PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 76158-WO-PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2015/027867	International filing date *(day/month/year)* 28.04.2015	Priority date *(day/month/year)* 20.05.2014

International Patent Classification (IPC) or national classification and IPC
INV. A61K9/48

Applicant
Dow Global Technologies Investments LLC

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 8 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions).
      ☐ sheets containing rectifications, where the decision was made by this Authority not to take them into account because they were not authorized by or notified to this Authority at the time when this Authority began to draw up this report, and any accompanying letters (Rules 66.4bis, 70.2(e), 70.16 and 91.2).
      ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in the international application as filed, or the superseding sheets were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in item 4 of Box No. I and the Supplemental Box (see Rule 70.16(b)).
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing, in the form of an Annex C/ST.25 text file, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 3*ter* of Annex C of the Administrative Instructions).

4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
08.12.2015	20.04.2016

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Authorized officer
Giménez Miralles, J
Telephone No. +49 89 2399-8655

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2015/027867

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a) and (b))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-23 as originally filed

   Claims, Numbers

   1-15 filed with the demand for preliminary international examination

   Drawings, Sheets

   1/3-3/3 as originally filed

   ☐ a sequence listing - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-*bis*)):
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:

5. ☐ This report has been established:
   - ☐ taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rules 66.1(d-*bis*) and 70.2(e)).
   - ☐ without taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91(Rules 66.4*bis* and 70.2(e)).

6. ☒ With regard to top-up searches (Rules 66.1*ter* and 70.2(f)):
   - ☒ A top-up search was carried out by this Authority on 08.04.2016 (all discovered documents are listed in the Supplemental Box Relating to Top-up Search).
     - ☐ Additional relevant documents have been discovered during the top-up search.
   - ☐ No top-up search was carried out by this Authority because it would serve no useful purpose.

7. ☐ Supplementary international search report(s) from Authority(ies) has/have been received and taken into account in establishing this report (Rule 45bis.8(b) and (c)).

* *If item 4 applies, some or all of those sheets may be marked "superseded".*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-15
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-15
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V

1. The relevant prior art documents are referred to as D1 to D4 as in the order of appearance in the International Search Report (ISR). Unless otherwise indicated, reference is made to the passages of said documents cited in the ISR.

2. Citations and explanations supporting the statement with regard to novelty (N), inventive step (IS) and industrial applicability (IA) (Rule 43*bis*.1(a)(i) and (b) PCT):

(N) The subject-matter of independent claims 1, 2, 8 and 9 is considered to be novel (Article 33(2) PCT).

The prior art does not anticipate an aqueous composition comprising a dispersion of a hydroxypropyl methyl cellulose acetate succinate (HPMCAS) at least partially neutralized with an ammonium salt of carbonic acid, formic acid or acetic acid, optionally comprising a plasticizer and a dispersant, wherein the weight of said HPMCAS is at least 80% of the total polymer in the aqueous composition, nor a polymeric capsule shell made of said aqueous composition.

(IS) The subject-matter of independent claims 1, 2, 8 and 9 is considered to involve an inventive step (Article 33(3) PCT) for the following reasons.

D1 or D2 can be seen as the closest prior art.

D1 discloses an aqueous dispersion comprising 15-25 wt.% partially neutralized HPMCAS, wherein partial neutralization is carried out by adding aqueous ammonium hydroxide; the aqueous dispersion is used as coating film for pharmaceutical dosage forms, and particularly for making enteric hard capsule shells by dip-moulding. In D1, it is explicitly disclosed that partial neutralization of HPMCAS renders an aqueous dispersion of colloidal size range having appropriate solid content, viscosity, and rheological properties for use in manufacturing capsule shells (paragraphs 10, 14 and 24). The aqueous dispersion comprises a dispersant in an amount of 6 wt.% based on the weight of the HPMCAS polymer.

D2 discloses an aqueous dispersion comprising partially neutralized HPMCAS or HPMCP, wherein partial neutralization is carried out by adding aqueous ammonium hydroxide and emulsification; the aqueous dispersion is used for coating films and in

manufacturing of enteric hard capsule shells by dip-moulding. In D2, when the polymer is HPMCAS, the aqueous dispersion comprises a large amount of 42.9 wt.% of non-esterified HPMC.

