre los núcleos y para mejorar la apariencia estética del producto. Se evaluaron muchos tipos de núcleos subrecubiertos, incluyendo un control, algunos sistemas poliméricos diferentes a niveles reducidos de subrecubrimiento, núcleos recubiertos con cera y núcleos de subrecubrimiento reducido sometidos a la acción de tambor giratorio para un método de semi-inmersión y núcleos no recubiertos. Las ganancias de peso de núcleo sumergido para los materiales de inmersión de 800 cps variaron entre 12-22 mg, en tanto que aquellas del material de 1500 cps variaron

entre 20-36 mg. Las lecturas de viscosidad en la planta fueron entre 100-200 cps más bajas que en el laboratorio. Los núcleos sumergidos tenían muchas burbujas grandes debido a desaireación incompleta del material de inmersión a la iniciación de los ensayos. Los recubrimientos a partir del material de inmersión de 800 cps fueron lustrosos pero delgados, en tanto que el material de inmersión de 1500 cps originó recubrimientos gruesos no uniformes.

La disolución de los núcleos recubiertos con HPMC E5/XG fue en general más rápida que la de los núcleos sumergidos en gelatina. La formulación fue hecha óptima en el laboratorio hasta 12% HPMC E5/0,13% XG hasta ganancia de peso de equilibrio, costo de material de inmersión, y aspecto estético aceptable.

Se hizo experimentación adicional con el sistema de HPMC E5/XG para evaluar los defectos de sustituir parcialmente el HPMC E5 con otros materiales, tales como polímeros, maltodextrinas, y almidones en un intento para reducir los costos de materia prima y mejorar la apariencia del producto (véase Tabla 4). Un sistema adecuado de recubrimiento por inmersión de combinación de HPMC E5 no fue identificado debido a fraccionamiento térmico y a falta de uniformidad, no obstante que gran parte de este aprendizaje fue utilizada para modificar el subrecubrimiento para reducir el nivel de subrecubrimiento y los costos de materia prima.

La Tabla 16 muestra una lista de algunos sistemas de subrecubrimiento alternativo para recubrimientos exteriores de HPMC/Goma de Xantano. En la Tabla 16, todos los núcleos fueron humedecidos con el sistema E5/XG excepto en donde se indicó (véase la clave en la parte superior de la primera página). La fecha de disolución (a RT) y los comentarios son para los núcleos sumergidos. Se intentaron muchos sistemas diferentes de recubrimiento para llenar el área de tierra. Polímeros, rellenos y plastificadores fueron como sigue:

- 10
1.

Polímeros: HPMC E5, E15, E50, K3, Natrosol 250L, PVP K29/32.
2.

Rellenos: Maltodextrinas, Almidones.
3.

Plastificantes: PEGs, CO, Tween 80.

15 Los mejores sistemas en términos de apariencia, disolución, potencial de CIP y funcionalidad de recubrimiento fueron:

1.

Nivel de 2% de subrecubrimiento, HPMC E5/CO, 9% de sólidos.
- 20

2.

Niveles de 2-4% de subrecubrimiento, 40% HPMC E5/53% Maltrin 040/7% PEG 400, 15% de sólidos.

3.

Niveles de 2-4% de subrecubrimiento, 24% de Natrosol 250L/71% Maltrin 180/5% PEG 400, 15% de sólidos.

4.

Niveles de 2-4% de subrecubrimiento, 28% HPMC E50/67% Maltrin 180/ 5% PEG 400, 15% de sólidos.
- 25



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME;

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

May 13, 2002

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/291,127

FILING DATE: May 15, 2001

**By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS**



M. K. Hawkins

**M. K. HAWKINS
Certifying Officer**

05-16-01

APPROV

287

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53 (c).

DOCKET NUMBER			MCP-0278
INVENTOR(S) / APPLICANT(S)			
LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE
Gillian	Cynthia	M.	117 Crestwood Dr., Lansdale, PA 19446
TITLE OF THE INVENTION (200 characters max)			
Tablets Dipped in Non-Gelatin Materials			
CORRESPONDENCE ADDRESS			
Direct all correspondence to:			
☒ Customer Number 000027777			
OR			
☐ Firm of Individual Name:			
ENCLOSED APPLICATION PARTS (check all that apply)			
☐ Specification	Number of Pages	22	☐ Application Data Sheet
☐ Claims	Number of Claims	—	☐ CD(s), Number
☐ Drawing(s)	Number of Sheets	—	☐ Other (specify)
METHOD OF PAYMENT (check one)			
☐ A check or money order is enclosed to cover the Provisional filing fees.		Provisional Filing Fee Amount (\$)	\$ 180.00
☒ The Commissioner is hereby authorized to charge filing fees and credit any overpayment to Deposit Account No. 10-0750			

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

SIGNATURE:

REGISTRATION NO. 35231

TYPED or PRINTED NAME

Sharon H. Hegadus

DATE: 5/15/01

TELEPHONE (732) 524-2242

PROVISIONAL APPLICATION FILING ONLY

288

DOCKET NO. MCP-0278

IN THE UNITED STATES
PATENT AND TRADEMARK OFFICE

Applicant: Cynthia Gulian

For : Tablets Dipped in Non-Gelatin Materials

Express Mail Certificate

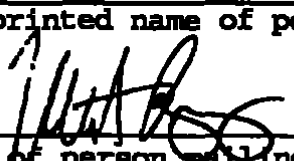
"Express Mail" mailing number: EL457887408US

Date of Deposit: May 15, 2001

I hereby certify that this complete Provisional application, including specification pages, is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

Martin Rizzi

(Typed or printed name of person mailing paper or fee)


(Signature of person mailing paper or fee)

502 1127-051501

TABLETS DIPPED IN NON-GELATIN MATERIALS

An elegant, shiny, consumer-preferred, capsule-like dosage form, commercially available as a "gelcap" is prepared by dipping each half of an elongated tablet in two different colors of gelatin solution, as described in US4,820,524, US5,538,125, US5,685,589, US5,770,225, US5,198,227 and US5,296,233. A similar dosage form, commercially available as a "geltab," is prepared by dipping each half of a round, convex tablet into different colors of gelatin solution, as described in US5,228,916, US5,436,026 and US5,679,406.

Prior to the development of dipping technology, tablets were generally coated with various polymers to improve their aesthetics, stability, and swallowability. The polymers were applied either from solution in organic solvents, or from aqueous dispersion by spraying. Tablets coated by this method lack the shiny surface and elegance of the gelcap and geltab. Additionally, it is not possible to spray-coat a tablet with a different color coating on each end.

