REYES & REYES
A B O G A D O S

SEÑOR
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
E. S. D.

REF: **Expediente 09 068.963.**

TÍTULO SOLICITADO: **FORMA DE DOSIS DE IBUPROFENO DE LIBERACIÓN MODIFICADA.**

PUBLICACIÓN: **Gaceta 619 de 19/08/2010, número de publicación 599.**

SOLICITANTE: **SCOLR PHARMA, INC.**

APODERADO: **MAURICIO JARAMILLO CAMPUZANO.**

TRÁMITE: **SUSTENTACION DE OPOSICIÓN**

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.,** dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2º de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada el 02 de Febrero de 2009, en los siguientes términos:

I. RATIFICACIÓN

Comedidamente me permito insistir en todos y cada uno de los argumentos planteados en la oposición referida, los cuales, como se dijo en su momento, demuestran que la solicitud de la referencia carece de los requisitos de patentabilidad establecidos por los artículos 14, 16, 18 y 20 literal d), de la Decisión 486 y que como tal, no rnerece recibir el beneficio patentario:

- En primer lugar, y ante la reivindicación textual de concentraciones (dosis) de Ibuprofeno, específicamente en las reivindicaciones 1, 2 y 11, es importante indicar que esto contraviene lo dispuesto en la Decisión 486 de 2000 que literalmente refiere a que *"No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnostico aplicados a los seres humanos o a animales."* Dicha mención de dosificaciones tiene el mismo efecto que las reivindicaciones sobre métodos de tratamiento médico, dado que la concentración, en este caso directamente referida a la dosificación de la formulación farmacéutica, no pertenece a la categoría de producto o procedimiento, sino que hace referencia la forma en la que un producto se utiliza terapéuticamente, y por lo tanto no hace parte de las actividades industriales, sino de la profesión médica.

- En el mismo sentido, carecen de vocación inventiva las reivindicaciones referidas a parámetros farmacocinéticos (reivindicaciones 1 y 2) y las que hacen referencia a valores de viscosidad y/o tamaño de partícula (reivindicaciones 1, 2, 4, 6, 7, 11, 13, 15 y 16), pues la determinación de tales parámetros, y por ende el Nivel Inventivo de las reivindicaciones que los comprenden, no depende de la previa revelación expresa de los mismos en el arte previo, (es decir, de si tales valores farmacocinéticos, de viscosidad o de tamaño de partícula se hayan publicado con anterioridad), pues dicha determinación hace parte de las actividades que necesariamente deben llevarse a cabo en cualquier proceso de pre-formulación de un producto farmacéutico, y resultan necesarios y obvios para cualquier persona medianamente versada en este campo tecnológico.

- Los parámetros farmacocinéticos se encuentran relacionados con las actividades clínicas (ensayos clínicos y preclínicos de rutina en la elaboración de todo medicamento) y no con actividades industriales.

- La viscosidad que presenta un excipiente o la variación del tamaño de partícula no son de ninguna manera características inventivas dentro de una formulación farmacéutica, pues reitero, hacen parte de las mencionadas etapas de preformulación y formulación en las cuales se establecen qué excipientes, y en qué proporciones, consiguen las características deseadas por el formulador, siendo además la variación en la viscosidad y el tamaño de partícula dos de las

estrategias más comunes y utilizadas cuando se requiere alterar la velocidad de liberación del fármaco en una formulación sólida de administración oral.

- Las técnicas de formulación y el conjunto de compuestos que se pueden utilizar para desarrollar productos farmacéuticos viables para liberación controlada del fármaco, son elementos que son claramente conocidos para una persona medianamente versada en la formulación de productos farmacéuticos, así que de ninguna manera puede ser inventivo escoger uno u otro excipiente con características predefinidas, para conseguir tales efectos en la modificación de la liberación de un fármaco.

- Cualquier persona medianamente versada en la materia reconoce que dentro del estado de la técnica, se reconocen dentro de la categoría de "comprimidos especiales" a aquellos comprimidos que presentan algunas características farmacocinéticas diferentes a las descritas para los comprimidos convencionales, y que dentro de esta categoría, los de mayor utilización son los sublinguales, bucales, masticables, efervescentes, multicapas, vaginales, de implantación, recubiertos y de liberación controlada[1]. A estos últimos en mención, corresponderían las características de la formulación que reivindica la solicitud colombiana en trámite. Específicamente, y dentro de las posibilidades de la liberación controlada que se reconocen en el estado de la técnica, las características de la formulación contenida en las reivindicaciones de la solicitud en cuestión, puede clasificarse como una formulación de liberación sostenida, en donde el principio activo se libera de forma continua cierta cantidad de fármaco durante un periodo de tiempo generalmente largo[2]. Como cualquier persona medianamente versada en la materia también debe reconocer, este tipo de formulaciones pueden obtenerse por distintos métodos, siendo el más simple, la incorporación del principio activo en una matriz de naturaleza polimérica que forme una barrera lo suficientemente viscosa que controle la difusión del principio activo o que se erosione lentamente permitiendo la liberación gradual del mismo[3].

- La formulación descrita por la solicitud en cuestión corresponde a una formulación que obtiene sus características de liberación sostenida a través de

[1] Vila Jato. J.L. Tecnología Farmacéutica. Volumen II, página 142.
[2] Ibíd. Página 145.

la inserción del fármaco en un sistema polimérico dual hinchable, tal y como se expone claramente en la reivindicación 1. Además, y teniendo en cuenta que dentro de dichas características descritas para la formulación reivindicada por la solicitud en trámite, se hace mención del hinchamiento a través del uso de polímeros que atribuyan características hidrofílicas a dicha matriz polimérica, es relevante señalar que dichas características también son ampliamente reconocidas en el estado de la técnica, dentro de los mecanismos posibles para una liberación controlada, mecanismos tales como los descritos para los sistemas de liberación controlada tipo matrices hidrofílicas. Más aún, es bien sabido que los polímeros que se involucran para obtener la formulación reivindicada por la solicitud en cuestión, son comúnmente utilizados en el estado de la técnica para la elaboración de este tipo de formulaciones, en tanto corresponden a polímeros naturales o semisintéticos, éteres de celulosa y polímeros de ácido acrílico[4]. Es importante resaltar que, precisamente, la HPMC es uno de los polímeros más comúnmente utilizados para conseguir este tipo de efectos de liberación modificada.