Starting from D1 or D2, present claims 1 and 2 thus differ in that the partial neutralization is carried out with an ammonium salt of carbonic acid, formic acid, or acetic acid; in that the aqueous dispersion comprises at least 80 wt.% of HPMCAS based on total polymer weight; and in that the aqueous dispersion comprises at most 2 wt.% of a dispersant.

The effect shown in the application is the provision of an aqueous HPMCAS polymer dispersion for forming enteric films for capsule shells, wherein film formation requires lower amounts of dispersant (up to 2 wt.%), this resulting in films which are less milky than customary HPMCAS films.

The solution claimed in claims 1 and 2 by using an ammonium salt of carbonic acid, formic acid, or acetic acid for partial neutralization is non-obvious. Use of an ammonium salt of carbonic acid, formic acid, or acetic acid instead of ammonium hydroxide for neutralization of acidic polymers such as HMPCAS or HPMCP would not have been a trivial option in the light of the prior art.

In D2, it is disclosed that the compositions of examples 6-7 result in films which are less milky or hazy; yet these compositions comprise HPMCP, but not HPMCAS.

D3 discloses an aqueous dispersion of an acidic polymer such as HPMCAS or HPMCP, among a list of polymers, partially neutralized with ammonium bicarbonate. The ammonium salt of the polymer enhances polymer solubility for the preparation of film coating for nanoparticles. However, the only polymers exemplified are HPMCP and Eudragit S100, but nothing is taught specifically about HPMCAS. Further, D3 does not relate to dip-molding of hard capsule shells.

In view of D2 and D3, it would not have been obvious for the skilled person to use ammonium bicarbonate instead of ammonium hydroxide for partial neutralization of aqueous dispersions of HPMCAS with an expectation of being able to reduce the amount of film-forming aid (dispersant) disclosed in D1.

Independent claims 8 (pharmaceutical or nutritional capsule comprising the capsule shell) and 9 (process for manufacturing the polymeric capsule shell by dip-molding) are also non-obvious for analogous reasons.

(IA) The subject-matter of claims 1-15 is considered to be industrially applicable (Article 33(4) PCT). The possibility of industrial application is beyond any doubt.

Dow International Holdings S.A.
Bachtobelstrasse 3, P.O. Box
CH-8810 Horgen
Switzerland

December 7, 2015

European Patent Office
D-80298 München
Germany

Fax: +49 89 2399 - 4465

IN THE EUROPEAN PATENT OFFICE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY (IPEA/EP)

Applicant(s): DOW GLOBAL TECHNOLOGIES LLC
International Application No.: PCT/US2015/027867
International filing date: 28 April 2015
DOW REFERENCE: 76158-WO-PCT

Amendments under Article 34 PCT

Dear Sir/Madam:

In response to the International Search Report and Written Opinion mailed on 10 July 2015, please find enclosed Replacement Pages 24 - 26 including amended and new claims 1 to 15 which replace claims 1 to 15 on file. A marked-up version showing the changes made as well as a clean version are enclosed. A Demand for International Preliminary Examination is being filed concurrently herewith. Please conduct an International Preliminary Examination based on the amended and new claims.

A) Basis for Amendment

The claims in the Replacement Pages are based on the original claims and on the original description as listed below.

Amended Claim(s)	Original claim(s)	Description
1	1	Page 7, lines 19 – 20; page 12, lines 22 – 27
2	2	Page 7, lines 19 – 20; page 12, lines 22 – 27
3	3	Page 7, lines 19 – 20

Amended Claim(s)	Original claim(s)	Description
4		page 12, lines 22 - 27
5 - 8	5 - 8	
9	9	Page 7, lines 19 – 20; page 12, lines 14 - 17 and 22 – 27
10 - 12	10 - 12	
13		Page 12, lines 28 – 32
14		Page 13, lines 5 - 9
15	15	

B) Novelty

Novelty of original claims 1 – 15 and specifically of independent claims 1, 2, 8 and 9 has been acknowledged. Amended independent claims 1, 2, (8) and 9 are within the scope of the original claims. Accordingly, the subject matter of the amended claims is also novel.

