



No. 08-007949- -00006-0000

Fecha: 2009-07-01 16:44:02 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 42

FORMULARIO UNICO DE OPOSICIÓN

①

OPOSICIÓN A:

- | | |
|--|--|
| ☒ Patente de Invención. | ☐ Marca Colectiva. |
| ☐ Patente de Modelo de Utilidad. | ☐ Marca de Certificación. |
| ☐ Diseño Industrial. | ☐ Lema Comercial. |
| ☐ Esquema de Trazado para Circuitos Integrados. | |
| ☐ Marcas de Productos o Servicios. | |

②

Numero del expediente: 08 007 949

Solicitante: PANACEA BIOTEC LIMITED

SOLICITUD

PUBLICADA

Apoderado: JUAN PABLO CADENA SARMIENTO

Título de la nueva creación o denominación del signo: COMPOSICIONES

FARMACEUTICAS DE LIBERACION MODIFICADA Y SUS PROCESOS

Gaceta: 602

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: PROCAPS S.A.	IDENTIFICACIÓN	
	Dirección: CALLE 80 No. 78b-201	C.C. ☐	NIT ☒
	Nacionalidad o Domicilio: COLOMBIA	C.E. ☐	Otro ☐
	Lugar de Constitución: BARRANQUILLA	Cual	
	Teléfono: 371 99 00 Fax: 373 08 18	Número 890.106.527-5	
	E-mail:		
REPRESENTANTE O APODERADO	Nombre: ELIANA ISAURA MORENO BOHORQUEZ	IDENTIFICACIÓN	
	Dirección: CARRERA 13 No. 119-95	C.C. ☒	NIT ☐
	Teléfono: (571)213 12 13 Fax: (571)612 19 79	C.E. ☐	Otro ☐
	E-mail: negocios@optimum-co.com	Cual	
		Número 51.975.664 TP.83823	

④ FUNDAMENTOS DE LA OPOSICIÓN:

Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor:

Justificación:

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la misma tal y como se demostrará en el capítulo "Fundamento de Hechos".

⑤ Comprobante de pago No. _____ Fecha _____

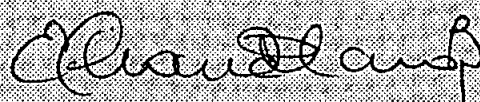
⑥ ANEXOS

- ☒ Comprobante de pago de la tasa.
- ☒ Poderes, si fuere el caso.
- ☒ Pruebas de los fundamentos de la oposición.
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso.
- ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE: ELIANA ISAURA MORENO BOHORQUEZ

FIRMA:



C.C. 51.975.664

TP. 83823



Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

Señora Jefe,
DIVISIÓN DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Referencia : Expediente N° 08007949
Asunto : Oposición a la solicitud de patente de Invención titulada
"COMPOSICIONES FARMACÉUTICAS DE
LIBERACIÓN MODIFICADA Y SUS PROCESOS"
Solicitante : PANACEA BIOTEC LTD
Opositora : PROCAPS S.A.

Publicada en la ~~Gaceta~~ de la Propiedad Industrial
N° 602 del 31 de Marzo de 2009

Yo, *ELIANA ISAURO MORENO BOHORQUEZ*, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad *PROCAPS S.A.* conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "COMPOSICIONES FARMACÉUTICAS DE LIBERACIÓN MODIFICADA Y SUS PROCESOS", cuyo titular es PANACEA BIOTEC LTD, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.



1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular oxacarbazepina, quetiapina, famciclovir, simvastatina, atorvastatina y/o tacrolimus. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

- 2.1. La solicitud objeto de la presente fue presentada el 28 de enero de 2008 reivindicando prioridad bajo la solicitud IN2005DE01681 del 2005-06-29; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 602 del 31 de Marzo de 2009, cuya publicación internacional corresponde a la WO2007000778 del 2007-01-04.
- 2.2. La solicitud colombiana 08007949 objeto de la presente oposición, se refiere a una composición farmacéutica de liberación modificada comprendiendo por lo menos uno o unos agente(s) activo(s) o sus sales, ésteres, profármacos, solvatos, hidratos o derivados de los mismos farmacéuticamente aceptables; un sistema polimérico en una cantidad menor de alrededor de 80% en peso/peso de la composición



comprendiendo por lo menos dos polímeros hinchables pH independientes y un polímero hidrófilo en una proporción de 1:20 hasta 20:1; opcionalmente otros excipientes farmacéuticamente aceptables; donde dicha composición proporciona un tiempo quieto inicial donde 5-15% o menos del ingrediente(s) activo(s) se libera seguido de una liberación sostenida de ingrediente(s) activo(s), de tal manera que la composición dispone de unas concentraciones terapéuticas de agente(s) activo(s) durante unos periodos de tiempo prolongados; donde el agente activo se selecciona entre un grupo que incluye inhibidores de la HMG CoA reductasa, inmunomoduladores, y sales, hidratos, polimorfos, ésteres y derivados de los mismos farmacéuticamente aceptables; donde el agente activo se selecciona de un grupo que comprende estatina, tacrolimus, oxcarbazepina, levetiracetam, quetiapina, tolterodina, famciclovir, y sales, hidratos, polimorfos, ésteres y derivados de los mismos farmacéuticamente aceptables; donde el diluyente se selecciona entre un grupo que comprende lactosa, celulosa, celulosa microcristalina, manitol, fosfato dicálcico y almidón pregelatinizado, empleados bien sea solos o combinados; y donde el polímero hidrófilo se selecciona entre el grupo que incluye gomas polisacáridas, ácido algínico, derivados del ácido algínico, arabinogalactana, pectina, tragacanto, escleroglucano, dextrano, amilosa, amilopectina, y dextrina.

- 2.3. En primera instancia, se debe advertir que las reivindicaciones también se refieren al uso y a un método de tratamiento y no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)"*, los usos no están contemplados como patentables; y, Artículo 20.- *"No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a"*



animales". Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente al uso y a un método de tratamiento no sería patentable.

2.4. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*. Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la patentabilidad de la presente solicitud:

- D1: EP0581676 publicada el 2 de febrero de 1994.

2.5. Ahora bien, el documento D1, particularmente en la descripción revela una formulación de liberación controlada que incluye un medicamento terapéuticamente activo, una matriz de goma heterodispersable, un diluyente farmacéuticamente aceptable, y una cantidad eficaz de surfactante farmacéuticamente aceptable y/o el agente humidificador para proporcionar un multi-fásico la liberación controlada de un medicamento terapéuticamente activo. y la anterioridad D1 también se relaciona con un método de preparar el mismo. Particularmente en la descripción y reivindicaciones de D1 se revela una forma farmacéutica que comprende dos polímeros hinchables pH independientes y por lo menos un polímero hidrófilo, agregando que comprende goma xantán. Así las cosas, como lo evidencia dicho documento D1, la presente solicitud no es novedosa pues lo revelado ya se encontraba en el estado de la técnica.

2.6. Por lo tanto, este documento objeto de oposición a la luz del documento D1 carece evidentemente de NOVEDAD.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 08007949 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

2.8. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.8.1. **CARECE DE NOVEDAD:** Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *“Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.”* A la fecha de prioridad, 29 de junio de 2005 ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1, una composición farmacéutica de liberación modificada comprendiendo por lo menos uno o unos agente(s) activo(s) o sus sales, ésteres, profármacos, solvatos, hidratos o derivados de los mismos farmacéuticamente aceptables; por lo menos dos polímeros hinchables pH independientes y un polímero hidrófilo y opcionalmente otros excipientes farmacéuticamente aceptables, sobre el cual busca protección en el capítulo reivindicatorio.

2.8.2. **CARENCIA DE APLICACIÓN INDUSTRIAL** La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*. La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, algunas cláusulas reclaman el método



terapéutico y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos y métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.

2.9. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial.”*. La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **“COMPOSICIONES FARMACÉUTICAS DE LIBERACIÓN MODIFICADA Y SUS PROCESOS”**, cuyo titular es PANACEA BIOTEC LTD, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 602 del 31 de Marzo de 2009.

3. PRUEBAS



Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- DI: EP0581676 publicada el 2 de febrero de 1994.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. En las demás normas concordantes.

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de PROCAPS S.A.
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:

- DI: EP0581676 publicada el 2 de febrero de 1994.



Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,

ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la-J.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA -: 09 - 47,641
FECHA : JULIO 1 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-007949- -00006-0000

Fecha: 2009-07-01 16:44:02 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 400 OPOSIOBSERVTER Folios: 42

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	104964941	11/06/2009	861,000.00
LAB. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	111824263	14/05/2009	861,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-04 PRESENTACION DE OBSERVACIONES	12 MARCAS Y LEMAS COMERCIALES	287,000.00
	TOTAL :	\$ 287,000.00

SON: DOSCIENTOS OCHENTA Y SIETE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____



PODER ESPECIAL

Yo, **WALTER TANAKA TATEKAWA**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 08 7949, titulada "**COMPOSICIONES FARMACEUTICAS DE LIBERACION MODIFICADA Y SUS PROCESOS**", cuyo titular es **PANACEA BIOTEC LTD.**, publicada en la gaceta No. 602 del 31 de marzo de 2009.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa y judicialmente todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Barranquilla (Colombia) a los 10 días del mes de Junio de 2009.

PROCAPS S.A.

C.C. N° 16'251.923

NIT: 890.106.527-5

Representante Legal

Acepto:

ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.

LA PRESENTE DILIGENCIA
SE PRACTICA A PETICION
DE INTERES

NOTARIA PRIMERA DEL CIRCULO
DE BARRANQUILLA
DILIGENCIA DE RECONOCIMIENTO

Compareció el Notario Primero de Barranquilla

Walter Tanaka Takakawa

CC 76251923 de Perú (valle)

Identificado con:
Declaro que es cierto el contenido del documento
anterior y suya la firma.
Barranquilla.

11 JUN. 2009

[Handwritten signature]



NOTARIA PRIMERA DE CHIA
PRESENTACION PERSONAL

Este memorial dirigido a Super Intendencia de Industria y Comercio.

fué presentado personalmente ante el suscrito notario por Eliana Isolina

Moiano Bohaguet.

Identificado C.C. 51975664. Bogotá.

T.P. de Abogado No. 83823

Chía. 01 JUL. 2009

[Handwritten signature]





EUROPEAN PATENT APPLICATION

Application number: **93401957.1**

Int. Cl.⁵: **A61K 9/20**

Date of filing: **27.07.93**

Priority: **30.07.92 US 922312**

Date of publication of application:
02.02.94 Bulletin 94/05

Designated Contracting States:
**AT BE CH DE DK ES FR GB GR IE IT LI LU MC
NL PT SE**

Applicant: **EDWARD MENDELL CO., INC.**
2981 Route 22
Patterson, NY 12563-9970 (US)

Inventor: **Balchwal, Anand R.**
5 Kendell Dr., Wappinger Fall, New York
N.Y. 12590 (US)
Inventor: **Stanforth, John N.**
High Trees, 170 Bloomfield Road
Bath, BA2 2AT (GB)

Representative: **Beauchamps, Georges et al**
Cabinet Z.Weinstein 20, avenue de Friedland
F-75008 Paris (FR)

Agglomerated hydrophilic complexes with multi-phasic release characteristics.