The use of gelatin as a pharmaceutical coating material presents certain disadvantages and limitations, including the potential for decreased dissolution rate after extended storage due to cross-linking (resulting in insolubilization) of the gelatin, potential for microbial contamination, and long processing times due to extensive drying requirements. Additionally, recent concern regarding bovine spongiform encephalitis (BSE, "mad cow disease") makes gelatin less desirable for use in pharmaceuticals.

It is desirable to find a material for dipping, which produces a similar elegant, shiny, consumer-preferred, capsule-like dosage form, but which is absent the limitations of gelatin, particularly those noted above.

Coated tablets were made using the following types of materials on the lab scale core dipper alone or in combination with each other, as well as with thickeners, plasticizers, and antifoamers:

1. High Solids Polymers – Eudragit, Suretlease, Aquacoat
2. Cellulosics – HPMC, HEC, CMC
3. Modified Food Starches – Purity Gum 59
4. Glucose Polymers – Maltodextrins
5. Miscellaneous – Opadry II, PVP K29/32

MCP-0278

See Table 1 for full details of the formulations, dipping results, and observations. Table 1 also contains some limited stability information for the dipped cores. The best two systems initially were 14% HPMC E5 and Purity Gum 59/Sucrose/Glycerin.

From this vast screen, further experimentation was done with HPMC E5 since it was the best candidate for gelatin replacement. The advantages to using HPMC over gelatin were that it could be:

1. Dipped at RT, thus decreasing the bubble defects;
2. Made and de-aerated readily;
3. Advantageous for use in the plant because of the potential for less machine-related problems associated with moisture and heat from the dip pans, and lower energy consumption;
4. Not as susceptible to microbial contamination;
5. Dried fast into a hard, non-tacky, glassy coating;
6. Dipped onto reduced subcoated or uncoated cores;
7. Stable at 40° C/75% RH and 50° C;
8. Run with no temperature or viscosity control in the dip pans.

The main disadvantage HPMC E5 was higher raw material costs than gelatin. Xanthan gum (XG) was used in combination with HPMC E5 to decrease the amount of HPMC E5 required in the coat and to improve the coat appearance.

Two sets of trials using the HPMC E5 material were run on plant scale dripping equipment. In the first trials, three types of subcoated cores were used with two types of HPMC E5/XG dip material. The cores were dipped room temperature with very few bubble defects and ran well on the machine. The issue with all of the dipped cores was too little weight gain (5-15mg) and a very thin appearance.

In the next set of trials, HPMC E5/XG dip materials were made at higher percent solids than the first trials to increase the dip material weight gain on the cores and improve product aesthetics. Many subcoated core types were evaluated, including a control, a few different polymer systems at reduced subcoat levels, wax coated and tumbled reduced subcoat cores for a half-dipped approach and uncoated cores. The dipped core weight gains for the 800 cps dip materials ranged from 12-22 mg, whereas those of the 1500 cps material ranged from 20-36 mg. The viscosity readings in the plant were between 100-200 cps lower than in the lab. The dipped cores had many large bubbles due to the incomplete de-aeration of the dip materials at the start of the runs. The coatings from the 800 cps dip

material were glossy but thin, whereas the 1500 cps dip material resulted in thick nonuniform coats.

The dissolution of the HPMC E5/XG coated cores was generally faster than the gelatin dipped cores. The formulation was optimized in the lab to 12% HPMC E5/0.13% XG to balance weight gain, dip material cost, and acceptable aesthetics.

Further experimentation was done with the HPMC E5/XG system to evaluate the effects of partially substituting the HPMC E5 with other materials, such as polymers, maltodextrins, and starches in an attempt to reduce the raw material costs and improve product appearance (see Table 4). A suitable HPMC E5 combination dip coat system was not identified due to cracking and nonuniformity, however much of this learning was used to modify the subcoat to reduce the subcoat level and raw material costs.

Table 16 lists some alternative subcoating systems for HPMC/Xanthan gum outer coatings. In Table 16, all of the cores were dipped with the E5/XG system except where indicated (see the key at the top of the first page). Dissolution data (at RT) and comments are for the dipped cores. Many different coating systems were tried to fill in the land area. Polymers, fillers and plasticisers were as follows:

- 1. Polymers: HPMC E5, E15, E50, K3, Natrosol 250L, PVP K29/32
- 2. Fillers: Maltodextrins, Starches
- 3. Plasticisers: PEGs, CO, Tween 80

The best systems in terms of appearance, dissolution, CIP potential and cost functionality were:

- 1. 2% subcoat level, HPMC E5/CO, 9% solids
- 2. 2-4% subcoat levels, 40% HPMC E5/53% Maltrin 040/7% PEG 400, 15% solids.
- 3. 2-4% subcoat levels, 24% Natrosol 250L/71% Maltrin 180/5% PEG 400, 15% solids.
- 4. 2-4% subcoat levels, 28% HPMC E50/67% Maltrin 180/5% PEG 400, 15% solids.

60291127-051501

[illegible]