C) Inventive Step

The Present Invention

The polymeric capsule shell of the present invention is prepared from an aqueous composition which comprises

A) a hydroxypropyl methyl cellulose acetate succinate (HPMCAS), wherein at least a part of the succinoyl groups are neutralized with an ammonium salt of carbonic acid, formic acid or acetic acid such that the HPMCAS is soluble in the aqueous composition,

(B) from 0 to 7 weight percent of a non-polymeric plasticizer, based on the weight of the esterified cellulose ether, and

(C) from 0 to 2 weight percent of a dispersant, based on the total weight of the hydroxypropyl methyl cellulose acetate succinate,

wherein the weight of said hydroxypropyl methyl cellulose acetate succinate is at least 80 percent of the total polymer weight in the aqueous composition.

The HPMCAS is dissolved in the aqueous composition. Example 1 illustrates an aqueous solution of HPMCAS wherein 86 mole % of the succinoyl groups are neutralized *(page 20, lines 29 – 32 and page 21, lines 1 – 9).* The solution does not require a substantial amount of dispersant, if any.

As discussed at page 17 of the instant patent application, when the aqueous composition is dried on the molding pins, residual ammonium salt(s) of carbonic acid, formic acid or acetic acid typically decompose at the drying temperature. For example, ammonium hydrogen carbonate (NH_4HCO_3) decomposes to NH_3, CO_2 and H_2O at about 60 °C or more at atmospheric pressure. Without wanting to be bound to the theory, Applicant believes that the evaporation of NH_3 and CO_2 in addition to H_2O contributes to setting of the film on the molding pins resulting in a homogeneous film.

Moreover, during drying of the capsule shells on the molding pins at elevated temperature, some or nearly all of the neutralized groups – C(O) – R – COO^- NH_4^+ in the esterified cellulose ether are transformed back into their acidic form:

- C(O) – R – COO^- NH_4^+ ↔ – C(O) – R – COOH + NH_3 (↑).

HPMCAS that comprises acidic succinoyl groups have enteric properties, i.e., they are substantially insoluble in gastric fluid and rapidly dissolve in intestinal fluid.

The aqueous solution of Example 1 of the invention contained HPMCAS wherein 86 mole % of the succinoyl groups were neutralized *(page 21, lines 4 - 8)*. In the produced and dried HPMCAS capsules of Example 1 the degree of neutralization was only 29 mole % *(page 21, lines 22 – 24)*.

The Prior Art

The Examiner indicated that **D1 (US 2013/295188)** or **D2 (EP 2 476 439)** can be seen as the closest prior art.

D1 (US 2013/295188) relates to bulk enteric capsule shells. D1 discloses hydroxypropyl methyl cellulose acetate succinate (HPMCAS) polymer dispersed in water *(Abstract, claim 1 and paragraph [0024])*. The HPMCAS polymer is partially neutralized to a pH of 4 – 5.5, more specifically 4.8 – 5.3, and even more specifically 5 – 5.2 *(paragraphs [0030] - [0031])*. The weight of the HPMCAS polymer in the dispersion is 15 – 25 % *(claim 3)*, and typically 20 % *(all Examples)*.

The dispersion comprises 0.5 – 2 wt.-% of a dispersant, based on the total weight of the composition. This means that the amount of the dispersant is 2.5 - 8 wt.-%, based on the weight of the HPMCAS polymer, when the weight of the HPMCAS polymer in the dispersion is 20%. In all examples the amount of the dispersant is 6 wt.-%, based on the weight of the HPMCAS polymer.

Furthermore, the dispersion of all examples comprises 10 wt.-% of triacetine, which is a non-polymeric plasticizer.

However, the use of such a large amount of dispersant and plasticizer is often undesirable. When starting from D1 as the closest prior art, the problem to be solved

by the present invention was how to provide compositions which are useful for preparing polymeric capsule shells having enteric properties but which do not require the high amounts of dispersant and non-polymeric plasticizer that are disclosed in D1.