The present invention relates to a controlled release formulation which includes a therapeutically active medicament, a heterodisperse gum matrix, a pharmaceutically acceptable diluent, and an effective amount of a pharmaceutically acceptable surfactant and/or wetting agent to provide a multi-phasic controlled release of a therapeutically active medicament. The invention also relates to a method of preparing the same.

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The advantages of controlled release products are well known in the pharmaceutical field and include the ability to maintain a desired blood level of a medicament over a comparatively longer period of time while increasing patient compliance by reducing the number of administrations necessary to achieve the same. These advantages have been attained by a wide variety of methods.

For example, different hydrogels have been described for use in controlled release medicines, some of which are synthetic, but most of which are semi-synthetic or of natural origin. A few contain both synthetic and non-synthetic material. However, some of the systems require special process and production equipment, and in addition some of these systems are susceptible to variable drug release.

Oral controlled release delivery systems should ideally be adaptable so that release rates and profiles can be matched to physiological and chronotherapeutic requirements.

For the most part, the release rate of oral delivery systems have been classified according to the mechanism of release, such as zero order, first order, second order, pseudo-first order, etc., although many pharmaceutical compounds release medicament via other, complicated mechanisms.

First order mechanisms refer to situations where the reaction rate is dependent on the concentration of the reacting substance (and therefore is dependent on the first power of the reactant). In such mechanisms, the substance decomposes directly into one or more products.

Second order mechanisms occur when the experimentally determined rate of reaction is proportional to the concentration of each of two reactants, or to the second power of the concentration of one reactant.

Pseudo first order reactions are generally defined as second order reactions which behave as though they are governed by a first order mechanism, and occur, for example, when the amount of one reacting material is manipulated by being present in great excess or being maintained at a constant concentration as compared to the other substance. In such circumstances, the reaction rate is determined by the manipulated substance.

Zero order mechanisms refer to situations where the reaction rate is independent of the concentration of the reacting substance (and therefore is dependent on the zero power of the reactant), the limiting factor being something other than the concentration of the reacting substance (e.g., the medicament). The limiting factor in a zero order mechanism may be, for example, the solubility of the reacting substance or the light intensity in photochemical reactions.

As previously mentioned, however, many chemical reactions are not simple reactions of zero-, first-, or second-order, etc., and instead comprise a combination of two or more reactions.

Moreover, other factors may influence the reaction rate, including temperature, pH, food effect variability, ions and ionic strength dependency, viscosity dependency, corrosion/ erosion variability, content uniformity problems, flow and weight uniformity problems, carrying capacity and mechanical strength problems, hydrolysis, photochemical decomposition, interaction between components (such as interactions between the drug and other ingredients in the formulation, such as buffers, preservatives, etc.), the concentration of solvents of low dielectric constant (when the reaction involves oppositely charged ions), etc.

Generally, controlled release pharmaceutical formulations which provide zero order release characteristics have been considered most desirable because such a mechanism would theoretically provide constant drug levels. This is based on the assumption that the rate of elimination is determinative of the release rate of the medicament from the formulation, rather than the rate of absorption, etc.

However, for medicaments which are not very soluble in the stomach and where absorption is desired for a prolonged period of time, a bimodal release mechanism is considered to be desirable.

Bimodal or multi-phasic release is characterized by an initial high rate followed by a slower rate as the dosage form passes the upper portion of the small intestine where absorption is maximum and finally another higher rate as the dosage form passes into the further end of the intestine where absorption is less than before.

Bimodal release is considered to be advantageous for a number of reasons, including but not limited to the fact that bimodal release allows the formulator to compensate for changing absorption rates of the medicament in the gastrointestinal tract by providing a rapid onset of action (when the formulation is located in the stomach) and compensate for relatively slow absorption by providing a relatively rapid release rate (e.g., when the formulation is located in the large intestine).

Bimodal release formulations have been provided in a number of different manners to date.

For example, International Publication Number WO/87/00044 describes therapeutic formulations including certain hydroxypropylmethylcellulose which are said to have bimodal release characteristics.

See also, A.C. Shah et al., "Gel-Matrix Systems Exhibiting Bimodal Controlled Release For Oral Drug Delivery", *Journal of Controlled Release*, 9(1989), pp. 169-175, which also reports that certain "types" of hydroxypropylmethylcellulose ethers are found to display a bimodal drug release profile. P. Giunchedi et al., "Ketoprofen Pulsatile Absorption From 'Multiple Unit' Hydrophilic Matrices", *International Journal of Pharmaceutics*, 77(1991), pp. 177-181 described an extended release oral formulation of Ketoprofen comprising a multiple unit formulation constituted by four hydrophilic matrices of identical composition, each containing 50 mg of drug

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and prepared with hydroxypropylmethylcellulose (Methocel®) and placed in a gelatin capsule. Pulsatile plasma levels (2 peaks at 2nd and 8th hours after dosing) were said to be obtained, whereas in vitro tests resulted in a fairly constant drug release. U. Conte et al., "A New Ibuprofen Pulsed Release Oral Dosage Form", Drug Development And Industrial Pharmacy, 15(14-16), pp. 2583-2596 (1989) reported that a pulsed released pattern was obtained from a 3-layer tablet wherein two layers contained a dose of drug, and an intermediate layer acted as a control element (a mixture of hydroxypropylmethylcelluloses) separating the drug layers. K. A. Kahn et al., "Pharmaceutical Aspects And In-Vivo Performance Of Brufen Retard - An Ibuprofen SR Matrix Tablet", *Proc. Intern. Symp. Control. Rel. Bioact. Mater.*, 18(1991), Controlled Release Society, Inc., describes a formulation containing 800 mg of ibuprofen which is said to provide a bimodal release pattern, the release retarding agent utilized therein being xanthan gum.

The Assignee's U.S. Patent Nos. 4,994,276, 5,128,143, and 5,135,757, reported that a controlled release excipient which is comprised of synergistic heterodisperse polysaccharides (e.g., a heteropolysaccharide such as xanthan gum in combination with a polysaccharide gum capable of cross-linking with the heteropolysaccharide, such as locust bean gum) is capable of processing into oral solid dosage forms using either direct compression, following addition of drug and lubricant powder, conventional wet granulation, or a combination of the two. The release of the medicament from the formulations therein proceeded according to zero-order or first-order mechanisms.

The controlled release excipients disclosed in U.S. Patent Nos. 4,994,276, 5,128,143, and 5,135,757 are commercially available under the tradename *TIMERx™* from Edward Mendell Co., Inc., Patterson, N.Y., which is the assignee of the present invention.

It is therefore an object of the present invention to provide a formulation capable of providing multiphasic or bi-phasic controlled release of a therapeutically active medicament.

It is a further object of the present invention to provide a means of converting the mechanism of drug release provided by formulations comprising the excipient described in U.S. Patent Nos. 4,994,276, 5,128,143, and 5,135,757 from zero-order or first-order to a bi-phasic or multi-phasic mechanism.

It is a further object of the present invention to provide a controlled release multi-phasic excipient which can be mixed with a medicament and tableted to thereby provide a multi-phasic release of the active agent when the tablet is exposed to aqueous fluids, gastro-intestinal fluids, etc.

It is a further object of the present invention to provide a controlled release tablet which releases a therapeutically active medicament according to bi- or multi-phasic kinetics.

The above-mentioned objects and others are achieved by virtue of the present invention, which relates in part to a controlled release formulation comprising a controlled release excipient comprising a heterodisperse polysaccharide component and a saccharide component; a further component comprising a surfactant and/or a wetting agent; and a therapeutically active medicament. More particularly, it has now been surprisingly discovered that combination of pharmaceutically acceptable surfactants and/or wetting agents in the controlled release excipients disclosed in U.S. Patent Nos. 4,994,276, 5,128,143, and 5,135,757 can be used to cause changes in release patterns and produce bi- or multi-phasic profiles of the final formulation, possibly via further changes in cross-linking, gel strength and gel-sol transitions.

The present invention further relates to a controlled release oral solid dosage form, comprising a heterodisperse material comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum in the presence of aqueous solutions, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum being from about 1:3 to about 3:1; an inert pharmaceutical diluent selected from the group consisting of monosaccharide, a disaccharide, a polyhydric alcohol, and mixtures thereof, the ratio of said inert diluent to said heterodisperse material being from about 3:7 to about 7:3; and an effective amount of a pharmaceutically acceptable surfactant or wetting agent to provide a multi-phasic release of a therapeutically active agent. In a preferred embodiment, the formulation of the present invention comprises a tablet.

The present invention further relates to a method for preparing an oral solid dose formulation providing a multi-phasic release of a therapeutically active medicament when said dosage form is exposed to aqueous or gastric fluid. In the method, a heteropolysaccharide gum is mixed with a homopolysaccharide gum capable of crosslinking said heteropolysaccharide gum in the presence of aqueous solutions, such that the ratio of said heteropolysaccharide gum to said homopolysaccharide gum is from about 1:3 to about 3:1, to obtain a heterodisperse gum matrix. An inert pharmaceutical diluent is added to said heterodisperse gum matrix such that the ratio of the inert diluent to said heterodisperse gum matrix is from about 3:7 to about 7:3.

An effective amount of a medicament is added to render a therapeutic effect. An effective amount of a pharmaceutically acceptable surfactant or wetting agent is added to provide a multi-phasic release of said medicament when the dosage form is exposed to aqueous fluid.

The present invention is further related to a controlled release multi-phasic pharmaceutical excipient com-

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prising a heterodisperse gum matrix comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking the heteropolysaccharide gum in the presence of aqueous solutions, an inert pharmaceutical diluent selected from the group consisting of monosaccharide, a disaccharide, a polyhydric alcohol, and mixtures thereof, and from about 1 to about 20 percent by weight of a pharmaceutically acceptable surfactant or wetting agent. The ratio of heteropolysaccharide gum to homopolysaccharide gum, as well as the ratio of inert diluent to heterodisperse gum matrix in the controlled release multi-phasic excipient is as set forth above with respect to the final formulation.

The present invention further relates to a method for preparing a controlled release dosage form which exhibits multi-phasic release of a medicament incorporated therein, comprising preparing a controlled release multi-phasic excipient as described above, and incorporating a therapeutically effective amount of a medicament along with any pharmaceutically necessary additives such as a lubricant, and tableting the mixture.

The following drawings are illustrative of embodiments of the invention and are not meant to limit the scope of the invention as encompassed by the claims.

Fig. 1 is a graphical representation of the dissolution curve (expressed as percent dissolved over time) provided by the tablets of Example 2 (no surfactant);

Figs. 2-9 are graphical representations of the dissolution curves (expressed as percent dissolved over time) provided by the tablets of Examples 3-10 (surfactant(s) included);

Fig. 10 is a graphical representation of the dissolution curve (expressed as release rate over time) provided by the tablets of Example 2 (no surfactant);

Figs. 11-18 are graphical representations of the dissolution curves (expressed as release rate over time) provided by the tablets of Examples 3-10 (surfactant(s) included).