Party	State	County	City	Address	Phone	Occupation	Age	Marital	Religion	Education	Service	Notes
John Doe	California	Los Angeles	Los Angeles	1234 Main St	555-1234	Engineer	45	Married	Catholic	High School	US Army	40°C - checked 1 week
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Robert Johnson	California	Los Angeles	Los Angeles	9101 Main St	555-9101	Doctor	55	Married	Catholic	College	US Army	40°C - checked 1 week
Patricia Brown	California	Los Angeles	Los Angeles	2345 Main St	555-2345	Nurse	40	Married	Catholic	College	US Navy	40°C - checked 1 week
William Davis	California	Los Angeles	Los Angeles	6789 Main St	555-6789	Lawyer	60	Married	Catholic	College	US Army	40°C - checked 1 week
Elizabeth Miller	California	Los Angeles	Los Angeles	1011 Main St	555-1011	Writer	30	Single	Catholic	College	US Navy	40°C - checked 1 week
James Wilson	California	Los Angeles	Los Angeles	4567 Main St	555-4567	Businessman	50	Married	Catholic	College	US Army	40°C - checked 1 week
Margaret Moore	California	Los Angeles	Los Angeles	8901 Main St	555-8901	Artist	25	Single	Catholic	College	US Navy	40°C - checked 1 week
Charles Taylor	California	Los Angeles	Los Angeles	3456 Main St	555-3456	Scientist	40	Married	Catholic	College	US Army	40°C - checked 1 week
Barbara White	California	Los Angeles	Los Angeles	7890 Main St	555-7890	Homemaker	38	Married	Catholic	College	US Navy	40°C - checked 1 week
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Thomas Gray	California	Los Angeles	Los Angeles	9101 Main St	555-9101	Doctor	55	Married	Catholic	College	US Army	40°C - checked 1 week
Linda King	California	Los Angeles	Los Angeles	2345 Main St	555-2345	Nurse	40	Married	Catholic	College	US Navy	40°C - checked 1 week
Michael Lee	California	Los Angeles	Los Angeles	6789 Main St	555-6789	Lawyer	60	Married	Catholic	College	US Army	40°C - checked 1 week
Carol Hall	California	Los Angeles	Los Angeles	1011 Main St	555-1011	Writer	30	Single	Catholic	College	US Navy	40°C - checked 1 week
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Steven Wright	California	Los Angeles	Los Angeles	3456 Main St	555-3456	Scientist	40	Married	Catholic	College	US Army	40°C - checked 1 week
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Christopher Hill	California	Los Angeles	Los Angeles	1234 Main St	555-1234	Engineer	45	Married	Catholic	College	US Army	40°C - checked 1 week
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Christina Ivers	California	Los Angeles	Los Angeles	7890 Main St	555-7890	Homemaker	38	Married	Catholic	College	US Navy	40°C - checked 1 week
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Victoria Lee	California	Los Angeles	Los Angeles	8901 Main St	555-8901	Artist	25	Single	Catholic	College	US Navy	40°C - checked 1 week
Walter Miller	California	Los Angeles	Los Angeles	3456 Main St	555-3456	Scientist	40	Married	Catholic	College	US Army	40°C - checked 1 week
Debra Wilson	California	Los Angeles	Los Angeles	7890 Main St	555-7890	Homemaker	38	Married	Catholic	College	US Navy	40°C - checked 1 week
Gregory Adams	California	Los Angeles	Los Angeles	1234 Main St	555-1234	Engineer	45	Married	Catholic	College	US Army	40°C - checked 1 week
Heather Baker	California	Los Angeles	Los Angeles	5678 Main St	555-5678	Teacher	35	Married	Catholic	College	US Navy	40°C - checked 1 week
Jonathan Clark	California	Los Angeles	Los Angeles	9101 Main St	555-9101	Doctor	55	Married	Catholic	College	US Army	40°C - checked 1 week
Stephanie Evans	California	Los Angeles	Los Angeles	2345 Main St	555-2345	Nurse	40	Married	Catholic	College	US Navy	40°C - checked 1 week
Timothy Fisher	California	Los Angeles	Los Angeles	6789 Main St	555-6789	Lawyer	60	Married	Catholic	College	US Army	40°C - checked 1 week
Rebecca Grant	California	Los Angeles	Los Angeles	1011 Main St	555-1011	Writer	30	Single	Catholic	College	US Navy	40°C - checked 1 week
Benjamin Harris	California	Los Angeles	Los Angeles	4567 Main St	555-4567	Businessman	50	Married	Catholic	College	US Army	40°C - checked 1 week
Christina Ivers	California	Los Angeles	Los Angeles	8901 Main St	555-8901	Artist	25	Single	Catholic	College	US Navy	40°C - checked 1 week
Samuel King	California	Los Angeles	Los Angeles	3456 Main St	555-3456	Scientist	40	Married	Catholic	College	US Army	40°C - checked 1 week
Victoria Lee	California	Los Angeles	Los Angeles	7890 Main St	555-7890	Homemaker	38	Married	Catholic	College	US Navy	40°C - checked 1 week
Walter Miller	California	Los Angeles	Los Angeles	1234 Main St	555-1234	Engineer	45	Married	Catholic	College	US Army	40°C - checked 1 week
Debra Wilson	California	Los Angeles	Los Angeles	5678 Main St	555-5678	Teacher	35	Married	Catholic	College	US Navy	40°C - checked 1 week
Gregory Adams	California	Los Angeles	Los Angeles	9101 Main St	555-9101	Doctor	55	Married	Catholic	College	US Army	40°C - checked 1 week
Heather Baker	California	Los Angeles	Los Angeles	2345 Main St	555-2345	Nurse	40	Married	Catholic	College	US Navy	40°C - checked 1 week
Jonathan Clark	California	Los Angeles	Los Angeles	6789 Main St	555-6789	Lawyer	60	Married	Catholic	College	US Army	40°C - checked 1 week
Stephanie Evans	California	Los Angeles	Los Angeles	1011 Main St	555-1011	Writer	30	Single	Catholic	College	US Navy	40°C - checked 1 week
Timothy Fisher	California	Los Angeles	Los Angeles	4567 Main St	555-4567	Businessman	50	Married	Catholic	College	US Army	40°C - checked 1 week
Rebecca Grant	California	Los Angeles	Los Angeles	8901 Main St	555-8901	Artist	25	Single	Catholic	College	US Navy	40°C - checked 1 week
Benjamin Harris	California	Los Angeles	Los Angeles	3456 Main St	555-3456	Scientist	40	Married	Catholic	College	US Army	40°C - checked 1 week
Christina Ivers	California	Los Angeles	Los Angeles	7890 Main St	555-7890	Homemaker	38	Married	Catholic	College	US Navy	40°C - checked 1 week
Samuel King	California	Los Angeles	Los Angeles	1234 Main St	555-1234	Engineer	45	Married	Catholic	College	US Army	40°C - checked 1 week
Victoria Lee	California	Los Angeles	Los Angeles	5678 Main St	555-5678	Teacher	35	Married	Catholic	College	US Navy	40°C - checked 1 week
Walter Miller	California	Los Angeles	Los Angeles	9101 Main St	555-9101	Doctor	55	Married	Catholic	College	US Army	40°C - checked 1 week
Debra Wilson	California	Los Angeles	Los Angeles	2345 Main St	555-2345	Nurse	40	Married	Catholic	College	US Navy	40°C - checked 1 week
Gregory Adams	California	Los Angeles	Los Angeles	6789 Main St	555-6789	Lawyer	60	Married	Catholic	College	US Army	40°C - checked 1 week
Heather Baker	California	Los Angeles	Los Angeles	1011 Main St	555-1011	Writer	30	Single	Catholic	College	US Navy	40°C - checked 1 week
Jonathan Clark	California	Los Angeles	Los Angeles	4567 Main St	555-4567	Businessman	50	Married	Catholic	College	US Army	40°C - checked 1 week
Stephanie Evans	California	Los Angeles	Los Angeles	8901 Main St	555-8901	Artist	25	Single	Catholic	College	US Navy	40°C - checked 1 week
Timothy Fisher	California	Los Angeles	Los Angeles	3456 Main St	555-3456	Scientist	40	Married	Catholic	College	US Army	40°C - checked 1 week
Rebecca Grant	California	Los Angeles	Los Angeles	7890 Main St	555-7890	Homemaker	38	Married	Catholic	College	US Navy	40°C - checked 1 week
Benjamin Harris	California	Los Angeles	Los Angeles	1234 Main St	555-1234	Engineer	45	Married	Catholic	College	US Army	40°C - checked 1 week
Christina Ivers	California	Los Angeles	Los Angeles	5678 Main St	555-5678	Teacher	35	Married	Catholic	College	US Navy	40°C - checked 1 week
Samuel King	California	Los Angeles	Los Angeles	9101 Main St	555-9101	Doctor	55	Married	Catholic	College	US Army	40°C - checked 1 week
Victoria Lee	California	Los Angeles	Los Angeles	2345 Main St	555-2345	Nurse	40	Married	Catholic	College	US Navy	40°C - checked 1 week
Walter Miller	California	Los Angeles	Los Angeles	6789 Main St	555-6789	Lawyer	60	Married	Catholic	College	US Army	40°C - checked 1 week
Debra Wilson	California	Los Angeles	Los Angeles	1011 Main St	555-1011	Writer	30	Single	Catholic	College	US Navy	40°C - checked 1 week
Gregory Adams	California	Los Angeles	Los Angeles	4567 Main St	555-4567	Businessman	50	Married	Catholic	College	US Army	40°C - checked 1 week
Heather Baker	California	Los Angeles	Los Angeles	8901 Main St	555-8901	Artist	25	Single	Catholic	College	US Navy	40°C - checked 1 week
Jonathan Clark	California	Los Angeles	Los Angeles	3456 Main St	555-3456	Scientist	40	Married	Catholic	College	US Army	40°C - checked 1 week
Stephanie Evans	California	Los Angeles	Los Angeles	7890 Main St	555-7890	Homemaker	38	Married	Catholic	College	US Navy	40°C - checked 1 week
Timothy Fisher	California	Los Angeles	Los Angeles	1234 Main St	555-1234	Engineer	45	Married	Catholic	College	US Army	40°C - checked 1 week
Rebecca Grant	California	Los Angeles	Los Angeles	5678 Main St	555-5678	Teacher	35	Married	Catholic	College	US Navy	40°C - checked 1 week
Benjamin Harris	California	Los Angeles	Los Angeles	9101 Main St	555-9101	Doctor	55	Married	Catholic	College	US Army	40°C - checked 1 week
Christina Ivers	California	Los Angeles	Los Angeles	2345 Main St	555-2345	Nurse	40	Married				