D2 (EP 2 476 439) relates to aqueous compositions for enteric hard capsules. D2 discloses an enteric base material, such as HPMCAS in water and a neutralization agent to solubilize the enteric base material *(paragraphs [0031] and [0035]).* However, D2 discloses the need of a large amount of a capsule forming aid, e.g., a cellulose ether such as HPMC, in the aqueous composition *(claims 1 and 3 and Table 1 at page 7).* When the enteric base material is HPMCAS, the amount of the cellulose ether (HPMC) is 42.9 wt.%, based on HPMCAS *(Example 13 in Table 1).* Such high amount of non-enteric capsule forming aid can jeopardize the enteric properties of the capsules.

When starting from D2 as the closest prior art, the problem to be solved by the present invention was how to provide compositions which are useful for preparing polymeric capsule shells which have enteric properties but which do not require the high amounts of capsule forming aid that are disclosed in D2.

D3 (US 2009/297565) relates to coated nanoparticles. An aqueous polymer solution is used as dispersion medium during the production of nanocrystals and for coating nanoparticles, specifically nanocrystals *(paragraph [0064]).* In the case of acidic polymers, such as HPMCAS, a sufficient amount of volatile bases, such as ammonium bicarbonate, is added to shift the pH into a range in which the polymer is soluble *(paragraph [0068]).*

The dispersion also contains plasticizers, surfactants, stabilizers or other auxiliaries *(paragraphs [0069] - [0070]).* The dispersion is subjected to spray-drying *(paragraphs [0072] - [0074]).* The amounts of surfactant/dispersant taught in the Examples are very high. As listed in the table below summarizing the examples, the dispersion comprise 20 – 25 wt.% surfactant/dispersant, based on the weight of dissolved polymer.

Example	Polymer I		Surfactant/dispersant		
	type	amount	type	amount	%, based on wt. of polymer I
9	HPMCP 55	5.0 g	Poloxamer 188	1.0 g	20 %
10	Eudragit S 100	4.0 g	Poloxamer 188	1.0 g	25 %
11	HPMCP 55	5.0 g	Poloxamer 188	1.0 g	20 %
12	Eudragit S 100	4.0 g	Poloxamer 188	1.0 g	25 %

Combination of D1 or D2 with D3

Regardless whether the skilled artisan starts from D1 or D2 as the closest prior art, the skilled artisan would not combine it with D3 with a reasonable expectation

- that the amount of dispersant disclosed in D1 could be reduced/eliminated or the amount of capsule forming aid disclosed in D2 could be reduced/eliminated.

First of all, D3 does not disclose capsules;
second, D3 does not disclose a dipping process but a spray-drying process; and
third, D3 would lead the skilled artisan to expect that a high amount of surfactant/dispersant is needed in view of the high amount of surfactant disclosed in D3.

D4 (GB 2 325 623) discloses dissolution of HPMCAS with ammonia, preferably in the form of aqueous ammonium hydroxide. It is further remote from the present invention because it does not relate to capsules. Moreover, the enteric coating requires a large amount of non-polymeric plasticizer. The use of 10 – 20 mg triethyl citrate per 60 – 90 mg HPMCAS-LF is disclosed at page 30 and in claim 15 of D4. In each of the Examples 1, 2 and 3 the percentage of triethyl citrate is 20 percent, based on the weight of HPMCAS-LF in the enteric layer.

Accordingly, amended Claim 1 – 15 are novel and inventive over the prior art cited by the Authorized Officer.

Yours Sincerely

By: B. Goldener

B. Goldener
Authorized European Patent Attorney
GA 45856
Direct phone: +41 1 728 26 08
Direct fax: +41 1 728 29 80

BEG/sb

WHAT IS CLAIMED IS:

1. A polymeric capsule shell comprising

(A) a hydroxypropyl methyl cellulose acetate succinate, wherein a part of the succinoyl groups are neutralized with an ammonium salt of carbonic acid, formic acid or acetic acid,

(B) from 0 to 7 weight percent of a non-polymeric plasticizer, based on the weight of the hydroxypropyl methyl cellulose acetate succinate, and

(C) from 0 to 2 weight percent of a dispersant, based on the total weight of the hydroxypropyl methyl cellulose acetate succinate,

wherein the weight of said hydroxypropyl methyl cellulose acetate succinate is at least 80 percent of the total polymer weight in the capsule shell.