- El tipo de formulaciones a las que se refiere la solicitud colombiana en trámite, corresponden a las características de la formulaciones de liberación controlada convencionales y ampliamente descritas en el estado de la técnica, y cualquier persona medianamente versada en la materia podría en principio involucrar cualquier fármaco en dicho tipo de formulaciones, aplicando adecuadamente los respectivos ensayos de preformulación y formulación.

- La publicación internacional WO/2006/039692 publicada el 13 de Abril de 2006 revela absolutamente todas las mismas estrategias técnicas que las mencionadas por la solicitud colombiana en cuestión, específicamente lo que se refiere a la combinación del mismo tipo de excipientes con dos tamaños de partículas distintos así como a dos polímeros hidrofílicos con dos valores de viscosidad diferentes. Teniendo en cuenta además que se hace mención específica de HPMC 100LV y K4M, así como celulosa microcristalina, carbonato de sodio, glicina, arginina croscarmelosa sódica en combinación con el mismo principio activo (Ibuprofeno) en rangos de dosificación que incluyen a los mencionados a la solicitud en cuestión, así como un comportamiento

[3] Ibíd. Página 145.

farmacocinético idéntico al que en dicha solicitud menciona (6.4 microgramos/ml durante un periodo prolongado de al menos 8 horas), es irrefutable el hecho que toda esta información revelada por la anterioridad es una clara guía para la obtención del mismo tipo de formulaciones farmacéuticas que las reivindicadas por la solicitud colombiana, por lo que queda en evidencia la carencia de nivel inventivo, así como la de novedad si nos ceñimos a los resultados obtenidos en ambas formulaciones.

II. COMPLEMENTO DE INFORMACIÓN

En complemento de los argumentos presentados oportunamente en la oposición correspondiente, se presentan nuevos argumentos relacionados a la tesis de falta de novedad y de nivel, veamos:

Existen documentos de carácter científico que evidencian el uso convencional de polímeros hidrofílicos de diversas clases, en especial hidroxipropilmetilcelulosa (HPMC), para conseguir diversos efectos en la velocidad de liberación del fármaco, veamos:

Modeling Of Drug Release From Delivery Systems Based On Hydroxypropyl Methylcellulose (HPMC)[5].

Abstract: The objective of this article is to review the spectrum of mathematical models that have been developed to describe drug release from hydroxypropyl methylcellulose (HPMC)-based pharmaceutical devices. The major advantages of these models are: (i) the elucidation of the underlying mass transport mechanisms; and (ii) the possibility to predict the effect of the device design parameters (e.g., shape, size and composition of HPMC-based matrix tablets) on the resulting drug release rate, thus facilitating the development of new pharmaceutical products. Simple empirical or semi-empirical models such as the classical Higuchi equation and the so-called power law, as well as more complex mechanistic theories that consider diffusion, swelling and dissolution processes simultaneously are presented, and their advantages and limitations are discussed. Various examples of practical applications to experimental drug release data are given. The choice of the appropriate mathematical model when developing new pharmaceutical products or elucidating drug release mechanisms strongly depends on the desired or required predictive ability and accuracy of the model. In many cases, the use of a simple empirical or semi-empirical model is fully sufficient. However, when reliable, detailed information are required, more complex, mechanistic theories

[4] Ibíd. Página 399 a 402.
[5] Siepmann J, Peppas NA. Adv Drug Deliv Rev. 2001 Jun 11;48(2-3):139-57.

must be applied. The present article is a comprehensive review of the current state of the art of mathematical modeling drug release from HPMC-based delivery systems and discusses the crucial points of the most important theories.

Role Of Cellulose Ether Polymers On Ibuprofen Release From Matrix Tablets[6].

Abstract: *Cellulose derivatives are the most frequently used polymers in formulations of pharmaceutical products for controlled drug delivery. The main aim of the present work was to evaluate the effect of different cellulose substitutions on the release rate of ibuprofen (IBP) from hydrophilic matrix tablets. Thus, the release mechanism of IBP with methylcellulose (MC25), hydroxypropylcellulose (HPC), and hydroxypropylmethylcellulose (HPMC K15M or K100M) was studied. In addition, the influence of the diluents lactose monohydrate (LAC) and beta-cyclodextrin (beta-CD) was evaluated. Distinct test formulations were prepared containing: 57.14% of IBP, 20.00% of polymer, 20.29% of diluent, 1.71% of talc lubricants, and 0.86% of magnesium stearate as lubricants. Although non-negligible drug-excipient interactions were detected from DSC studies, these were found not to constitute an incompatibility effect. Tablets were examined for their drug content, weight uniformity, hardness, thickness, tensile strength, friability, porosity, swelling, and dissolution performance. Polymers MC25 and HPC were found to be unsuitable for the preparation of this kind of solid dosage form, while HPMC K15M and K100M showed to be advantageous. Dissolution parameters such as the area under the dissolution curve (AUC), the dissolution efficiency (DE(20 h)), dissolution time (t 50%), and mean dissolution time (MDT) were calculated for all the formulations, and the highest MDT values were obtained with HPMC indicating that a higher value of MDT signifies a higher drug retarding ability of the polymer and vice-versa. The analysis of the drug release data was performed in the light of distinct kinetic mathematical models-Kosmeyer-Peppas, Higuchi, zero-, and first-order. The release process was also found to be slightly influenced by the kind of diluent used.*

Different HPMC Viscosity Grades As Coating Agents For An Oral Time And/Or Site-Controlled Delivery System: A Study On Process Parameters And In Vitro Performances[7].