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1000 1001 1002 1003 1004 1005 1006 1007 1008 1009 1010 1011 1012 1013 1014 1015 1016 1017 1018 1019 1020 1021 1022 1023 1024 1025 1026 1027 1028 1029 1030 1031 1032 1033 1034 1035 1036 1037 1038 1039 1040 1041 1042 1043 1044 1045 1046 1047 1048 1049 1050 1051 1052 1053 1054 1055 1056 1057 1058 1059 1060 1061 1062 1063 1064 1065 1066 1067 1068 1069 1070 1071 1072 1073 1074 1075 1076 1077 1078 1079 1080 1081 1082 1083 1084 1085 1086 1087 1088 1089 1090 1091 1092 1093 1094 1095 1096 1097 1098 1099 1100 1101 1102 1103 1104 1105 1106 1107 1108 1109 1110 1111 1112 1113 1114 1115 1116 1117 1118 1119 1120 1121 1122 1123 1124 1125 1126 1127 1128 1129 1130 1131 1132 1133 1134 1135 1136 1137 1138 1139 1140 1141 1142 1143 1144 1145 1146 1147 1148 1149 1150 1151 1152 1153 1154 1155 1156 1157 1158 1159 1160 1161 1162 1163 1164 1165 1166 1167 1168 1169 1170 1171 1172 1173 1174 1175 1176 1177 1178 1179 1180 1181 1182 1183 1184 1185 1186 1187 1188 1189 1190 1191 1192 1193 1194 1195 1196 1197 1198 1199 1200 1201 1202 1203 1204 1205 1206 1207 1208 1209 1210 1211 1212 1213 1214 1215 1216 1217 1218 1219 1220 1221 1222 1223 1224 1225 1226 1227 1228 1229 1230 1231 1232 1233 1234 1235 1236 1237 1238 1239 1240 1241 1242 1243 1244 1245 1246 1247 1248 1249 1250 1251 1252 1253 1254 1255 1256 1257 1258 1259 1260 1261 1262 1263 1264 1265 1266 1267 1268 1269 1270 1271 1272 1273 1274 1275 1276 1277 1278 1279 1280 1281 1282 1283 1284 1285 1286 1287 1288 1289 1290 1291 1292 1293 1294 1295 1296 1297 1298 1299 1300 1301 1302 1303 1304 1305 1306 1307 1308 1309 1310 1311 1312 1313 1314 1315 1316 1317 1318 1319 1320 1321 1322 1323 1324 1325 1326 1327 1328 1329 1330 1331 1332 1333 1334 1335 1336 1337 1338 1339
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HPMC E5/100 NON GELATIN

104

109

UNIT 10

60291137-051501

All cores dipped in 12% ES/CO 17% 200 colored with 3% Copper Sulphate 15% 120A/4.5% 100 Yellow 100 3/25
 Except • Yellow Dip Material = 10% ES/CO 17% 200, Red Dip Material = 12% ES/CO 17% 200
 ** Modified Cobalt (10% cobalt)
 *** Modified Cobalt (7.5% cobalt / 2.5% modified)
 / Cobalt Cobalt (~4% up)
 All cores TY Blank except (TY 827)