2. A polymeric capsule shell prepared from an aqueous composition comprising

(A) a hydroxypropyl methyl cellulose acetate succinate, wherein at least a part of the succinoyl groups are neutralized with an ammonium salt of carbonic acid, formic acid or acetic acid such that the hydroxypropyl methyl cellulose acetate succinate is soluble in the aqueous composition,

(B) from 0 to 7 weight percent of a non-polymeric plasticizer, based on the weight of the esterified cellulose ether, and

(C) from 0 to 2 weight percent of a dispersant, based on the total weight of the hydroxypropyl methyl cellulose acetate succinate,

wherein the weight of said hydroxypropyl methyl cellulose acetate succinate is at least 80 percent of the total polymer weight in the aqueous composition.

3. The capsule shell of claim 1 or 2 wherein the weight of said hydroxypropyl methyl cellulose acetate succinate is at least 85 percent of the total polymer weight in the capsule shell.

4. The capsule shell of any one of claims 1 to 3 comprising from 0 to 1 weight percent of a dispersant, based on the total weight of the hydroxypropyl methyl cellulose acetate succinate.

5. The capsule shell of any one of claims 1 to 4 comprising hydroxypropyl methyl cellulose acetate succinate that is partially neutralized with ammonium carbonate or ammonium hydrogen carbonate.

6. The capsule shell of any one of claims 1 to 5 additionally comprising at least one adjuvant selected from the group consisting of gelling agents, coloring agents, pigments, opacifiers, flavor and taste improvers, and antioxidants.

7. The capsule shell of any one of claims 1 to 6 being a hard capsule shell.

8. A capsule comprising a capsule shell of any one of claims 1 to 7 and further comprising a drug or a nutritional or food supplement or a combination thereof.

9. A process for producing polymeric capsule shells comprising the steps of

providing an aqueous composition comprising (A) a hydroxypropyl methyl cellulose acetate succinate, wherein the succinoyl groups are fully or partially neutralized to such extent with an ammonium salt of carbonic acid, formic acid or acetic acid such that the hydroxypropyl methyl cellulose acetate succinate is soluble in the aqueous composition, (B) from 0 to 7 weight percent of a non-polymeric plasticizer, based on the weight of the esterified cellulose ether, and (C) from 0 to 2 weight percent of a dispersant, based on the total weight of the hydroxypropyl methyl cellulose acetate succinate, wherein the weight of said hydroxypropyl methyl cellulose acetate succinate is at least 80 percent of the total polymer weight in the aqueous composition,

dipping molding pins into the aqueous composition,

forming a film on said molding pins by withdrawing said pins from said aqueous composition, and

drying the film on the molding pins.

10. The process of claim 9 which comprises the steps of

pre-heating molding pins to a temperature higher than the aqueous composition,

dipping the pre-heated molding pins into the aqueous composition,

forming a film on said molding pins by withdrawing said pins from said aqueous composition, and

drying the film on the molding pins.

11. The process of claim 9 which comprises the steps of

providing an aqueous composition which additionally comprises a gelling agent,

pre-heating the aqueous composition to a temperature higher than the molding pins,

dipping the molding pins into the pre-heated aqueous composition,

forming a film on said molding pins by withdrawing said pins from said aqueous composition, and

drying the film on the molding pins.

12. The process of any one of claims 9 to 11 wherein the weight of said at least one esterified cellulose ether is at least 85 percent of the total polymer weight in the capsule shell.

13. The process of any one of claims 9 to 12 wherein at least 75 mole percent of the succinoyl groups are neutralized with an ammonium salt of carbonic acid, formic acid or acetic acid.

14. The process of any one of claims 9 to 13 wherein the pH of the aqueous composition is at least 5.5.

15. The process of any one of claim 10 or 14 wherein the film on the molding pins is dried at a temperature of at least 60 °C to partially remove the ammonium salt of carbonic acid, formic acid or acetic acid or its decomposition products from the produced capsule shells.