The term "heteropolysaccharide" as used in the present invention is defined as a water-soluble polysaccharide containing two or more kinds of sugar units, the heteropolysaccharide having a branched or helical configuration, and having excellent water-wicking properties and immense thickening properties. When admixed with an appropriate homopolysaccharide gum capable of cross-linking with the heteropolysaccharide in accordance with the present invention and exposed to an aqueous solution, gastric fluid, etc., the gums pack closely and many intermolecular attachments are formed which make the structure strong and provide a hydrophilic gum matrix having high gel strength.

Xanthan gum, the preferred heteropolysaccharide, is produced by microorganisms, for instance, by fermentation with the organism *xanthomonas campestris*. Most preferred is xanthan gum which is a high molecular weight ($>10^6$) heteropolysaccharide.

Other preferred heteropolysaccharides include derivatives of xanthan gum, such as deacylated xanthan gum, the carboxymethyl ether, and the propylene glycol ester.

The homopolysaccharide gums used in the present invention which are capable of cross-linking with the heteropolysaccharide include the galactomannans, i.e., polysaccharides which are composed solely of mannose and galactose.

A possible mechanism for the interaction between the galactomannan and the heteropolysaccharide involves the interaction between the helical regions of the heteropolysaccharide and the unsubstituted mannose regions of the galactomannan. Galactomannans which have higher proportions of unsubstituted mannose regions have been found to achieve more interaction with the heteropolysaccharide. Hence, locust bean gum, which has a higher ratio of mannose to the galactose, is especially preferred as compared to other galactomannans such as guar and hydroxypropyl guar.

The inert filler of the excipient preferably comprises a pharmaceutically acceptable saccharide, including a monosaccharide, a disaccharide, and/or mixtures thereof. Examples of suitable inert pharmaceutical fillers include sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol, mixtures thereof and the like. However, it is preferred that a soluble pharmaceutical filler such as lactose, dextrose, sucrose, or mixtures thereof be used.

The excipient of the present invention has uniform packing characteristics over a range of different particle size distributions and is capable of processing into tablets using either direct compression, following addition of drug and lubricant powder or conventional wet granulation.

The properties and characteristics of a specific excipient system prepared according to the present invention is dependent in part on the individual characteristics of the homo and heteropolysaccharide constituents, in terms of polymer solubility, glass transition temperatures etc., as well as on the synergism both between different homo and heteropolysaccharides and between the homo and heteropolysaccharides and the inert saccharide constituent(s) in modifying dissolution fluid-excipient interactions.

A homodisperse system of a heteropolysaccharide typically produces a highly ordered, helical or double helical molecular conformation which provides high viscosity without gel formation. In contrast, a homodisperse system of a homopolysaccharide typically is only slowly soluble and ungelled at low temperatures. Two steps

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which are generally required for gelation are the fast hydration of the macromolecules which comprise the hydrodisperse polysaccharide material and thereafter the association of the molecules to form gels. These two important properties which are necessary to achieve a slow release hydrophilic matrix are maximized in the present invention by the particular combination of materials. Prolonged exposure to the dissolution fluid promotes solubilization, which allows molecules to associate and undergo gelation, and may result in inter-macromolecular cross-linking in ribbon or helical "smooth" regions.

The heterodisperse excipient of the present invention comprises both hetero- and homo- polysaccharides which exhibit synergism. The heteropolysaccharide component acts to produce a faster gelation of the homopolysaccharide component and the homopolysaccharide acts to cross-link the normally free heteropolysaccharide helices. The resultant gel is faster-forming and more rigid. Heteropolysaccharides such as xanthan gum have excellent water wicking properties which provide fast hydration. On the other hand, the combination of xanthan gum with homopolysaccharide gums which are capable of cross-linking the rigid helical ordered structure of the xanthan gum (i.e. with unsubstituted mannose regions in the galactomannans) thereby act synergistically to provide a higher than expected viscosity (i.e., high gel strength) of the matrix. The combination of xanthan gum with locust bean gum with or without the other homopolysaccharide gums is especially preferred. However, the combination of any homopolysaccharide gums known to produce a synergistic effect when exposed to aqueous solutions may be used in accordance with the present invention. By synergistic effect, it is meant that the combination of two or more polysaccharide gums produce a higher viscosity and/or faster hydration than that which would be expected by either of the gums alone.

It is also possible that the type of synergism which is present with regard to the gum combination of the present invention could also occur between two homogeneous or two heteropolysaccharides.

In the present invention, it has been discovered that the controlled release properties of the tablets are optimized when the ratio of heteropolysaccharide gum to homopolysaccharide material is about 1:1, although heteropolysaccharide gum in an amount of from about 20 to about 80 percent or more by weight of the heterodisperse polysaccharide material provides an acceptable slow release product.

The mixed individual and synergistic viscosity modifying and gel-forming characteristics of the excipient system of the present invention produce a variety of possible release-controlling mechanisms in any given excipient system. Some of this behavior has been described, for example, by Frisch, "Sorption and Transport in Glassy Polymers - A Review", Polymer Eng. Sci. 20 (1980), pp. 2-13, Fan & Singh, "Controlled Release: A Quantitative Treatment", published by Springer Verlag, Berlin and London (1989), pp. 111-156; and Korsmeyer et al., "Mechanisms of Solute Release from Porous Hydrophilic Polymers", Int. J. Pharm. 15 (1983), pp. 25-35.

The rate-limiting step for the dissolution of tablets of the present invention is believed to be dependent to a large extent upon the penetration of water (or gastric fluid) into the tablet to dissolve the polysaccharides and the drug(s). It is further believed that the presence of the surfactant in the formulation allows faster initial penetration of fluid and an initial "burst" of drug release from the formulation. A second burst of drug release may then occur due to the further action of the surfactant, as the fluid front from one side of the tablet meets the fluid front on the opposite side. The above hypotheses are included for discussion purposes only and are not intended to limit the scope of the present invention.

The chemistry of certain of the ingredients comprising the excipients of the present invention such as xanthan gum is such that the excipients are considered to be self-buffering agents which are substantially insensitive to the solubility of the medicament and likewise insensitive to the pH changes along the length of the gastrointestinal tract.

The final formulation of the present invention comprises a sufficient amount of surfactant or wetting agent to provide a multi-phasic release of the drug(s). In certain preferred embodiments, the surfactant or wetting agent comprises from about 1 to about 10 of the final formulation, by weight. However, the upper limit of the amount of surfactant or wetting agent included in the formulations of the present invention may be higher than 10%; the limiting concern being that the final product should provide a pharmaceutically acceptable formulation. For example, in the case of tablets, the upper limit of the amount of surfactant or wetting agent included is determined by the production of a pharmaceutically acceptable tablet, e.g., a tablet which has a friability of less than about 1% and a hardness of 6-8 kg.

The surfactants which may be used in the present invention generally include pharmaceutically acceptable anionic surfactants, cationic surfactants, amphoteric (amphipathic/amphophilic) surfactants, and non-ionic surfactants. Suitable pharmaceutically acceptable anionic surfactants include, for example, monovalent alkyl carboxylates, acyl lactylates, alkyl ether carboxylates, N-acyl sarcosinates, polyvalent alkyl carbonates, N-acyl glutamates, fatty acid-polypeptide condensates, sulfuric acid esters, alkyl sulfates (including sodium lauryl sulfate (SLS)), ethoxylated alkyl sulfates, ester linked sulfonates (including docusate sodium or dioctyl sodium succinate (DSS)), alpha olefin sulfonates, and phosphated ethoxylated alcohols.

Suitable pharmaceutically acceptable cationic surfactants include, for example, monoalkyl quaternary am-

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monium salts, dialkyl quaternary ammonium compounds, amidoamines, and aminimides.

Suitable pharmaceutically acceptable amphoteric (amphipathic/amphophilic) surfactants, include, for example, N-substituted alkyl amides, N-alkyl betaines, sulfobetaines, and N-alkyl 6-aminopropionates.

Suitable pharmaceutically acceptable wetting (solubilizing) agents, include pharmaceutically acceptable non-ionic surfactants such as, for example, polyoxyethylene compounds, ethoxylated alcohols, ethoxylated esters, ethoxylated amides, polyoxypropylene compounds, propoxylated alcohols, ethoxylated/ propoxylated block polymers, and propoxylated esters, alkanolamides, amine oxides, fatty acid esters of polyhydric alcohols, ethylene glycol esters, diethylene glycol esters, propylene glycol esters, glyceryl esters, polyglyceryl fatty acid esters, sorbitan esters, sucrose esters, and glucose (dextrose) esters.

Other suitable pharmaceutically acceptable wetting (solubilizing) agents include acacia, benzalkonium chloride, cholesterol, emulsifying wax, docusate sodium, glyceryl monostearate, lanolin alcohols, lecithin, poloxamer, poloxyethylene castor oil derivatives, poloxyethylene sorbitan fatty acid esters, poloxyethylene stearates, sodium lauryl sulfates, sorbitan esters, stearic acid, and triethanolamine.

Mixed surfactant/wetting agent systems are also useful in conjunction with the present invention. Examples of such mixed systems include, for example, sodium lauryl sulfate/polyethylene glycol (PEG) 6000 and sodium lauryl sulfate/PEG 6000/stearic acid.

The change in the mechanism of drug release from the excipients of the present invention from monophasic to bi- or multi-phasic release may further be altered or enhanced by process changes during the manufacture of the excipient, or by formulation alteration. Further modifications in bi- or multi-phasic release profiles can be effected by addition of synergism-modifying components. For example, this can occur as a result of selection of interacting polysaccharides in which the synergism is potentiated by ionic strength of pH. In addition, the saccharide component may also be changed, although the effect of different saccharides on drug release is much smaller than that of different polysaccharides, but may still be important in achieving fine control of drug release. The dissolution profiles of a tablet formulation containing an excipient system with a given heterodisperse polysaccharide component can also be modified by alteration of the ratios of heteropolysaccharide to homopolysaccharide. Alternatively or additionally, the drug release profiles can also be controlled by changing the ratio of heterodisperse polysaccharides to saccharides in the excipient system.

Delays in the onset of mono or multi-phasic release, which may be desirable in order to optimize colonic absorption, can be produced through changes in core formulation or by application of tablet coatings to further modify drug release patterns.

In addition to the inclusion of surfactants/wetting agents, the drug release mechanism of the controlled release excipient of the present invention may be further manipulated by altering the process utilized for tableting i.e. direct compression v/s wet granulation v/s combination of both, and via changes in the formulation itself (i.e., changes in the ratio of heterodisperse polysaccharide to inert saccharide, etc.).

An effective amount of any generally accepted pharmaceutical lubricant, including the calcium or magnesium soaps may be added to the above-mentioned ingredients of the excipient be added at the time the medicament is added, or in any event prior to compression into a said dosage form. Most preferred is magnesium stearate in any amount of about 0.5-3% by weight of the solid dosage form.