TABLE 16: Alternate Subcoating Systems for HPMC E5/XG Dipped Cores

Pile Coat	PC WL Gals	DC WL Gals	Time/lot % S / 10 / 15 min.	Comments
Uncoated (TY 820)	—	33	94 / 101 / 102	light d, nonuniform red color, d. rough, very glossy, signs. lead area
Uncoated (TY 820)	—	21	79 / 902 / 102	good red color, rough, d. gloss, signs. lead area
4.5% ES/CO (TY 820) mechanical product	—	—	0 / 85 / 100	very glossy, lead filled in well
4.5% ES/CO mechanical product	—	—	0 / 10 / 72	very glossy, lead filled in well
2% ES/CO (TY 820)	9	16	68 / 98 / 99	glossy, d. nonuniform red, d. lead area, few bubbles
2% ES/CO (TY 820), (C-103-126A)	12	13	68 / 98 / 100	light color, thin, d. lead area, uniform
4.5% ES/CO (TY 820)	20	26	0 / 59 / 96	d. nonuniform, good color, d. lead area, some bubbles
4.5% ES/CO (TY 820)	20	27	1 / 68 / 100	glossy, good color, uniform, d. lead area, some bubbles at top of each core
4.5% ES/CO (TY 820)	20	17	0 / 90 / 100	d. nonuniform, good color, d. lead area, some bubbles
4.5% ES/CO (TY 820), (1% TW 89 in dip coat)	20	38	5 / 93 / 101	very nonuniform, bubbles, d. lead area
4.5% ES/CO (TY 820)	—	25	23 / 95 / 99	very glossy, uniform (blue color), d. lead area
4.5% ES/CO (TY 820)	—	25	40 / 98 / 100	very glossy, nonuniform red color, d. lead area
4.5% ES/CO (TY 820)	—	43	0 / 77 / 100	very glossy, uniform, good color, no lead area
2% ES/CO (TY 820)	—	47	—	glossy, uniform, d. lead area, cracked
1% ES/CO (TY 820)	—	40	—	glossy, uniform, d. lead area, cracked
3% Natural/PSB, 3.5% white	15	21	0 / 13 / 61	glossy, uniform, good color, lead filled in moderately
3% 42% ES/17% TWB, (TY 820), 10% white	13	26	3 / 95 / 101	good gloss, color, uniform, d. lead area
3% 42% ES/17% Mycojet 945, (TY 820), 10% white	13	24	0 / 68 / 99	good gloss, color, uniform, lead area filled in moderately
3% 44% ES/16% MAR/16% PRM/4% CO, (TY 820), 10% white	10	21	2 / 92 / 101	good gloss, color, uniform, lead area filled in moderately
3% 44% ES/16% MAR/16% PRM/4% CO (TY 820) 10% white	10	—	—	points pulled off
3% 44% ES/16% Marsh 901/ 16% PRM/4% CO (TY 820) 10% white	14	25	4 / 73 / 99	good gloss, color, uniform, d. lead area
3% 44% ES/16% Marsh 901/ 16% PRM/4% CO (TY 820) 10% white	14	—	—	points pulled off
3% 44% ES/16% Marsh 901/ 16% PRM/4% CO (TY 820) 10% white	14	48	—	looked good but cracked

File Cat	PC Wt.	DC Wt.	Identification	Comments
105150-2116289	Obs	Obs	5 / 10 / 15 min.	
5-48 S 83/32 S 901 / 16 S P804 S CO (TY 800) 10 S cells	15	20	1 / 25 / 90	good glass, color, uniform, d. head area
5-48 S 83/32 S 901 / 16 S P804 S CO (TY 800) 10 S cells	15	—	—	petals pointed off
5-48 S 83/32 S 901 / 16 S P804 S CO (TY 800) 10 S cells	15	47	—	looked good but cracked
35-48 S 83/32 S 140712 S P804 S CO (TY 800) 10 S cells	15	20	22 / 99 / 90	glassy, d. light color, d. head area, uniform
35-48 S 83/32 S 140712 S P804 S CO (TY 800) 10 S cells	15	—	—	petals pointed off
35-48 S 83/32 S 140712 S P804 S CO (TY 800) 10 S cells	14	19	40 / 90.5 / 101	glassy, d. light color, d. head area, uniform
66.5 S 83/28.5 S 8305 S P80, 10 S cells	10	27	0 / 1 / 26	good color, glassy, d. rough, uniform, d. head area
66.5 S 83/28.5 S 8305 S P80, 10 S cells	21	20	0 / 1 / 15.5	good color, glassy, d. rough, head filled in well
33.3 S 83/28.5 S 8305 S P80, 10 S cells	5	23	0 / 34 / 90	good color, glass, uniform, head filled in moderately well
33.3 S 83/28.5 S 8305 S P80, 10 S cells	15	21	0 / 35 / 96	good color, glassy, uniform, d. head area
33.3 S 83/28.5 S 8305 S P80, 10 S cells	22	23	0 / 16 / 95	good color, glassy, head filled in moderately
40 S Natural/33 S 140407 S P80, 15 S cells	1	21	2 / 80 / 90	glassy, uniform, d. head area, d. light color
40 S Natural/33 S 140407 S P80, 15 S cells	7	24	1 / 70 / 90	good color, glassy, uniform, d. head area
40 S Natural/33 S 140407 S P80, 15 S cells	17	20	0 / 50 / 96	good color, glassy, uniform, head filled in moderately
40 S Natural/33 S 140407 S P80, 15 S cells	4	19	3 / 71 / 90	good glass, uniform, head filled in moderately
40 S 83/33 S 140407 S P80, 15 S cells	4	45	56 / 100 / 101	light red color, d. head area, glassy, uniform, d. darker red tips, cracked
40 S 83/33 S 140407 S P80, 15 S cells	14	22	0 / 43 / 95	good color, glassy, uniform, d. head area
40 S 83/33 S 140407 S P80, 15 S cells	20	22	0 / 35 / 95	good color, glassy, uniform, d. head area
40 S 83/33 S 141007 S P80, 20 S cells	15	26	0 / 26 / 84	d. somewhat light red color, glassy, d. head area
40 S 83/33 S 141007 S P80, 20 S cells	22	22	1 / 62 / 97	d. light red, uniform, glassy, d. head area
33.3 S 83/28.5 S 8305 S P80, 10 S cells	15	20	0 / 77 / 86	good color, glass, uniform, d. head area
33.3 S 83/28.5 S 8305 S P80, 10 S cells	20	20	0 / 1 / 30	good color, glass, uniform, d. head area
40 S Natural/33 S 141007 S P80, 20 S cells	10	29	0 / 60 / 96	d. light red color, uniform, glassy, d. rough, d. head area
40 S Natural/33 S 141007 S P80, 20 S cells	20	20	0 / 44 / 90	good color, glass, uniformity, d. rough, head area filled in moderately
66.5 S 83/28.5 S 8305 S P80, 10 S cells	19	23	0 / 2 / 64	d. light red color, glassy, uniform, d. head area
66.5 S 83/28.5 S 8305 S P80, 10 S cells	31	21	0 / 5 / 36	good color, glass, uniformity, head area filled in moderately
66.5 S 83/28.5 S 8305 S P80, 10 S cells	31	16	0 / 22 / 87	d. light red color, glassy, uniform, head area filled in moderately
47.5 S 83/47.5 S 8155 S P80, 10 S cells	13	37	0 / 1 / 64	good color, glass, uniformity, head area filled in moderately
47.5 S 83/47.5 S 8155 S P80, 10 S cells	24	34	0 / 2 / 53	good color, glass, uniformity, head area filled in moderately