Abstract: *Currently, delayed/pulsatile release and colon delivery represent topics of remarkable interest. The present paper deals with the study and development of an oral dosage form devised to release drugs following a programmed time period after administration or, when opportune design modifications are introduced, to target the colon. The system is composed of a drug-containing core and a hydrophilic swellable polymeric coating capable of delaying drug release through slow interaction with aqueous fluids. An optional external gastroresistant film is applied to overcome gastric emptying variability, thus allowing colon delivery to be*

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[6] Vueba ML, Batista de Carvalho LA, Veiga F, Sousa JJ, Pina ME. Drug Dev Ind Pharm. 2005 Aug;31(7):653-65.

[7] Sangalli ME, Maroni A, Foppoli A, Zema L, Giordano F, Gazzaniga A. Eur J Pharm Sci. 2004 Aug;22(5):469-76.

pursued according to the time-dependent approach. The aim of this work was to evaluate different hydroxypropyl methylcellulose (HPMC) viscosity grades as possible materials for the attainment of the system retarding hydrophilic layer. Both the relevant suitability for application onto tablet cores by aqueous spray-coating in fluid bed and capability of delaying drug release for a programmable period were explored and compared. Methocel E50 was found to afford the best balance among different important items, i.e. process time, retarding ability, dimensions of the coated units and possibility of finely tuning the delay duration. Further results pointed out the robustness of Methocel E50-based systems, which have shown to be practically unaffected by the concentration of the employed coating solution and the pH of the release medium, as well as only poorly influenced by ionic strength, at least with regard to values encompassed in the physiological range for gastrointestinal fluids.

Como se puede apreciar claramente, en estas tres publicaciones científicas se evidencia que el manejo de la viscosidad en polímeros hidrófilos como los derivados de celulosa, especialmente HPMC, es una estrategia reconocida con anterioridad en el estado de la técnica para obtener cambios en la velocidad de liberación de fármacos, incluyendo Ibuprofeno, y por lo tanto, cualquier persona medianamente versada en la materia podría aplicar dichos conocimientos para conseguir los efectos descritos en la composición reivindicada en la solicitud colombiana en trámite.

Otro documento como la patente americana US 5.009.895 publicada el 23 de Abril de 1991 y titulada "SUSTAINED RELEASE WITH HIGH AND LOW VISCOSITY HPMC" revela:

> **Sustained release formulations are disclosed which contain a therapeutically active medicament and a high and low viscosity HPMC and which exhibit a zero order release profile.** (...)
>
> **The medicament in the present invention may be selected from ibuprofen, or salts of ibuprofen. Most preferably the medicament is ibuprofen lysine which should be taken to mean all stereoisomeric configurations including racemic ibuprofen lysine and (S)-ibuprofen-(S)-lysine; i.e. the salt formed from (S)-ibuprofen and (S)-lysine.**

En donde nuevamente se hace evidente la utilidad de la inclusión de HPMC con diferentes grados de viscosidad como estrategia para modificación de la liberación del fármaco, y nuevamente se relaciona dicha estrategia con la liberación modificada de Ibuprofeno.

Otras publicaciones como la publicación internacional WO 96/41617 publicada el 27 de Diciembre de 1996 no solamente revelan la utilidad de los polímeros derivados de celulosa en la liberación modificada de fármacos, sino que además describe dicha aplicación para formulaciones de liberación dual (inmediata + modificada) tal y como sucede para el caso de la solicitud en cuestión, veamos:

> 1. Solid pharmaceutical form for the oral administration of at least one active ingredient, with release of the latter at successive times and at different rates, characterised in that it comprises at least two fractions, of which:
> (a) in the first fraction, the active ingredient is contained in the form of a soluble derivative together with technological excipients and adjuvants enabling the mass to be compressed and/or processed and ensuring an immediate release of the active ingredient (or active ingredients if more than one) contained in that fraction;
> (b) in the second fraction, the same active ingredient is contained in non-derivative form, characterised by a substantially lower solubility in water and/or aqueous liquids, together with technological excipients and adjuvants which, in this case too, enable the mass to be compressed but which are such that they modulate, in accordance with accurately programmable kinetics and rates, the release of the active ingredient(s) contained in that fraction.
>
> (...)
>
> 3. Solid pharmaceutical form according to Claim 2, characterised in that the anti-inflammatory drug is selected from ibuprofen, ketoprofen, acetylsalicylic acid, mefenamic acid, flufenamic acid, tiprofenic acid, tolfenamic acid, diflunisal, piroxicam, naproxen, flurbiprofen, sodium diclofenac and indomethacin.
>
> (...)
>
> 23. Pharmaceutical form according to Claim 22, characterised in that the hydrophilic polymers are selected from the class consisting of hydroxypropylmethylcellulose having a molecular weight of from 1000 to 2,000,000 Daltons, carboxyvinyl polymer, polyvinyl alcohols, glucans, xanthans, mannans, galactomannans, scleroglucans, alginates, pectin, amylose having different degrees of crosslinking, carboxymethylcellulose and its derivatives, methylcellulose, ethylcellulose and their salts and/or derivatives.

Finalmente también existen documentos, como la patente americana US 6.103.219 publicada el 15 de agosto de 2000 y titulada "PHARMACEUTICAL EXCIPIENT HAVING IMPROVED COMPRESSIBILITY", que con anterioridad describen las aplicaciones técnicas de la celulosa microcristalina silisificada (entre

estas la compresión directa) en composiciones tipo tableta para administración oral, tal y como se describe en las reivindicaciones 1 a 8, 11 y 15 a 17 de la solicitud colombiana en trámite, veamos:

> A microcrystalline cellulose-based excipient having improved compressibility, whether utilized in direct compression, dry granulation or wet granulation formulations, is disclosed. The excipient is an agglomerate of microcrystalline cellulose particles and from about 0.1% to about 20% silicon dioxide particles, by weight of the microcrystalline cellulose, wherein the microcrystalline cellulose and silicon dioxide are in intimate association with each other. The silicon dioxide utilized in the novel excipient has a particle size from about 1 nanometer to about 100 microns. Most preferably, the silicon dioxide is a grade of colloidal silicon dioxide.
>
> (...)
>
> **20**. A method of preparing a solid dosage form, comprising:
>
> (a) forming an aqueous slurry containing a mixture of microcrystalline cellulose in the form of a wet cake and silicon dioxide having a particle size from about 1 nm to about 100 μm, the amount of silicon dioxide being from about 0.1% to about 20% relative to the amount of microcrystalline cellulose, by weight;
>
> (b) drying said slurry to obtain an excipient comprising a plurality of agglomerated particles of microcrystalline cellulose in intimate association with said silicon dioxide;
>
> (c) mixing an active ingredient with said excipient in a ratio from about 1:99 to about 99:1;
>
> (d) incorporating said mixture obtained in step (c) into a plurality of solid unit doses.