The combination of the heterodisperse polysaccharide material (i.e., a mixture of xanthan gum and locust bean gum) with the inert saccharide diluent provides a ready-to-use product in which a formulator need only blend the desired active medicament and an optional lubricant with the excipient and then compress the mixture to form slow release tablets. The excipient may comprise a physical admix of the gums along with a soluble excipient such as compressible sucrose, lactose or dextrose, although it is preferred to granulate or agglomerate the gums with plain (i.e., crystalline) sucrose, lactose, dextrose, etc., to form an excipient. The granulate form has certain advantages including the fact that it can be optimized for flow and compressibility; it can be tableted, formulated in a capsule, extruded and spheronized with an active medicament to form pellets, etc.

The pharmaceutical excipients prepared in accordance with the present invention may be prepared according to any agglomeration technique to yield an acceptable excipient product. In wet granulation techniques, the desired amounts of the heteropolysaccharide gum, the homopolysaccharide gum, and the inert saccharide diluent are mixed together and thereafter a moistening agent such as water, propylene glycol, glycerol, alcohol or the like is added to prepare a moistened mass. Next, the moistened mass is dried. The dried mass is then milled with conventional equipment into granules. Therefore, the excipient product is ready to use.

The excipient is free-flowing and directly compressible. Accordingly, the excipient may be mixed in the desired proportion with a therapeutically active medicament and optional lubricant (dry granulation). Alternatively, all or part of the excipient may be subjected to a wet granulation with the active ingredient and thereafter tableted. The complete mixture, in an amount sufficient to make a uniform batch of tablets, is then subjected to tableting in a conventional production scale tableting machine at normal compression pressure, i.e. about 2000-

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1600 lbs/sq in. However, the mixture should not be compressed to such a degree that there is subsequent difficulty in its hydration when exposed to gastric fluid.

One of the limitations of direct compression as a method of tablet manufacture is the size of the tablet. If the amount of active is high a pharmaceutical formulator may choose to wet granulate the active with other excipients to attain an acceptable tablet size with the correct compact strength. Usually the amount of filler/binder or excipients needed in wet granulation is less than that in direct compression since the process of wet granulation contributes to some extent toward the desired physical properties of a tablet.

The average tablet size for round tablets is preferably about 500 mg to 750 mg and for capsule-shaped tablets about 750 mg to 1000 mg. The average particle size of the granulated excipient of the present invention ranges from about 50 microns to about 400 microns and preferably from about 185 microns to about 265 microns. The particle size of the granulation is not narrowly critical, the important parameter being that the average particle size of the granules, must permit the formation of a directly compressible excipient which forms pharmaceutically acceptable tablets. The desired tap and bulk densities of the granulation of the present invention are normally between from about 0.3 to about 0.8 g/ml, with an average density of from about 0.5 to about 0.7 g/ml. For best results, the tablets formed from the granulations of the present invention are from about 6 to about 8 kg hardness. The average flow of the granulations prepared in accordance with the present invention are from about 25 to about 40 g/sec. Tablets compacted using an instrumented rotary tablet machine have been found to possess strength profiles which are largely independent of the inert saccharide component. Scanning electron photomicrographs of largely tablet surfaces have provided qualitative evidence of extensive plastic deformation on compaction, both at the tablet surface and across the fracture surface, and also show evidence of surface pores through which initial solvent ingress and solution egress may occur.

A wide variety of therapeutically active agents can be used in conjunction with the present invention. The therapeutically active agents (e.g., pharmaceutical agents) which may be used in the compositions of the present invention include both water soluble and water insoluble drugs. Examples of such therapeutically active agents include antihistamines (e.g., dimenhydrinate, diphenhydramine, chlorpheniramine and dexchlorpheniramine maleate), analgesics (e.g., aspirin, codeine, morphine, dihydromorphone, oxycodone, etc.), anti-inflammatory agents (e.g., naproxyn, diclofenac, indomethacin, ibuprofen, acetaminophen, aspirin, sulindac), gastro-intestinals and anti-emetics (e.g., metoclopramide), anti-epileptics (e.g., phenytoin, meprobamate and nitrazepam), vasodilators (e.g., nifedipine, papaverine, diltiazem and nicardipine), anti-tussive agents and expectorants (e.g., codeine phosphate), anti-asthmatics (e.g., theophylline), anti-spasmodics (e.g., atropine, scopolamine), hormones (e.g., insulin, heparin), diuretics (e.g., ethacrynic acid, bendrofluazide), anti-hypotensives (e.g., propranolol, clonidine), broncho-dilators (e.g., albuterol), anti-inflammatory steroids (e.g., hydrocortisone, triamcinolone, prednisone), antibiotics (e.g., tetracycline), antihemorrhoidals, hypnotics, psychotropics, antidiarrheals, mucolytics, sedatives, decongestants, laxatives, antacids, vitamins, stimulants (including appetite suppressants such as phenylpropanolamine). The above list is not meant to be exclusive.

The ratio of medicament to the heterodisperse polysaccharide is based in part upon the relatively solubility of the medicament and the desired rate of release.

A computer aided pharmacokinetic model can be used to predict likely in vivo drug blood levels from condition-independent in-vitro drug profiles.

The following examples illustrate various aspects of the present invention. They are not to be construed to limit the claims in any manner whatsoever.

EXAMPLE 1 (Prior Art)

Tablets containing appropriate amounts of propranolol hydrochloride together with a homodisperse polysaccharide (locust bean gum) and a heterodisperse polysaccharide controlled release excipient (xanthan gum/locust bean gum in a 1:1 ratio), inert pharmaceutical diluent (saccharide component), and 1% magnesium stearate are prepared either using direct compression or following wet granulation in a high speed mixer processor (Baker Perkins Ltd., Stoke on Trent, U.K.), as described in U.S. Patent Nos. 4,994,276, 5,128,143 and 5,135,757. Tablets are compacted to approximately 14kP crushing force and in-vitro testing is carried out using an automated dissolution apparatus and the U.S.P. paddle method with a stirring speed of 50 rev min⁻¹. All of the dissolution studies are carried out in distilled water.

In-vitro release profiles for propranolol hydrochloride tablets are found to have first order profiles using a homodisperse polysaccharide whereas a heterodisperse polysaccharide excipient provides a zero order release profile.

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EXAMPLE 2 - Prior Art

A slow release excipient is prepared by combining xanthan gum, locust bean gum, and dextrose in the amounts set forth in Table 1 below, and dry blending (Baker Perkin [Machine # 5407], blender settings (chopper = 1000rpm, impeller = 800 rpm)) the mixture for 2 minutes.

Table 1 - Excipient Granulation

Ingredient	%	g/1000g
Xanthan gum	25.0	225.0
Locust bean gum	25.0	225.0
Dextrose	50.0	450.0
Total	100.0%	900g

Thereafter, water (115 ml) is added slowly and the mixture is blended for 1.5 minutes. The mixture is then dried overnight at 50°C in an oven. Next, the mixture is screened through a 20 mesh screen, with particles larger than 20 mesh being discarded.

Next, 354.5 grams of the granulated slow release excipient and 35.5 grams of phenylpropanolamine HCl are added into a 2 quart V-blender and blended for 10 minutes. Next, 8 grams of Lubritab™ is added, and the mixture is blended for 5 minutes. Thereafter, 2.0 grams of magnesium stearate is added and the mixture is blended for 5 minutes. Finally, the mixture is tableted to provide tablets of approximately 846 mg and approximately 5-7 Kp. Further information concerning Example 2 is set forth in Table 2 below:

Table 2 - Example 2

Ingredient	mg/tablet	%	g/400g
Excipient	750.0	88.6	354.5
Phenylpropanolamine	75.0	8.9	35.5
Lubritab	17.0	2.0	8.0
Magnesium stearate	4.0	0.5	2.0
Total	846mg/tab	100%	400g

EXAMPLES 3 - 10

In Example 3, the slow release granulation is prepared in similar fashion to Example 2, except that after the gums and dextrose are combined, 130 ml of water is added, and the mixture is dried in an aeromatic fluid bed dryer for 45 minutes at 70°C (Type Strea-I). The ingredients of the slow release granulation of Example 3 are set forth in Table 3 below:

Table 3 - Excipient Granulation

Ingredient	%	g/1000g
Xanthan gum	25.0	250.0
Locust bean gum	25.0	250.0
Dextrose	50.0	500.0
Total	100.0%	1000g

Thereafter, 336.4 grams of the granulated slow release excipient and 33.6 grams of phenylpropanolamine

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HCl are added into a 2 quart V-blender and blended for 10 minutes. Next, 20.0 grams of surfactant (sodium lauryl sulfate) and 8 grams of lubritab™ are added, and the mixture is blended for 5 minutes. Thereafter, 2.0 grams of magnesium stearate is added and the mixture is blended for 5 minutes. Finally, the mixture is tableted to provide tablets of approximately 892 mg and approximately 5-7 Kp. Further information concerning Example 3 is set forth in Table 4 below:

Table 4 - Example 3

<u>Ingredient</u>	<u>mg/tablet</u>	<u>%</u>	<u>g/400g</u>
Excipient	750/0	84.1	336.4
Phenylpropanolamine	75.0	8.4	33.6
*Surfactant (SLS)	44.7	5.0	20.0
Lubritab	17.8	2.0	8.0
<u>Magnesium stearate</u>	<u>4.5</u>	<u>0.5</u>	<u>2.0</u>
Total	892mg/tab	100.0%	400g

Examples 4-10 are prepared in similar fashion to Example 3. In each of Examples 4-10, the formulations are dry blended with a 1:5 drug:gum ratio. The percent of gum in the xanthan gum/locust bean gum/dextrose mixture in each formulation is 50%. Each formulation contains 75 mg phenylpropanolamine HCl and 750 mg of the slow release excipient granulation, and this mixture is blended in a 2 quart v-blender for 10 minutes. Then, 2% lubritab is added along with the surfactant, and blended for 5 minutes. The surfactant used is sodium lauryl sulfate and/or docusate sodium. Finally, 0.5% of magnesium stearate is added and the mixture is blended for 5 minutes, and tableted to the specified tablet weight. The tablet weights, amount (percentage) and type of surfactants used in Examples 3-10 are set forth in Table 5 below:

TABLE 5

<u>Example</u>	<u>Surfactant*</u>	<u>Granulation % Surfactant</u>	<u>Tablet wt. (mg)</u>
Ex. 3	SLS	2	863.9
Ex. 4	SLS	5	891.9
Ex. 5	SLS	10	942.9
Ex. 6	DSS	2	863.9
Ex. 7	DSS	5	891.9
Ex. 8	DSS	10	942.9
Ex. 9	SLS + DSS	1 + 1	863.9
Ex. 10	SLS + DSS	2 + 2	882.4

*SLS refers to sodium lauryl sulfate, and DSS refers to docusate sodium.