File Code	PC Wt.	DC Wt.	Dimension 8	Comments
IN 150	gms	Gals	5 / 10 / 15 mls.	
28% ES0475 M10055 PEO, 15% mld	10	16	1 / 47 / 99	glazy, uniform, sl. light color, sl. rough, lead area filled in moderately
28% ES0475 M10055 PEO, 15% mld	19	34	0 / 12 / 73	good color, glass, uniformity, lead area filled in moderately
28% ES0475 M10055 PEO, 15% mld	31	30	0 / 36 / 92	good color, glass, uniformity, lead area filled in moderately
24% ES245 ES0485 M10055 PEO, 15% mld	9	19	1 / 45 / 93	good color, glazy, uniform, lead area filled in moderately well
24% ES245 ES0485 M10055 PEO 15% mld	10	31	0 / 10 / 83	good color, glass, uniformity, lead area filled in moderately
24% ES245 ES0485 M10055 PEO 15% mld	26	37	0 / 9 / 30	good color, glass, uniformity, lead area filled in moderately
24% ES715 M04055 TWR, 20% mld	4	23	13 / 11 / 98	glazy, uniform, good color, lead area filled in well
24% ES715 M04055 TWR, 20% mld	4	19	26 / 96 / 99	sl. light color, sl. lead area, sl. rough, v. sl. nonuniform
24% ES715 M04055 TWR, 20% mld	4	—	—	plateau peaked off
24% ES715 M04055 TWR, 20% mld	13	21	3 / 26 / 97	glazy, uniform, sl. light color
24% ES715 M04055 TWR, 20% mld	16	20	0 / 47 / 96	glazy, uniform, sl. light color
24% ES715 M04055 PEO, 20% mld	7	—	—	plateau cracked at edges
24% ES715 M04055 PEO, 20% mld	13	21	0 / 38 / 94	glazy, sl. light color, lead area filled in moderately well
24% ES715 M04055 PEO, 20% mld	31	16	0 / 19 / 71	glazy, nonuniform, sl. light color
66.5% PVP28.5% ES055 PEO, 10% mld	14	24	0 / 5 / 42	glazy, uniform, lead area filled in well
66.5% PVP28.5% ES055 PEO, 10% mld	22	23	0 / 3 / 32	glazy, uniform, lead area filled in well
24% ES715 M10055 PEO, 20% mld	9	48	45 / 97 / 100	very glazy, light red color, uniform, sl. lead area, cracked (2.4)
24% ES715 M10055 PEO, 20% mld	18	24	4 / 41 / 93	glazy, sl. nonuniform, sl. light color
24% ES715 M10055 PEO, 20% mld	27	9	7 / 40 / 94	glazy, sl. nonuniform, good color
24% M040715 M10055 PEO, 20% mld	8	16	9 / 96 / 99	glazy, good color, uniform, sl. lead area
24% M040715 M10055 PEO, 20% mld	17	23	2 / 43 / 97	glazy, uniform, good color
24% M040715 M10055 PEO, 20% mld	25	23	1 / 32 / 98	glazy, uniform, good color, lead area filled in well
22.5% ES07.5% M040705 TWR, 20% mld	6	21	0 / 91 / 100	glazy, sl. light color, uniform, lead filled in moderately
22.5% ES07.5% M040705 TWR, 20% mld	13	19	4 / 68 / 95	sl. light color, bubbles, sl. nonuniform
22.5% M040705 M040705 TWR, 20% mld	7	19	2 / 43 / 18	glazy, good color, uniform, sl. lead area
22.5% M040705 M040705 TWR, 20% mld	14	17	1 / 45 / 97	glazy, good color, some bubbles, uniform, sl. lead area

Plot Cont	PC Wt.	DC Wt.	Dissection S	Comments
TESTO-111-118	Gals	Gals	5 / 10 / 15 cts.	
22.5% Mar./07.5% M04070% TW00, 20% white	14.5	19	0 / 32 / 92	glossy, good color, some bubbles, uniform, d. head area
24.5% B3/04.5% B0405% P00, 10% white	11	13	4 / 86 / 99	slts, d. rough, d. light color, d. dull, uniform
24.5% B3/04.5% B0405% P00, 10% white	16	14	1 / 32 / 96	d. dull, d. light color, slts, uniform
24.5% B3/04.5% B0405% P00, 10% white	24	17	0 / 39 / 94	d. dull, d. rough, d. light color, uniform, d. head area
24% B3/24% B3040% B0405% P00, 10% white	9	21	1 / 54 / 96	glossy, d. rough, good color, uniform, d. head area
24% B3/24% B3040% B0405% P00, 10% white	17	18	0 / 18 / 78	glossy, good color, uniform, d. head area
24% B3/24% B3040% B0405% P00, 10% white	28	16	0 / 6 / 73	glossy, good color, uniform, head area filled to moderately well
23% B3/09.5% M0407.5% TW00, 20% white	3	33	1 / 74 / 99	glossy, d. light color, some bubbles, d. head area, uniform
23% B3/09.5% M0407.5% TW00, 20% white	10	32	4 / 60 / 98	glossy, good color, bubbles, head area filled to mod., uniform
23% Mar./09.5% M0407.5% TW00, 20% white	6	30	12 / 83 / 98	glossy, good color, uniform, head area filled to mod.
23% Mar./09.5% M0407.5% TW00, 20% white	8	28	4 / 76 / 100	glossy, good color, uniform, head area filled to mod.
23% Mar./09.5% M0407.5% TW00, 20% white	13	25	4 / 57 / 96	glossy, good color, uniform, head area filled to mod., some bubbles
24% Mar./71% M0405% TW00, 20% white	5	26	21 / 94 / 100	glossy, good color, d. head area uniform
24% Mar./71% M0405% TW00, 20% white	12	29	6 / 65 / 98	glossy, good color, uniform, head area filled to mod.
24% Mar./71% M0405% TW00, 20% white	20	26	2 / 57 / 98	glossy, good color, uniform, head area filled to mod.
24% Mar./71% M0405% TW00, 20% white	10	26	8 / 61 / 91	glossy, good color, uniform, head area filled to mod.
23% B3047% M0405% TW00, 15% white	19.5	27	0 / 13 / 76	glossy, good color, uniform, head area filled to mod.
23% B3047% M0405% TW00, 15% white	26	31	0 / 4 / 49	glossy, good color, uniform, head area filled to mod.
24% B3/24% B3047% M0405% TW00, 15% white	8	29	3 / 57 / 96	glossy, good color, uniform, head area filled to mod.
24% B3/24% B3047% M0405% TW00, 15% white	17	28	2 / 32 / 65	glossy, good color, uniform, head area filled to mod.
24% B3/24% B3047% M0405% TW00, 15% white	23	27	0 / 6 / 54	glossy, good color, uniform, head area filled to mod.
24% B3/24% B3047% M0405% TW00, 15% white	9	24	13 / 83 / 94	glossy, good color, uniform, d. head area
24.5% B3 / 72.5% M40 / 15% TW00, 20% white	6	30	18 / 95 / 98	glossy, good color, uniform, d. head area
25% B3 / 72.5% M40 / 15% TW00, 20% white	7	28	9 / 83 / 96	glossy, good color, uniform, d. head area
25.5% B3 / 72.5% M40 / 15% TW00, 20% white	5	31	5 / 79 / 98	glossy, good color, uniform, d. head area
25.5% B3 / 72.5% M40 / 15% TW00, 20% white	5	—	—	gels pulled off
25.5% B3 / 72.5% M40 / 15% TW00, 20% white	14	25	0 / 32 / 98	glossy, good color, uniform, d. head area
25.5% B3 / 72.5% M40 / 15% TW00, 20% white	23	25	0 / 29 / 95	glossy, good color, uniform, d. head area
25.5% B3 / 72.5% M40 / 15% TW00, 20% white	7	22	17 / 96 / 99	glossy, good color, uniform, d. head area
22% B3 / 72% M40 / 15% TW00, 20% white	13	27	8 / 82 / 98	glossy, good color, uniform, d. head area
22% B3 / 72% M40 / 15% TW00, 20% white	8	28	1 / 57 / 96	" "
30% B3 / 09% M40 / 25% TW00, 15% white				