En conclusión, y en sustentación de los argumentos expuestos en la respectiva oposición presentada en su momento, se hace aun más evidente que la solicitud colombiana en trámite carece absolutamente de nivel inventivo, y que la formulación descrita en su capítulo reivindicatorio, corresponde al resultado de la aplicación de diversas estrategias tecnológicas que deben ser reconocidas por cualquier persona medianamente versada en la formulación de productos farmacéuticos.

Por todo lo anterior, le solicito Señor Superintendente, que analice los argumentos citados con el rigor y detenimiento habituales y que decrete, además de la negación de la solicitud en comento, el archivo del citado expediente.

III. ANEXOS

- Abstracts de todas las publicaciones científicas mencionadas en el acápite de Complemento de Información.
- La patente americana US 5.009.895 publicada el 23 de Abril de 1991 y titulada "SUSTAINED RELEASE WITH HIGH AND LOW VISCOSITY HPMC".
- La publicación internacional WO 96/41617 publicada el 27 de Diciembre de 1996, capítulo reivindicatorio.
- La patente americana US 6.103.219 publicada el 15 de agosto de 2000 y titulada "PHARMACEUTICAL EXCIPIENT HAVING IMPROVED COMPRESSIBILITY".

Señor Superintendente,

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Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC)

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Abstract

The objective of this article is to review the spectrum of mathematical models that have been developed to describe drug release from hydroxypropyl methylcellulose (HPMC)-based pharmaceutical devices. The major advantages of these models are: (i) the elucidation of the underlying mass transport mechanisms; and (ii) the possibility to predict the effect of the device design parameters (e.g., shape, size and composition of HPMC-based matrix tablets) on the resulting drug release rate, thus facilitating the development of new pharmaceutical products. Simple empirical or semi-empirical models such as the classical Higuchi equation and the so-called power law, as well as more complex mechanistic theories that consider diffusion, swelling and dissolution processes simultaneously are presented, and their advantages and limitations are discussed. Various examples of practical applications to experimental drug release data are given. The choice of the appropriate mathematical model when developing new pharmaceutical products or elucidating drug release mechanisms strongly depends on the desired or required predictive ability and accuracy of the model. In many cases, the use of a simple empirical or semi-empirical model is fully sufficient. However, when reliable, detailed information are required, more complex, mechanistic theories must be applied. The present article is a comprehensive review of the current state of the art of mathematical modeling drug release from HPMC-based delivery systems and discusses the crucial points of the most important theories.

Keywords: Controlled drug delivery; HPMC; Hydrophilic matrices; Hydroxypropyl methylcellulose; Modeling; Release mechanism

Contents

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1. Introduction

Hydroxypropyl methylcellulose (HPMC) is the most important hydrophilic carrier material used for the preparation of oral controlled drug delivery systems [1,2]. One of its most important characteristics is the high swellability, which has a significant effect on the release kinetics of an incorporated drug. Upon contact with water or biological fluid the latter diffuses into the device, resulting in polymer chain relaxation with volume expansion [3,4]. Then, the incorporated drug diffuses out of the system.

For the design of new controlled drug delivery systems which are based on HPMC and aimed at providing particular, pre-determined release profiles, it is highly desirable: (i) to know the exact mass transport mechanisms involved in drug release; and (ii) to be able to predict quantitatively the resulting drug release kinetics. The practical benefit of an adequate mathematical model is the possibility to simulate the effect of the design parameters of HPMC-based drug delivery systems on the release profiles [5]. In the ideal case, the required composition (type and amount of drug, polymer and additives) and geometry (size and shape) of the new controlled drug delivery system designed to achieve a certain drug release profile can be predicted theoretically. Thus, the number of necessary experiments can be minimized and the development of new pharmaceutical products significantly facilitated.

Diffusion, swelling and erosion are the most important rate-controlling mechanisms of commercially available controlled release products [6]. Diffusion can be described using Fick's second law [7–9]. There are various ways to apply the respective equations [10]. First of all, the considered geometry is important. Assuming one-dimensional transport in thin films results in rather simple mathematical expressions, but this approach is only valid for flat, planar devices. In the case of HPMC-based drug delivery systems three-dimensional, cylindrical geometries (tablets) are more relevant, but mathematically more difficult to treat. In addition, it is necessary to decide whether to assume constant or non-constant diffusivities. The mathematical treatment of constant diffusivity problems is much simpler, but only valid in the case of polymers that do not significantly swell upon contact with water (e.g., ethylcellulose). For HPMC tablets, the drug diffusion coefficients are strongly dependent on the water content of the system [11]. Here, the assumption of constant diffusivities leads to less realistic mathematical models. Depending on the degree of substitution and chain length of the HPMC type used, polymer dissolution might be observed during drug release. This will complicate the solution of Fick's second law of diffusion, leading to moving boundary conditions. In addition to the physicochemical properties of the polymer also the characteristics of the drug have to be considered. For example, drug dissolution has to be taken into account in case of poorly water-soluble drugs.

Depending on the complexity of the resulting system of mathematical equations describing diffusion, swelling and/or dissolution processes, analytical and/or numerical solutions can be derived. Analytical solutions have the major advantage of being more informative. The involved design and physicochemical parameters still appear in the equations.