EXAMPLES 11 - 12

DISSOLUTION TESTS - PERCENT DISSOLVED OVER TIME AND RELEASE RATE

Next, dissolution studies are conducted for the tablets of Examples 2-10 in order to determine the percent dissolved of drug over time, as well as the release rate of the drug (phenylpropanolamine HCl). The dissolution tests were conducted in a DI water medium having a volume of 1000 mL by the paddle method. The mixer rotation is 100 rpm, the height is 2.5 cm, the temperature is 37° C, and the wavelength used is 210 nm. The calibration factor is determined according to the following equation:

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$$\text{calibration factor} = \frac{\text{concentration of standard} \cdot 100}{\text{concentration of sample} \cdot \text{absorbance of std}}$$

The percent of the drug dissolved is then determined according to the following equation:

$$\% \text{ active dissolved} = \text{calibration factor} \cdot \text{absorbance of sample}$$

5 The dissolution and release rate data for Examples 2-10 is based on a 6 tablet dissolution study. Figs. 1-9 are graphical representations of the dissolution curves (expressed as percent dissolved over time) provided by the tablets of Example 2 (no surfactant added) and Examples 3-10 (surfactant(s) included), respectively. Figs. 10-18 are graphical representations of the dissolution curves (expressed as release rate over time) provided by the tablets of Example 2 (no surfactant added) and Examples 3-10 (surfactant(s) included). As is readily apparent from the results, the formulations of Examples 3-10 provide a multi-phasic release of phenylpropanolamine HCl.

EXAMPLES 13-1615 Preparation of Controlled Release Excipient For Multiphasic Dosage Forms

Controlled release excipients for multiphasic dosage forms according to the present application are prepared as follows.

20 In Examples 13-14, 250 grams of xanthan gum, 250 grams of locust bean gum, 50 grams of surfactant and 450 grams of dextrose are blended for two minutes in a mixer (Baker Perkins blender), blender setting (chopper = 1,000 rpm, Impeller = 800 rpm).

In Examples 15-16, 100 grams of surfactant and 400 grams of dextrose are blended with 250 grams of xanthan gum and 250 grams of locust bean gum for two minutes.

25 The surfactant in Examples 13 and 16 is sodium lauryl sulfate (SLS), while in Examples 14 and 15, the surfactant is docusate sodium succinate (DSS).

Thereafter, about 112 ml of water is slowly added to the mixtures and then blended for an additional 1.5 minutes. The mixed product, which is now in the form of granules, is removed from the blender and dried in an aeromatic fluid bed dryer (type: Strea-1) for 30 minutes at a temperature of 70°C. The dried granulation is then passed through a 20 mesh screen.

30 In Examples 13-14, the final composition of the mixture is 25.0% xanthan gum, 25.0% locust bean gum, 5.0% surfactant and 45.0% dextrose by weight. In Examples 15-16, the final composition of the mixture is 25.0% xanthan gum, 25.0% locust bean gum, 10.0% surfactant and 40.0% dextrose by weight.

The product of Examples 13-16 is now ready to be used as a controlled release excipient for multiphasic dosage forms, and may now be admixed with one or more active ingredients and any other pharmaceutically necessary additives, and tableted.

35 The weight and percentages of the ingredients for the controlled release excipients used in Examples 13-16 are set forth in Tables 12-15 below:

TABLE 12

EXAMPLE 13		
Ingredient	g/1000g	%
Xanthan Gum	250.0	25.0
Locust Bean Gum	250.0	25.0
Surfactant (TYPE)	50.0 (SLS)	5.0
Dextrose	450.0	45.0
TOTAL	1000g	100%

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TABLE 13

EXAMPLE 14		
Ingredient	g/1000g	%
Xanthan Gum	250.0	25.0
Locust Bean Gum	250.0	25.0
Surfactant (TYPE)	50.0 (DSS)	5.0
Dextrose	450.0	45.0
TOTAL	1000g	100%

TABLE 14

EXAMPLE 15		
Ingredient	g/1000g	%
Xanthan Gum	250.0	25.0
Locust Bean Gum	250.0	25.0
Surfactant (TYPE)	100.0 (DSS)	10.0
Dextrose	400.0	40.0
TOTAL	1000g	100%

TABLE 15

EXAMPLE 20		
Ingredient	g/1000g	%
Xanthan Gum	250.0	25.0
Locust Bean Gum	250.0	25.0
Surfactant (TYPE)	100.0 (SLS)	10.0
Dextrose	400.0	40.0
TOTAL	1000g	100%

EXAMPLES 17-21Preparation of Controlled Release Tablets

Controlled release tablets according to the present invention are prepared as follows.

In Examples 17-19, 278.43 grams of the excipient of the present invention is first blended with 27.82 grams of phenylpropanolamine HCl for 10 minutes in a 2-quart V-blender.

The excipient of Example 13 is used in Example 17, the excipient of Example 14 is used in Example 18 and the excipient of Example 16 is used in Example 19.

After the initial blending of the mixtures in Examples 17-19, 7 grams of Lubritab™ and 35 grams of MCC-50M are blended with each mixture for an additional 5 minutes. Thereafter, 1.75 grams of magnesium stearate is added to the mixtures of Examples 17-19, and then blended for another 5 minutes.

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Finally, the mixtures in Examples 17-19 are tableted to provide tablets of approximately 942.8 mg and approximately 2.0 Kp.

In Examples 17-19, the final composition of the mixture is 79.5% excipient, 7.95% phenylpropanolamine HCl, 2.0% Lubritab™, 10.0% MCC-50M (microcrystalline cellulose) and 0.5% of magnesium stearate by weight.

Further information concerning Examples 17-19 are set forth in Tables 16-18 below:

TABLE 16

EXAMPLE 17

<u>Ingredient</u>	<u>mg/tab</u>	<u>%</u>	<u>g/350g</u>
Excipient	750.0	79.55	278.43
PPA	750.0	7.95	27.82
Lubritab	18.86	2.00	7.00
MCC-50M	94.28	10.00	35.00
<u>Mag. Stear.</u>	<u>4.71</u>	<u>0.50</u>	<u>1.75</u>
TOTAL	942.85	100%	350g

PPA HCl = Phenylpropanolamine Hydrogen Chloride
Mag. Stear. = Magnesium Stearate

TABLE 17

EXAMPLE 18

<u>Ingredient</u>	<u>mg/tab</u>	<u>%</u>	<u>g/350g</u>
Excipient	750.0	79.55	278.43
PPA	75.0	7.95	27.82
Lubritab	18.86	2.00	7.00
MCC-50M	94.28	10.00	35.00
<u>Mag. Stear.</u>	<u>4.71</u>	<u>0.50</u>	<u>1.75</u>
TOTAL	942.85	100%	350g

PPA HCl = Phenylpropanolamine Hydrogen Chloride
Mag. Stear. = Magnesium Stearate

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TABLE 16**EXAMPLE 19**

<u>Ingredient</u>	<u>mg/tab</u>	<u>%</u>	<u>g/350g</u>
Excipient	750.0	79.55	278.43
PPA	75.0	7.95	27.82
Lubritab	18.86	2.00	7.00
MCC-50M	94.28	10.00	35.00
<u>Mag. Stear.</u>	<u>4.71</u>	<u>0.50</u>	<u>1.75</u>
TOTAL	942.85	100%	350g

PPA HCl = Phenylpropanolamine Hydrogen Chloride

Mag. Stear. = Magnesium Stearate

In Example 20, 292.50 grams of the excipient of Example 13 are blended with 48.75 grams of phenylpropanolamine HCl for 10 minutes in a 2-quart V-blender.

After the initial blending, 7 grams of Lubritab™ and 1.75 grams of magnesium stearate are added to the mixture which is then blended for another 5 minutes.

Finally, the mixture is tableted to provide tablets of approximately 538.46 mg and approximately 20 Kp.

In Example 20, the final composition of the mixture is 83.57% excipient of Example 13, 13.93% phenylpropanolamine HCl, 2.0% Lubritab™ and 0.5% magnesium stearate by weight. Further information concerning Example 20 is set forth in Table 19 below:

TABLE 19**EXAMPLE 20**

<u>Ingredient</u>	<u>mg/tab</u>	<u>%</u>	<u>g/350g</u>
Excipient	450.0	83.57	292.50
PPA HCl	75.0	13.93	48.75
Lubritab	10.77	2.00	7.00
<u>Mag. Stear.</u>	<u>2.69</u>	<u>0.50</u>	<u>1.75</u>
TOTAL	538.46	100%	350g

PPA HCl = Phenylpropanolamine Hydrogen Chloride

Mag. Stear. = Magnesium Stearate

In Example 21, 487.5 grams of the excipient of Example 15 is first blended with 48.75 grams of phenylpropanolamine HCl for 10 minutes in a 2-quart V-blender.

After the initial blending, 11 grams of Lubritab™ and 2.75 grams of magnesium stearate is added to the mixture and blended for an additional 5 minutes.

The mixture is then tableted to provide tablets of approximately 846.15 mg and approximately 2.0 kg.

In Example 21, the final composition of the mixture is 88.64% excipient of Example 15, 8.86% phenylpropanolamine HCl, 2.0% Lubritab™ and 0.5% magnesium stearate by weight. Further information concerning Example 21 is set forth in Table 20 below:

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TABLE 20**EXAMPLE 21**

	<u>Ingredient</u>	<u>mg/tab</u>	<u>%</u>	<u>G/350g</u>
5	Excipient	750.0	88.64	487.50
	PPA HCl	75.0	8.86	48.75
	Lubritab™	16.92	2.00	11.00
10	<u>Mag. Stear.</u>	<u>4.23</u>	<u>0.50</u>	<u>2.75</u>
	TOTAL	846.15	100%	550g

PPA HCl = Phenylpropanolamine Hydrogen Chloride

Mag. Stear. = Magnesium Stearate

The examples provided above are not meant to be exclusive. Many other variations of the present invention would be obvious to those skilled in the art, and are contemplated to be within the scope of the appended claims.

Claims

1. A controlled-release oral solid dosage form for absorption of an active medicament in the gastro-intestinal tract, comprising
 - an effective amount of a medicament to render a therapeutic effect;
 - a controlled release excipient comprising a heterodisperse gum matrix comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum in the presence of aqueous solutions, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum being from about 1:3 to about 3:1; and
 - an inert pharmaceutical diluent selected from the group consisting of monosaccharide, a disaccharide, a polyhydric alcohol, and mixtures thereof, the ratio of said inert diluent to said heterodisperse gum matrix being from about 3:7 to about 7:3;
 - and an effective amount of a pharmaceutically acceptable surfactant or wetting agent to provide a multi-phasic release of said medicament when said dosage form is exposed to aqueous fluid.
2. A controlled release oral solid dosage form, comprising
 - (i) a heterodisperse gum matrix comprising xanthan and locust bean gum in a ratio of about 1:1;
 - (ii) an inert pharmaceutically acceptable diluent selected from the group consisting of a monosaccharide, a disaccharide, a polyhydric alcohol, and mixtures thereof, the ratio of said diluent to said heterodisperse gum matrix being from about 3:7 to about 7:3;
 - (iii) an effective amount of a medicament to render a therapeutic effect; and
 - (iv) from about 1 to about 10 by weight of a pharmaceutically acceptable surfactant or wetting agent, said surfactant or wetting agent being selected from the group consisting of anionic surfactants, cationic surfactants, amphoteric surfactants, non-ionic surfactants, and mixtures of any of the foregoing, said medicament having a multi-phasic release of said medicament when exposed to aqueous fluid.
3. The oral solid dosage form of claims 1 or 2, wherein said a heteropolysaccharide gum comprises xanthan gum and said homopolysaccharide gum comprises locust bean gum.
4. The oral solid dosage form of claim 1, wherein said surfactant or wetting agent comprises from about 1 to about 10 percent of said formulation, by weight.
5. The oral solid dosage form of claims 1 or 2, which releases said medicament according to bi-phasic kinetics.
6. The oral solid dosage form of claims 1 or 2, wherein the ratio of said inert diluent to said heterodisperse gum matrix is about 1:1.