File No.	PC Wt.	DC Wt.	Discoloration \$	Comments
TESTED	Grain	Grain	51/10/15 min.	
30% ES 140% 140% 15% TWB, 15% mids	8	—	—	gelsol washed at apex
30% ES 140% 140% 15% TWB, 15% mids	19	21	3 / 56 / 93	glossy, good color, uniform, d. head area
35% ES 140% 140% 15% TWB, 15% mids	10	26	3 / 67 / 99	" "
35% ES 140% 140% 15% TWB, 15% mids	20	21	0 / 37 / 90	" "
35% ES 140% 140% 15% TWB, 15% mids	20	26	1 / 60 / 92	" "
40% ES 140% 140% 15% TWB, 15% mids	10	30	42 / 94 / 101	very glossy, light red color, d. head area, d. darker red at tips, uniform, washed
40% ES 140% 140% 15% TWB, 15% mids	19	22	1 / 53 / 90	glossy, good color, uniform, d. head area
40% ES 140% 140% 15% TWB, 15% mids	20	24	0 / 37 / 81	d. nonuniform color, glossy, d. head area
45% ES 140% 140% 15% TWB, 15% mids	10	30	14 / 75 / 96	glossy, uniform, good color, d. head area
45% ES 140% 140% 15% TWB, 15% mids	20	26	1 / 67 / 96	" "
45% ES 140% 140% 15% TWB, 15% mids	20	21	4 / 45 / 91	" "
30% ES 140% 140% 15% TWB, 15% mids	10	23	2 / 68 / 99	" "
30% ES 140% 140% 15% TWB, 15% mids	10	37	46 / 101 / 103	very glossy, uniform, d. head area, light red color, washed
30% ES 140% 140% 15% TWB, 15% mids	14	33	0 / 32 / 84	glossy, uniform, good color, d. head area
30% ES 140% 140% 15% TWB, 15% mids	20	23	0 / 30 / 81	d. nonuniform color, glossy, d. head area
35% ES 140% 140% 15% TWB, 15% mids	23	18	4 / 77 / 97	glossy, uniform, good color, d. head area
35% ES 140% 140% 15% TWB, 15% mids	18	21	0 / 43 / 97	" "
35% ES 140% 140% 15% TWB, 15% mids	20	19	0 / 20 / 85	" "
35% ES 140% 140% 15% TWB, 15% mids	12	23	0 / 18 / 85	" "
40% ES 140% 140% 15% TWB, 15% mids	11	40	41 / 99 / 100	very glossy, uniform, d. head area, light red color
40% ES 140% 140% 15% TWB, 15% mids	20	23	0 / 27 / 97	glossy, uniform, good color, d. head area
40% ES 140% 140% 15% TWB, 15% mids	20	23	0 / 15 / 84	d. nonuniform color, glossy, d. head area
40% ES 140% 140% 15% TWB, 15% mids	20	20	1 / 57 / 95	glossy, uniform, d. light red, d. head area
41.25% ES 140% 140% 15% CO, 15% mids	6	19	0 / 40 / 96	glossy, uniform, d. light red, d. head area
41.25% ES 140% 140% 15% CO, 15% mids	16	15	0 / 42 / 100	glossy, uniform, d. light red, d. head area
41.25% ES 140% 140% 15% CO, 15% mids	24	15	1 / 43 / 99	glossy, uniform, d. light red, d. head area
30.25% ES 140% 140% 15% CO, 15% mids	9	18	0 / 4 / 67	glossy, uniform, d. light red, d. head area
30.25% ES 140% 140% 15% CO, 15% mids	17	17	0 / 5 / 54	glossy, uniform, d. light red, d. head area
30.25% ES 140% 140% 15% CO, 15% mids	20	22	4 / 82 / 101	" "
26.25% Nmr / 73.25% M400.5% CO, 15% mids	9	16	3 / 90 / 99	" "
26.25% Nmr / 73.25% M400.5% CO, 15% mids	17	16	0 / 8 / 76	" "
26.25% Nmr / 73.25% M400.5% CO, 15% mids	20	22	13 / 77 / 90	" "
24.25% ES 140% 140% 15% CO, 20% mids	11	40	0 / 70 / 99	very glossy, good color, no head area, uniform, washed
41.25% ES 140% 140% 15% CO, 15% mids	6	40		