In the case of explicit analytical solutions, we can obtain direct relationships between the dependent and independent variables. In the case of implicit analytical solutions, this dependence is not as obvious. However, compared to numerical solutions, it is still much easier to get an idea of the effect of certain independent variables on particular dependent variables. Thus, it is highly desirable to derive explicit analytical solutions. Unfortunately, this is only possible in the case of rather simple forms of the diffusion equations, e.g., assuming constant diffusivities. In general, physically more realistic models are mathematically more complex and very often it is difficult to find analytical solutions of the respective set of equations [12]. Three important methods to derive exact mathematical solutions can

be distinguished: (i) the method of reflection and superposition; (ii) the method of separation of variables; and (iii) the method of the Laplace transform. For a discussion of the advantages and disadvantages of these methods the reader is referred to other literature (e.g., [7,13,14]). Also a description of the principles of numerical analysis is beyond the scope of this review, but excellent textbooks are available (e.g., [7,13–15]). In contrast to analytical solutions, only approximate solutions are derived. The resulting error can be controlled using various different methods. Generally, cumbersome mathematical calculations are required to reduce the approximation error to an acceptable level (e.g. $<0.1\%$). The development of digital computers dramatically decreased the time necessary to perform the calculations, so that nowadays numerical methods have become economic even for routine use.

It is the scope of this article to review the most important mathematical models which have been developed to describe drug release from HPMC-based pharmaceutical systems. Simple and very comprehensive theories are presented and their advantages and limitations are discussed. For a better understanding of the described theories, first the most relevant physicochemical properties of HPMC and the major principles of the overall drug release mechanisms from HPMC-based delivery systems are presented. Due to the substantially high number of variables, no effort was made in this review to present a uniform picture of the different systems of notation defined by the respective authors. The original nomenclatures are used and only some cases are modified by using more common abbreviations to avoid misunderstandings.

2. Physicochemical characterization of HPMC

HPMC is a propylene glycol ether of methylcellulose; its chemical structure is illustrated in Fig. 1. The substituent R represents either a $-CH_3$, or a $-CH_2CH(CH_3)OH$ group, or a hydrogen atom. The physicochemical properties of this polymer are strongly affected by: (i) the methoxy group content; (ii) the hydroxypropoxy group content; and (iii) the molecular weight. The USP distinguishes four different types of HPMC, classified according to their

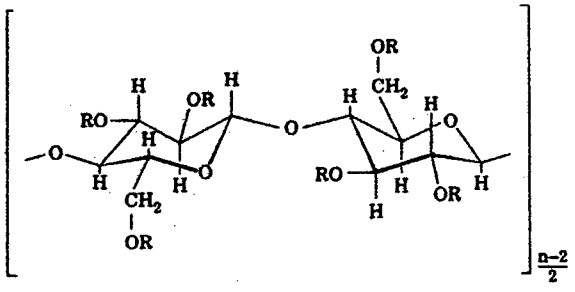

Fig. 1. Chemical structure of HPMC. The substituent R represents either a $-CH_3$, or a $-CH_2CH(CH_3)OH$ group, or a hydrogen atom.

relative $-OCH_3$ and $-OCH_2CH(CH_3)OH$ content: HPMC 1828, HPMC 2208, HPMC 2906 and HPMC 2910. The first two numbers indicate the percentage of methoxy-groups, the last two numbers the percentage of hydroxypropoxy-groups, determined after drying at 105°C for 2 h. The exact limits for the degree of substitution defining the respective HPMC types are given in Table 1. In addition, the USP describes a method to determine the apparent viscosity of an aqueous 2% solution of the polymer using a suitable viscosimeter of the Ubbelohde type. This apparent viscosity serves as a measure for the average chain length of the polymer. The measured value must lie within the 80.0 to 120.0% range of the viscosity stated on the label for HPMC types of 100 mPa s or less, and within the 75.0 to 140.0% range for HPMC types of higher viscosity.

Interestingly, Dahl et al. [16] reported broad variations concerning important characteristics of seven batches HPMC 2208 with a labeled viscosity of 15,000 mPa s, provided by two different manufacturers. All samples had similar viscosities, except one batch which was outside the USP specifications. The methoxy-group content was uniformly high and

Table 1
USP specifications for different types of HPMC, classified according to their degree of methoxy- and hydroxypropoxy-substitution

Substitution type	Methoxy (%)		Hydroxypropoxy (%)	
	Min.	Max.	Min.	Max.
1828	16.5	20.0	23.0	32.0
2208	19.0	24.0	4.0	12.0
2906	27.0	30.0	4.0	7.5
2910	28.0	30.0	7.0	12.0

three batches fell outside the USP limits of 19.0 to 24.0%. The hydroxypropoxy-group content (although within the USP specifications of 4.0 to 12.0%), varied relatively more than the methoxy group content. These variations lead to significant differences concerning the resulting release rate of naproxen from compressed matrix tablets in vitro. The authors concluded that each batch (even from the same manufacturer) should be carefully controlled and that the specifications of the USP and other pharmacopoeas might have to be reinforced.

The glass transition temperature, T_g, of a polymer is an important characteristic constant, in particular with respect to applications in the field of controlled drug delivery. Below the T_g the mobility of the macromolecules is very low. The material is in its glassy state resulting in extremely small diffusion rates [10]. In contrast, above the glass transition temperature the mobility of the polymer chains is markedly increased (rubbery state), leading to much higher mass transfer rates of water and drug. Thus, we must know the T_g of the polymer when modeling drug release from controlled delivery systems. A good summary of work that has been done to determine the T_g of HPMC has been provided by Doelker [17]. He compares the results of various researchers [18–26] and lists values ranging from 154 to 184°C (Table 2). Various techniques have been used to determine the glass transition temperature: differential scanning calorimetry (DSC), differential thermal analysis (DTA), thermomechanical analysis (TMA), torsional braid analysis (TBA) and dynamic mechanical analysis (DMA). Different methods often lead to different T_g-values, and usually only the results achieved with one special method can be compared directly. In addition, the variation of the degree of substitution and the molecular weight plays a role in the observed variance of the T_g. Furthermore, a 57°C-value was reported by Conte et al. [26], which seems to correspond to a low-energy secondary transition. The relevance of this low-temperature transition is yet unknown, but could be of significance in the diffusion of oxygen and water.