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7. The oral solid dosage form of claims 1 or 2, wherein said surfactant or wetting agent is selected from the group consisting of pharmaceutically acceptable anionic surfactants, cationic surfactants, amphoteric (amphipathic/amphophilic) surfactants, non-ionic surfactants, and mixtures of any of the foregoing.
- 5 8. The oral solid dosage form of claim 7, wherein said surfactant or wetting agent is an anionic surfactant selected from the group consisting of monovalent alkyl carboxylates, acyl lactylates, alkyl ether carboxylates, N-acyl sarcosinates, polyvalent alkyl carbonates, N-acyl glutamates, fatty acid-polypeptide condensates, sulfuric acid esters, alkyl sulfates (including sodium lauryl sulfate (SLS)), ethoxylated alkyl sulfates, ester linked sulfonates (including docusate sodium or dioctyl sodium succinate (DSS)), alpha olefin sulfonates, phosphated ethoxylated alcohols; a cationic surfactant selected from the group consisting of monoalkyl quaternary ammonium salts, dialkyl quaternary ammonium compounds, amidoamines, aminimides; an amphoteric surfactant selected from the group consisting of N-substituted alkyl amides, N-alkyl betaines, sulfobetaines, N-alkyl 6-aminopropionates; a non-ionic surfactant selected from the group consisting of polyoxyethylene compounds, ethoxylated alcohols, ethoxylated esters, ethoxylated amides, polyoxypropylene compounds, propoxylated alcohols, ethoxylated/propoxylated block polymers, propoxylated esters, alkanolamides, amine oxides, fatty acid esters of polyhydric alcohols, ethylene glycol esters, diethylene glycol esters, propylene glycol esters, glyceryl esters, polyglyceryl fatty acid esters, sorbitan esters, sucrose esters, glucose (dextrose) esters; or mixtures of any of the foregoing.
- 10 9. The oral solid dosage form of claim 1, wherein said surfactant or wetting agent is a wetting agent selected from the group consisting of acacia, benzalkonium chloride, cholesterol, emulsifying wax, docusate sodium, glyceryl monostearate, lanolin alcohols, lecithin, poloxamer, poloxyethylene castor oil derivatives, poloxyethylene sorbitan fatty acid esters, poloxyethylene stearates, sodium lauryl sulfates, sorbitan esters, stearic acid, triethanolamine, and mixtures of any of the foregoing.
- 15 10. The oral solid dosage form of claim 7, wherein said surfactant or wetting agent is selected from the group consisting of sodium lauryl sulfate/polyethylene glycol (PEG) 6000 and sodium lauryl sulfate/PEG 6000/stearic acid.
- 20 11. The oral solid dosage form of claim 7, wherein said surfactant or wetting agent comprises sodium lauryl sulfate, docusate sodium, or a combination of sodium lauryl sulfate and docusate sodium.
- 25 12. The oral solid dosage form of claims 1-11, wherein said therapeutically active medicament is selected from the group consisting of antihistamines, analgesics, anti-inflammatory agents, gastro-intestinals, anti-emetics, anti-epileptics, vasodilators, anti-tussive agents, expectorants, anti-asthmatics, anti-spasmodics, hormones, diuretics, anti-hypotensives, bronchodilators, anti-inflammatory steroids, antibiotics, antihemorrhoidals, hypnotics, psychotropics, antidiarrheals, mucolytics, sedatives, decongestants, laxatives, antacids, vitamins, and stimulants.
- 30 13. The oral solid dosage form of claims 1-12 which is a tablet.
- 35 14. A method of treating a human patient, comprising orally administering to the patient the oral solid dosage form of claims 1-13.
- 40 15. A method for preparing an oral solid dose formulation providing a multi-phasic release of a therapeutically active medicament when said dosage form is exposed to aqueous or gastric fluid, comprising
 - 45 mixing a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum in the presence of aqueous solutions, such that the ratio of said heteropolysaccharide gum to said homopolysaccharide gum is from about 1:3 to about 3:1, to obtain a heterodisperse gum matrix;
 - 50 adding an inert pharmaceutical diluent selected from the group consisting of monosaccharide, a disaccharide, a polyhydric alcohol, and mixtures thereof, to said heterodisperse gum matrix such that the ratio of said inert diluent to said heterodisperse gum matrix is from about 3:7 to about 7:3;
 - adding an effective amount of a medicament to render a therapeutic effect, and
 - adding an effective amount of a pharmaceutically acceptable surfactant or wetting agent to provide
 - 55 a multi-phasic release of said medicament when said dosage form is exposed to aqueous fluid.
16. A method for preparing a controlled release dosage form which exhibits multi-phasic release of a medicament incorporated therein, comprising

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5 preparing a controlled release multi-phasic excipient by mixing (i) a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum in the presence of aqueous solutions, such that the ratio of said heteropolysaccharide gum to said homopolysaccharide gum is from about 1:3 to about 3:1, with (ii) an inert pharmaceutical diluent selected from the group consisting of monosaccharide, a disaccharide, a polyhydric alcohol, and mixtures thereof, the ratio of said inert diluent to said heterodisperse gum matrix being from about 3:7 to about 7:3; and (iii) a pharmaceutically acceptable surfactant or wetting agent;

10 adding a therapeutically effective amount of a medicament to said controlled release multi-phasic excipient; and tableting said mixture of controlled release multi-phasic excipient and medicament, said surfactant or wetting agent being included in an amount sufficient to provide a multi-phasic release of said medicament from said tablet when said tablet is exposed to aqueous fluids.

17. The method of claims 15 or 16, further comprising compressing the final mixture into tablets.

15 18. The method of claims 15 or 16, wherein from about 1 to about 10 percent by weight surfactant or wetting agent is added.

19. The method of claims 15 or 16, wherein said surfactant or wetting agent is selected from the group consisting of anionic surfactants, cationic surfactants, amphoteric surfactants, non-ionic surfactants, and mixtures of any of the foregoing.

20 20. A controlled release multi-phasic pharmaceutical excipient, comprising:

25 a heterodisperse gum matrix comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum in the presence of aqueous solutions, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum being from about 1:3 to about 3:1;

an inert pharmaceutical diluent selected from the group consisting of monosaccharide, a disaccharide, a polyhydric alcohol, and mixtures thereof, the ratio of said inert diluent to said heterodisperse gum matrix being from about 3:7 to about 7:3; and

30 from about 1 to about 20 percent by weight of a pharmaceutically acceptable surfactant or wetting agent.

21. The pharmaceutical excipient of claim 20, wherein said heteropolysaccharide gum comprises xanthan gum and said homopolysaccharide gum comprises locust bean gum, and said inert diluent comprises lactose, dextrose, sucrose, fructose, microcrystalline cellulose, xylitol, sorbitol or mixtures thereof.

35 22. The pharmaceutical excipient of claim 20, wherein said surfactant or wetting agent comprises from about 1 to about 10 percent of said formulation by weight.

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FIGURE 1

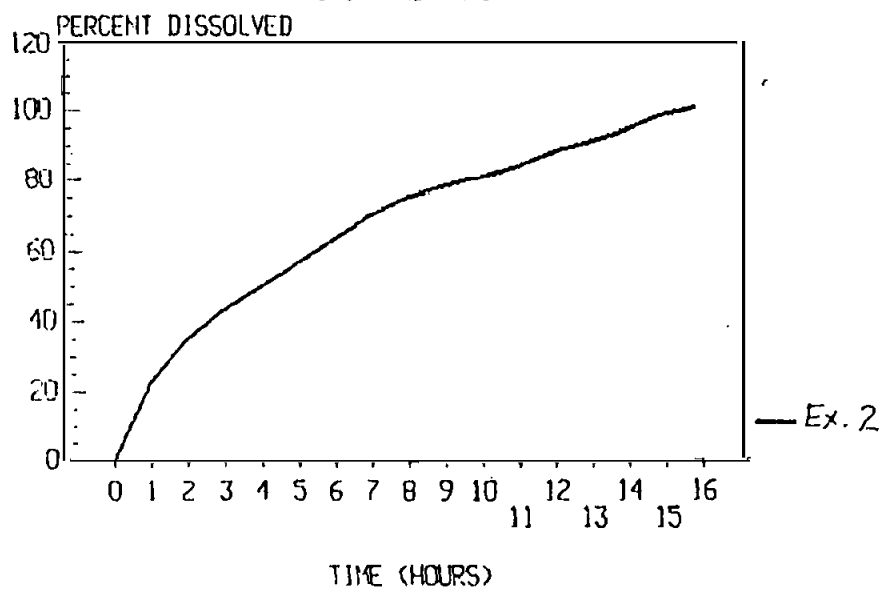
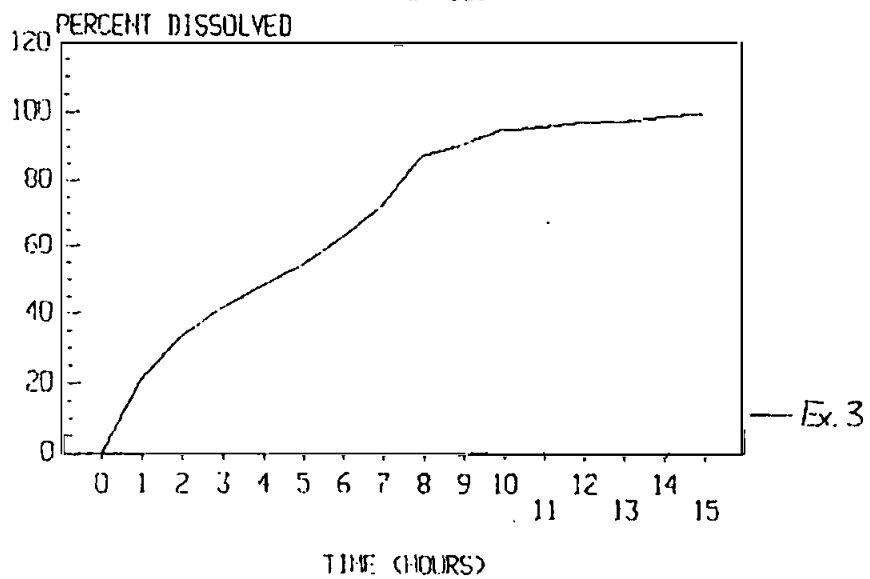
DISSOLUTION PROFILE
NO SURFACTANTS