File No.	PC Wt.	DC Wt.	Discoloration	Comments
105150-24116889				
40.25% E3409.25% M400.5% CO, 15% mbls	16	49	1 / 50 / 94	very glossy, good color, no head area, uniform, cracked
40.25% E3409.25% M400.5% CO, 15% mbls	24	38	0 / 26 / 98	very glossy, good color, no head area, uniform, cracked
30.25% E3409.25% M400.5% CO, 15% mbls	9	46	7 / 57 / 92	very glossy, good color, no head area, uniform, cracked
30.25% E3409.25% M400.5% CO, 15% mbls	17	36	2 / 29 / 83	very glossy, good color, no head area, uniform, cracked
30.25% E3409.25% M400.5% CO, 15% mbls	28	48	0 / 5 / 45	very glossy, good color, no head area, uniform, cracked
26.25% Hec./73.25% M400.5% CO, 15% mbls	9	47	23 / 81 / 101	very glossy, good color, no head area, uniform, cracked
26.25% Hec./73.25% M400.5% CO, 15% mbls	17	30	11 / 92 / 105	very glossy, good color, no head area, uniform, cracked
26.25% Hec./73.25% M400.5% CO, 15% mbls	28	42	0 / 44 / 103	very glossy, good color, no head area, uniform, cracked
24.45% E3475.25% M400.5% CO, 20% mbls	7	30	1 / 33 / 93	glossy, uniform, d. head area, d. light red color
24.45% E3475.25% M400.5% CO, 20% mbls	7,15,26	49,30,-	---	very glossy, good color, uniform, no head area, cracked
24.45% E3475.25% M400.5% CO, 20% mbls	15	24	6 / 62 / 91	glossy, uniform, d. head area, d. light red color
26.25% E3475.25% M400.5% CO, 20% mbls	7	21	1 / 37 / 97	glossy, uniform, d. head area, d. light red color
26.25% P3475.25% M400.5% CO, 20% mbls	7,14,27	52,47,33	---	very glossy, good color, uniform, no head area, cracked
26.25% E3475.25% M400.5% CO, 20% mbls	16	21	3 / 30 / 95	glossy, uniform, d. head area, d. light red color
26.25% E3475.25% M400.5% CO, 20% mbls	27	19	0 / 17 / 81	glossy, uniform, d. head area, d. light red color
30.25% E15409.25% M400.5% CO, 15% mbls	9,18,34	-33,54	---	very glossy, good color, uniform, no head area, cracked
30.25% E3409.25% M400.5% CO, 15% mbls	10,15,28	49,36,-	---	very glossy, good color, uniform, no head area, cracked
30.25% E15409.25% M400.5% CO, 15% mbls	9	28	0 / 28 / 87	good color, uniform, d. head area
30.25% E15409.25% M400.5% CO, 15% mbls	18	26	1 / 26 / 94	" "
30.25% E15409.25% M400.5% CO, 15% mbls	24	24	0 / 2 / 34	" "
30.25% E15409.25% M400.5% CO, 15% mbls	18	25	1 / 27 / 89	" "
30.25% E3409.25% M400.5% CO, 15% mbls	15	30	1 / 25 / 81	" "
30.25% E3409.25% M400.5% CO, 15% mbls	28	28	0 / 7 / 83	" "
30.25% E3409.25% M400.5% CO, 15% mbls	7	28	1 / 33 / 83	" "
34.5% E3409.5% M400.5% CO, 15% mbls	16	19	3 / 33 / 83	" "
34.5% E3409.5% M400.5% CO, 15% mbls	21	25	0 / 25 / 71	" "

769T50-22T16209		DC Wt. Gals	Distances to S / 10 / 13 mls.	Comments
54.5% ES405 M400.5% CO, 15% solids	7,14,31	47,47,41	—	look good, cracked 30
49.5% ES305 M400.5% CO, 15% solids	19	28	2 / 70 / 93	good color, uniform, sl. hard area
49.5% ES305 M400.5% CO, 15% solids	17	28	0 / 22 / 79	" "
49.5% ES305 M400.5% CO, 15% solids	26	23	0 / 11 / 39	" "
49.5% ES305 M400.5% CO, 15% solids	10,17,26	48,49,54	—	look good, cracked
49.5% ES305 M400.5% CO, 15% solids	11	17	2 / 37 / 91	good color, uniform, sl. hard area
49.5% ES305 M400.5% CO, 15% solids	19	19	0 / 31 / 82	" "
49.5% ES305 M400.5% CO, 15% solids	28	15	0 / 36 / 82	" "
49.5% ES305 M400.5% CO, 15% solids	10,19,28	48,50,49	—	look good, cracked
49.5% ES305 M400.5% CO, 15% solids	7	26	2 / 39 / 94	good color, uniform, sl. hard area
49.5% ES305 M400.5% CO, 15% solids	14	21	1 / 46 / 82	" "
49.5% ES305 M400.5% CO, 15% solids	27	17	0 / 22 / 78	" "
49.5% ES305 M400.5% CO, 15% solids	7,14,27	48,48,48	—	look good, cracked
49.5% ES305 M400.5% CO, 15% solids	12	23	0 / 5 / 65	good color, uniform, sl. hard area
59.5% ES405 M400.5% CO, 15% solids	21	21	1 / 31 / 91	" "
59.5% ES405 M400.5% CO, 15% solids	31	26	0 / 27 / 30	" "
59.5% ES405 M400.5% CO, 15% solids	12,21,31	48,41,43	—	look good, cracked
59.5% ES405 M400.5% CO, 15% solids	12, 19, 38	51,53,49	—	look good, shiny, uniform
ES, 9% solids	4,13,28	78,77,81	—	look good
49.5% ES305 M400.5% CO, 15% solids	9,13,21	78,73,82	—	" "
49.5% ES405 M400.5% CO, 15% solids	10,18,25	81,76,89	—	" "
49.5% ES305 ES405 M400.5% CO, 15% solids	11,19,28	88,88,83	—	" "
28% ES0475 M1805 P80400, 15% solids	11,17,27	68,72,68	—	all sl. this
49% ES0355 M1805 P80400, 15% solids	9,14,27	71,76,73	—	all sl. this
50% ES1945 M1805 P80400, 15% solids	10,19,24	69,69,72	—	2.5 - sl. this, 4 - look good
60% ES300.5% M1800.5% CO, 15% solids	9,19,26	71,69,64	—	2.5 - sl. this, 4 - look good
60% ES300.5% ES405 M1800.5% CO, 15% solids	6,19,26	57,59,57	—	2 - sl. this, 3.4 - look good
49% ES0355 ES405 M1805 P80400, 15% solids	13,20,29	58,57,61	—	2 - sl. this, 3.4 - look good