Numerous studies have been reported in the literature investigating the drug release kinetics from HPMC-based delivery systems [27–31]. Various techniques have been used to elucidate the physical processes involved. For example, Melia and coworkers [32–35] characterized the water mobility in the gel layer of hydrating HPMC matrices using NMR imaging. It has been shown that there is a diffusivity gradient across this layer and that it is affected by the degree of substitution of the polymer. Also Fyfe and Blazek [36] investigated the HPMC hydrogel formation by NMR spectroscopy pointing out the complications due to the presence of trapped gas [37]. Recently, they studied the release behavior of two model drugs, triflupromazine–HCl and 5-fluorouracil from HPMC tablets [38]. The tablet swelling was restricted to one dimension and distributions of the water and model drugs were obtained by ^{1}H and ^{19}F imaging. The distributions of triflupromazine–HCl and HPMC paralleled each other and the drug was only released at the eroding edge of the tablet where the HPMC concentration dropped below 10%. In contrast, 5-fluorouracil was released much more rapidly from the tablet and appeared to escape by diffusion from regions as high as 30% HPMC. They also developed a system for performing NMR imaging experiments on drug delivery devices within a flow-through dissolution apparatus, USP Apparatus 4 [39].

Ford and coworkers [40–42] used DSC techniques to study the distribution and amount of water in

Table 2
Reported glass transition temperatures for HPMC (adapted from Doelker [17], with permission from Springer–Verlag)

Material	Method	T_g (°C)	Ref.
HPMC Type 2910			
Methocel® E15	TMA	172–175[a]	[18]
Pharmacoat® 606	DSC	177	[19]
Pharmacoat® 606	DSC	155	[20]
Pharmacoat® 606	DSC	180	[21]
Pharmacoat® 606	DTA	169–174	[21]
Pharmacoat® 606	TBA	153.5, 158.5	[21]
Pharmacoat® 606	DSC	155.8	[22]
Pharmacoat® 606	TMA	163.8, 174.4	[22]
Pharmacoat® 603	DMA	160	[23]
Pharmacoat® 606	DMA	170	[23]
Pharmacoat® 615	DMA	175	[23]
Pharmacoat® 606	DMA	154	[24]
HPMC Type 2208			
Methocel® K4M	DSC	184	[25]
Methocel® K4M	DSC	(57)	[26]

[a] The values obtained by TMA in the penetration mode have been reported by the authors as softening temperatures.

HPMC gels. Water loosely bound to the polymer was detected as one or more events appearing at the low-temperature side of the main endotherm for the melting of free water in the DSC scans. The HPMC molecular weight, HPMC substitution type, gel storage time, and added drug influenced the appearance of these melting events [43,44]. Pham and Lee [28] designed a new flow-through cell to provide well-defined hydrodynamic conditions during the experimental studies and to allow precise measurements of dissolution and swelling front positions versus time. The rate of polymer swelling and dissolution as well as the corresponding rate of drug release were found to increase with either higher levels of drug loading or lower viscosity grades of HPMC. Gao and Meury [45] developed an optical image analysis method to examine the dynamic swelling behavior of HPMC-based matrix tablets in situ. In addition to providing precise determinations of the apparent gel layer thickness and the tablet dimensions, this method is also capable of estimating the HPMC concentration profile across the gel layer. They used this technique to characterize the effect of the HPMC/lactose ratio and HPMC viscosity grade (molecular weight) on the swelling of the matrix [46]. For all formulations tested it was found that (i) swelling is anisotropic with a preferential expansion in the axial direction; and (ii) swelling is isotropic with respect to the gel layer thickness and composition in both, axial and radial directions.

The modification of the surface area of HPMC tablets in order to achieve a desired release rate has been studied by Colombo et al. [47,48]. Different surface portions of an HPMC matrix tablet were covered with an impermeable coating. They investigated the drug release mechanisms and studied the influence of the type of coating on the resulting release rate. In order to facilitate the industrial production, the manual film-coating process can be avoided using press-coating techniques [49].

3. Overall drug release mechanism from HPMC-based systems

The overall drug release mechanism from HPMC-based pharmaceutical devices strongly depends on the design (composition and geometry) of the particular delivery system. The following phenomena are involved:

(i) At the beginning of the process, steep water concentration gradients are formed at the polymer/water interface resulting in water imbibition into the matrix. To describe this process adequately, it is important to consider (i) the exact geometry of the device; (ii) in case of cylinders, both, axial and radial direction of the mass transport; and (iii) the significant dependence of the water diffusion coefficient on the matrix swelling ratio [50,51]. In dry systems the diffusion coefficient is very low, whereas in highly swollen gels it is of the same order of magnitude as in pure water. Water acts as a plasticizer and reduces the glass transition temperature of the system. Once the T_g equals the temperature of the system, the polymer chains undergo the transition from the glassy to the rubbery state.

(ii) Due to the imbibition of water HPMC swells, resulting in dramatic changes of polymer and drug concentrations, and increasing dimensions of the system.

(iii) Upon contact with water the drug dissolves and (due to concentration gradients) diffuses out of the device.

(iv) With increasing water content the diffusion coefficient of the drug increases substantially.

(v) In the case of poor water-solubility, dissolved and non-dissolved drug coexist within the polymer matrix. Non-dissolved drug is not available for diffusion.

(vi) In the case of high initial drug loadings, the inner structure of the matrix changes significantly during drug release, becoming more porous and less restrictive for diffusion upon drug depletion.

(vii) Depending on the chain length and degree of substitution of the HPMC type used, the polymer itself dissolves more or less rapidly. In certain cases this phenomenon is negligible, for example if all drug has already been released before polymer dissolution becomes important.

As a result of conditions (i), (ii), (iv), (vi), and (vii) the mathematical description of the diffusional processes requires strongly time-dependent terms.

From the aforementioned possible phenomena it is obvious that there is no universal drug release mechanism that is valid for all kinds of HPMC-based systems. In contrast, there are many devices that

exhibit various mechanisms that control drug release, mechanisms such as polymer swelling, drug dissolution, drug diffusion or combinations of the above. The physicochemical characteristics and geometry of each device determine the resulting governing processes. Concerning the mathematical modeling of drug release from HPMC-based systems, one must identify the most important transport phenomenon for the investigated device and neglect the other processes, otherwise the mathematical model becomes too complex for facile use.