FIGURE 2

DISSOLUTION PROFILE
PPA W/ 2% SLS

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FIGURE 3

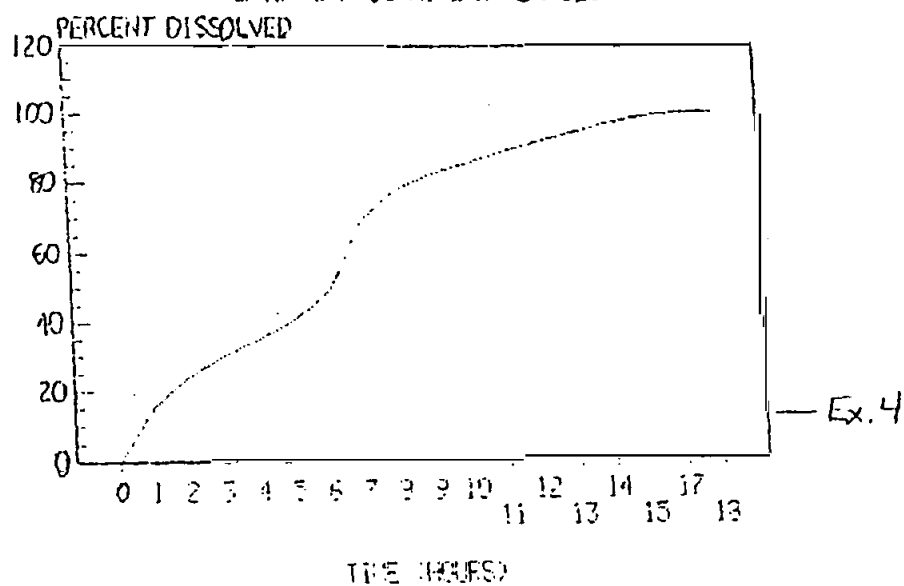
DISSOLUTION PROFILE
PHENYLPROPANOLAMINE IN 5% SLS

FIGURE 4

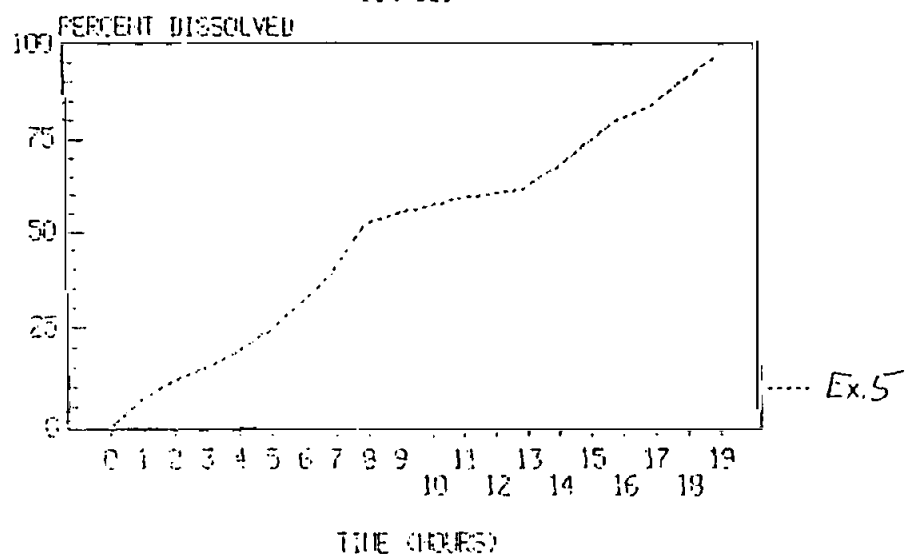
DISSOLUTION PROFILE
PHENYLPROPANOLAMINE
10% SLS

FIGURE 5

DISSOLUTION PROFILE
PPA W/ 2% DSS

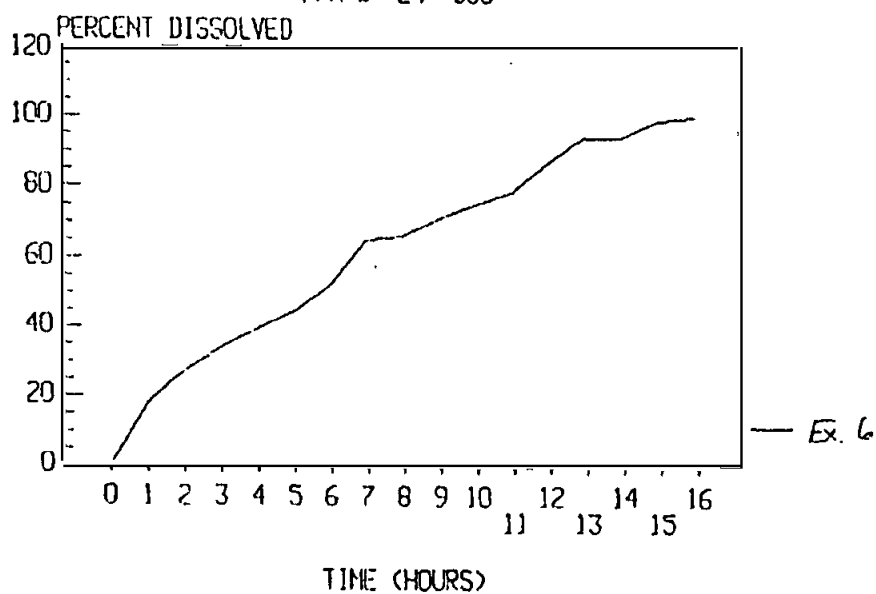
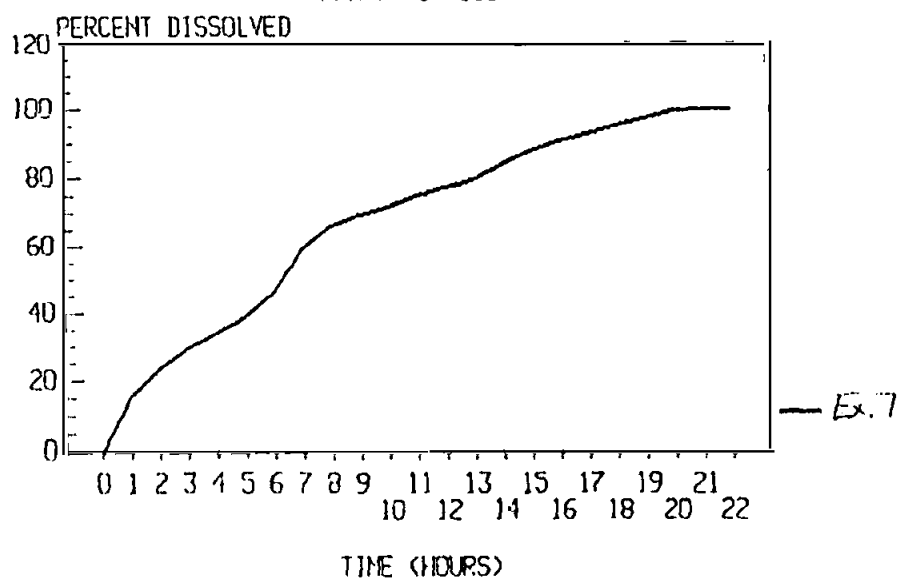


FIGURE 6

DISSOLUTION PROFILE
PPA W/ 5% DSS



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FIGURE 7
DISSOLUTION PROFILE
PPA W/ 10% DSS

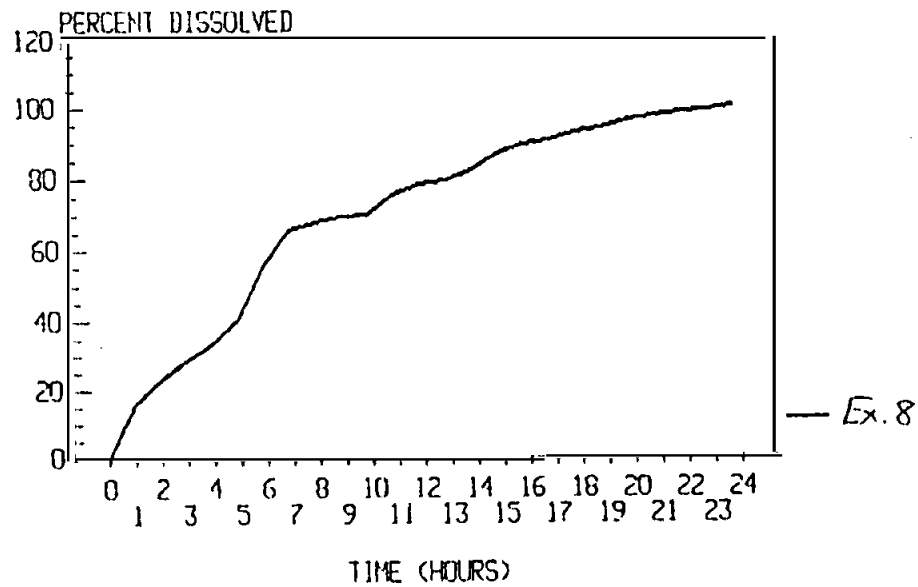
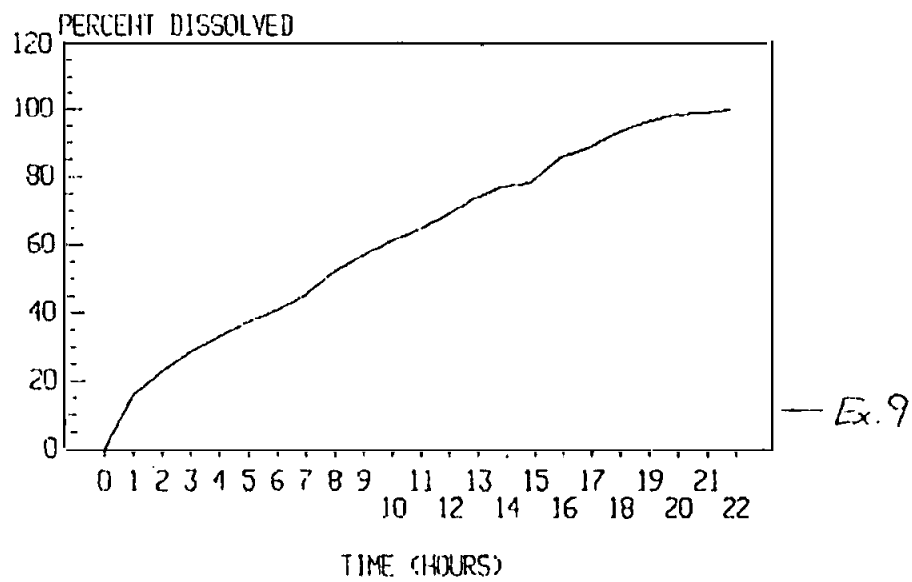


FIGURE 8
DISSOLUTION PROFILE
PPA W/ 1% SLS + 1% DSS



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FIGURE 9
DISSOLUTION PROFILE
PIPA W/ 2% SLS + 2% DSS