4. Empirical and semi-empirical mathematical models

4.1. Higuchi equation

In 1961, Higuchi [52] published the probably most famous and most often used mathematical equation to describe the release rate of drugs from matrix systems. Initially valid only for planar systems, it was later modified and extended to consider different geometries and matrix characteristics including porous structures [53–57]. We have pointed out in the past [9] that the classical Higuchi equation [52] was derived under pseudo-steady state assumptions and generally cannot be applied to 'real' controlled release systems.

The basic equation of the Higuchi model is:

$$\frac{M_t}{A} = \sqrt{D(2c_0 - c_s)c_s t} \qquad \text{for } c_0 > c_s \tag{1}$$

where M_t is the cumulative absolute amount of drug released at time t, A is the surface area of the controlled release device exposed to the release medium, D is the drug diffusivity in the polymer carrier, and c_0 and c_s are the initial drug concentration, and the solubility of the drug in the polymer, respectively. Clearly, Eq. (1) can be expressed as:

$$\frac{M_t}{M_\infty} = K\sqrt{t} \tag{2}$$

where M_∞ is the absolute cumulative amount of drug released at infinite time (which should be equal to the absolute amount of drug incorporated within the system at time $t=0$), and K is a constant reflecting the design variables of the system. Thus, the fraction of drug released is proportional to the square root of time. Alternatively, the drug release rate is proportional to the reciprocal of the square root of time.

An important advantage of these equations is their simplicity. However, when applying them to controlled drug delivery systems, the assumptions of the Higuchi derivation should carefully be kept in mind:

(i) The initial drug concentration in the system is much higher than the solubility of the drug. This assumption is very important, because it provides the basis for the justification of the applied pseudo-steady state approach. The resulting concentration profiles of a drug initially suspended in an ointment are illustrated in Fig. 2. The solid line represents the drug concentration profile after exposure of the ointment to perfect sink for a certain time t.

As can be seen there is a sharp discontinuity at distance h from the surface. For this distance h above the absorbing surface the concentration gradient is essentially constant, provided, the initial drug concentration within the system, c_0, is much greater than the solubility of the drug ($c_0 >> c_s$). After an additional time interval, Δt, the new concentration profile of the drug is given by the broken line. Again, a sharp discontinuity and otherwise linear concentration profiles result. Under these particular conditions Higuchi derived the very simple relationship between the release rate of the drug and the square root of time.

(ii) Mathematical analysis is based on one-dimen-

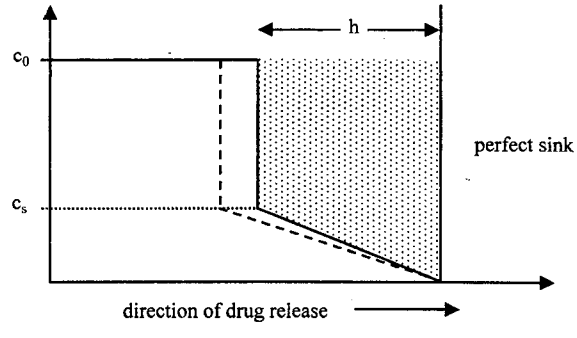

Fig. 2. Pseudo-steady state approach applied for the derivation of the classical Higuchi equation. Theoretical concentration profile existing in an ointment containing suspended drug and in contact with a perfect sink (adapted from [52] with permission from Wiley & Sons).

sional diffusion. Thus, edge effects must be negligible.

(iii) The suspended drug is in a fine state such that the particles are much smaller in diameter than the thickness of the system.

(iv) Swelling or dissolution of the polymer carrier is negligible.

(v) The diffusivity of the drug is constant.

(vi) Perfect sink conditions are maintained.

It is evident that these assumptions are not valid for most controlled drug delivery systems based on HPMC. However, due to the extreme simplicity of the classical Higuchi equation (Eq. (1)), the latter is often used to analyze experimental drug release data to get a rough idea of the underlying release mechanism. But the information obtained should be viewed with caution. The superposition of various different effects, such as HPMC swelling, transition of the macromolecules from the glassy to the rubbery state, polymer dissolution, concentration-dependent water and drug diffusion etc. might also result in an apparent square root of time kinetics. In addition, a proportionality between the fractional amount of drug released and the square root of time can as well be derived from an exact solution of Fick's second law of diffusion for thin films of thickness δ under perfect sink conditions, uniform initial drug concentration with $c_0 < c_s$ (monolithic solutions) and assuming constant diffusivities ([7,58,59]):

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\delta^2}\right)^{1/2}\left\{\pi^{-1/2} + 2\sum_{n=1}^{\infty}(-1)^n \text{ierfc}\frac{n\delta}{2\sqrt{Dt}}\right\} \quad (3)$$

Here, M_t and M_∞ are the absolute cumulative amount of drug released at time t and infinite time, respectively; D represents the diffusivity of the drug within the polymeric system. As the second term in the second brackets vanishes at short times, a sufficiently accurate approximation of Eq. (3) for $M_t/M_\infty < 0.60$ can be written as follows:

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\pi\delta^2}\right)^{1/2} = k'\sqrt{t} \quad (4)$$

where k' is a constant.

Thus, a proportionality between the fraction of drug released and the square root of time can also be based on these physical circumstances which are substantially different from those studied by Higuchi for the derivation of his classical equation (monolithic solutions versus monolithic dispersions). However, in both cases diffusion is the dominating mechanism and hence a proportionality between the cumulative amount of drug released and the square root of time is commonly regarded as an indicator for diffusion-controlled drug release.

Various researchers used the Higuchi equation to interpret their experimental drug release data. For example, Sung et al. [60] investigated the effect of formulation variables (HPMC/lactose ratio and HPMC viscosity grade) on the resulting Higuchi rate constants of a water-soluble model drug, adinazolam mesylate. For HPMC K15M and HPMC K100M they found similar values, whereas for HPMC K4M and HPMC K100LV and various HPMC/lactose ratios significantly different constants were obtained. This study is a good example for the use of the Higuchi equation for HPMC-based drug delivery systems, because although good fittings were obtained, the authors make clear that additional mathematical analysis is needed to make definitive mechanistic conclusions. Talukdar and Kinget [61] not only determined Higuchi constants, but used Eq. (1) to obtain the diffusivities of three model drugs (indometacin, indometacin sodium and caffeine) in hydrated HPMC and xanthan gum gels. In addition, they used a special apparatus for the experimental studies, restricting drug release to one surface only.