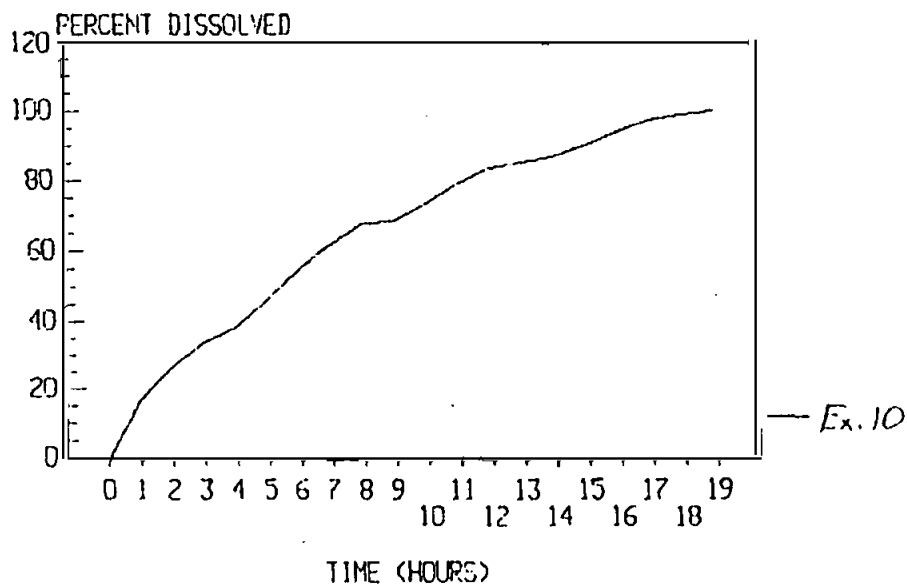


FIGURE 10
RELEASE PROFILE
NO SURFACTANTS



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FIGURE 11
RELEASE RATE PROFILE
PPA W/ 2% SLS

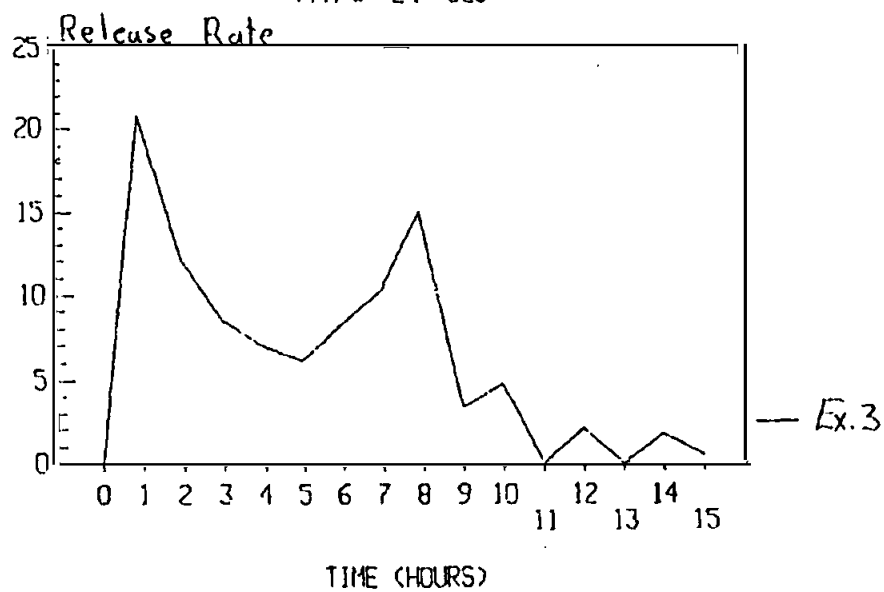
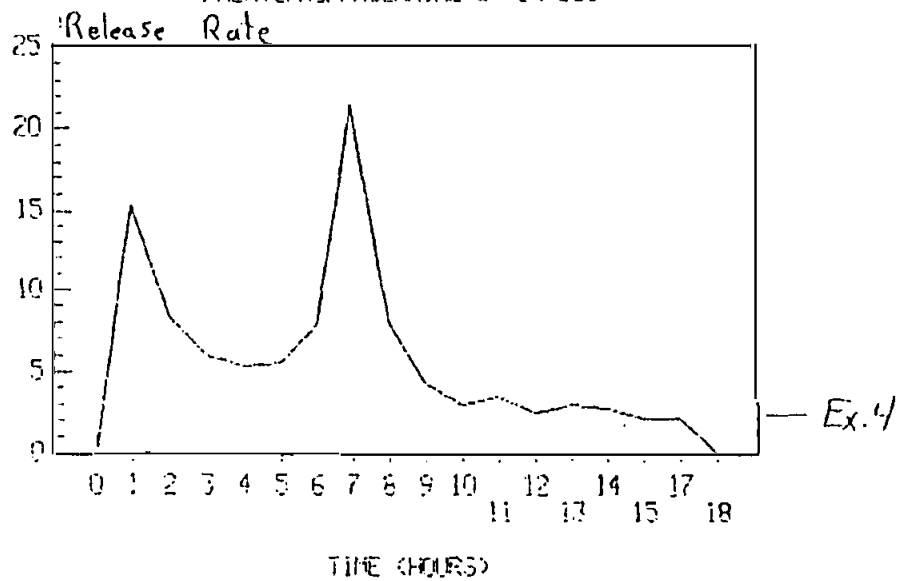


FIGURE 12
RELEASE PROFILE
PHENYLPROPANOLAMINE W/ 5% SLS



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FIGURE 13

Release Rate PROFILE
PHENYLPROFANOLAMINE
10% SLS

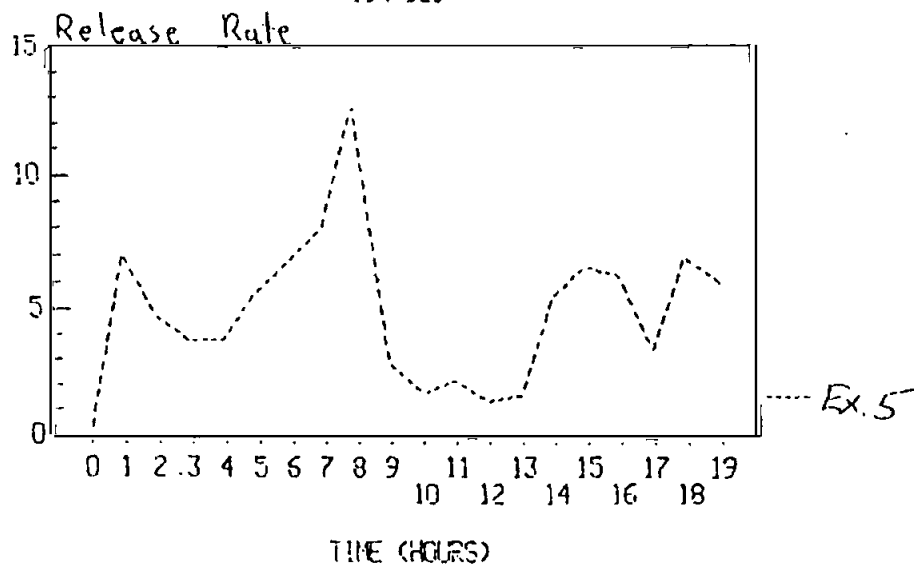


FIGURE 14

RELEASE RATE PROFILE
PPA W/ 2% DSS



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FIGURE 15
RELEASE RATE Profile
PPA W/ 5% DSS

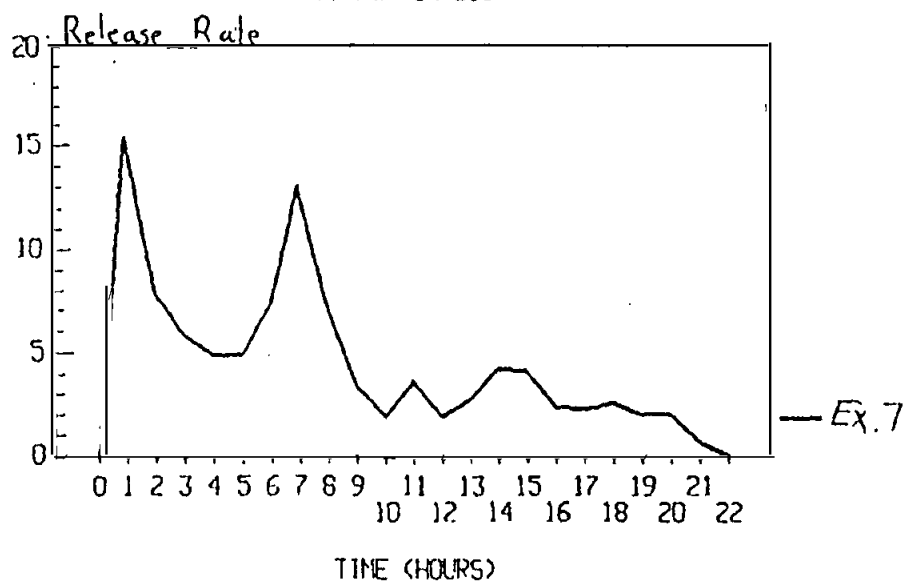
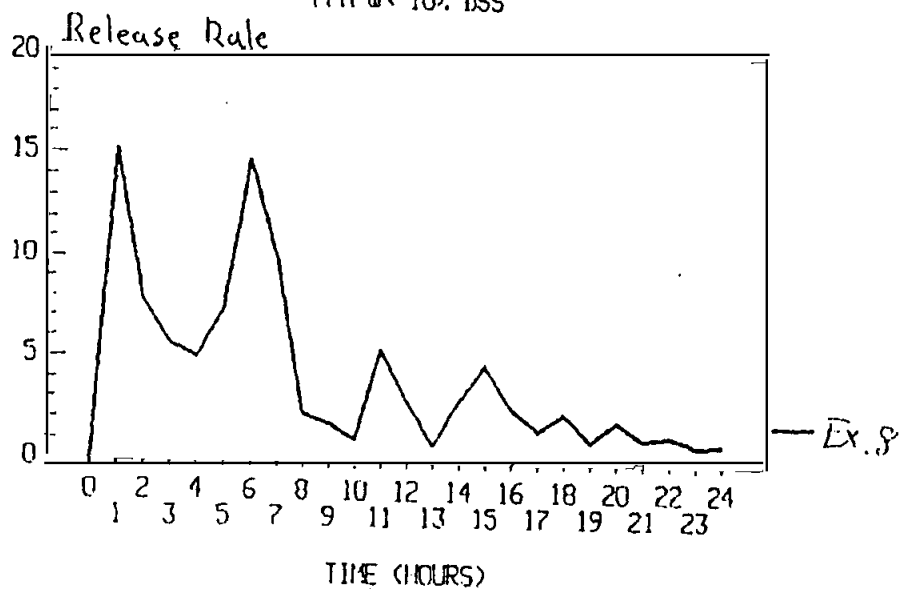


FIGURE 16
RELEASE RATE PROFILE
PPA W/ 10% DSS



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FIGURE 17



FIGURE 18