4.2. Power law

A more comprehensive, but still very simple, semi-empirical equation to describe drug release from polymeric systems is the so-called power law:

$$\frac{M_t}{M_\infty} = kt^n \quad (5)$$

Here, M_t and M_∞ are the absolute cumulative amount of drug released at time t and infinite time, respectively; k is a constant incorporating structural and geometric characteristics of the device, and n is the release exponent, indicative of the mechanism of drug release.

As can be seen, the classical Higuchi equation (Eq. (1)) as well as the above described short time

approximation of the exact solution of Fick's second law for thin films (Eq. (4)) represent the special case of the power law where $n=0.5$. Peppas and coworkers [62,63] were the first to give an introduction into the use and the limitations of this equation. The power law can be seen as a generalization of the observation that superposition of two apparently independent mechanisms of drug transport, a Fickian diffusion and a case-II transport [64,65], describes in many cases dynamic swelling of and drug release from glassy polymers, regardless of the form of the constitutive equation and the type of coupling of relaxation and diffusion [66].

It is clear from Eq. (5) that when the exponent n takes a value of 1.0, the drug release rate is independent of time. This case corresponds to zero-order release kinetics. For slabs, the mechanism that creates the zero-order release is known among polymer scientists as case-II transport. Here the relaxation process of the macromolecules occurring upon water imbibition into the system is the rate-controlling step. Water acts as a plasticizer and decreases the glass transition temperature of the polymer. Once the T_g equals the temperature of the system, the polymer chains undergo the transfer from the glassy to the rubbery state, with increasing mobility of the macromolecules and volume expansion.

Thus, Eq. (5) has two distinct physical realistic meanings in the two special cases of $n=0.5$ (indicating diffusion-controlled drug release) and $n=1.0$ (indicating swelling-controlled drug release). Values of n between 0.5 and 1.0 can be regarded as an indicator for the superposition of both phenomena (anomalous transport). It has to be kept in mind that the two extreme values for the exponent n, 0.5 and 1.0, are only valid for slab geometry. For spheres and cylinders different values have been derived [67,68], as listed in Table 3. Unfortunately, this fact is not always taken into account, leading to misinterpretations of experimental results.

In the case of HPMC-based systems it has to be pointed out that the application of the power law can only give limited insight into the exact release mechanism of the drug. Even if values of the exponent n are found that would indicate a diffusion-controlled drug release mechanism, this is not automatically valid for HPMC. The derivation of the Higuchi equation and the above described short time approximation of Fick's second law for slab geometry assume constant diffusivities and constant dimensions of the device during drug release. However, HPMC swells to a significant extend, the diffusion coefficients of water and incorporated drugs are strongly concentration dependent [69], and HPMC itself dissolves more or less rapidly. An apparent square root of time release kinetics can thus result from the superposition of various effects, and is not necessarily based on a simple drug diffusion-control. As in the case of the Higuchi equation the information obtained should be viewed with caution. However, the power law is already more comprehensive than the Higuchi equation.

Conte et al. [70] used the power law to describe drug release from HPMC-based multi-layer matrix tablets. The effect of the addition of one or two barrier layer(s) added to the planar surface(s) of a drug-containing HPMC core was studied. These additional barrier layers limit the core hydration process by maintaining the planar surfaces of the tablet covered during drug release. Moreover, the barrier layers reduce the surface area of the drug-containing core directly exposed to the release medium. As a result, the release rate was decreased and the kinetics shifted towards constant drug release. Trapidil and sodium diclofenac were used as model drugs. Recently, Rekhi et al. [71] applied the power law to gain information about the release

Table 3
Exponent n of the power law and drug release mechanism from polymeric controlled delivery systems of different geometry

Exponent, n			Drug release mechanism
Thin Film	Cylinder	Sphere	
0.5	0.45	0.43	Fickian diffusion
$0.5<n<1.0$	$0.45<n<0.89$	$0.43<n<0.85$	Anomalous transport
1.0	0.89	0.85	Case-II transport

mechanism of Methocel K100LV-based tablets containing metoprolol tartrate. The overall aim of their study was to examine the influence of critical formulation and processing variables as described in the AAPS/FDA Workshop II report on scale-up of oral extended-release dosage forms. They found values for the exponent n ranging from 0.46 to 0.59 and concluded that the release seemed to be predominantly diffusion-controlled and that the investigated formulation and processing variables did not alter the drug release mechanism. Also recently, Colombo and co-workers [72] applied the power law to experimental drug release data of a very water-soluble drug, buflomedil pyridoxal phosphate from HPMC-based matrix tablets. They found a value of 0.73 for the exponent n, indicating anomalous drug transport from the swellable matrix. As evident from these examples [70–72], the entire range of values for the exponent n can be obtained from HPMC-based controlled release dosage forms, corresponding to a wide range of possible dominating drug release mechanisms.

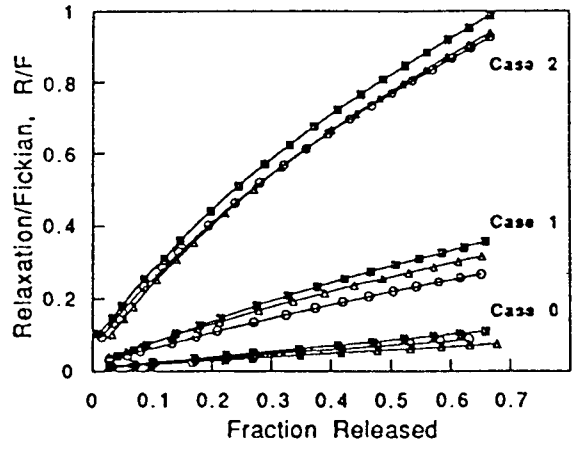

Fig. 3. Use of the Peppas–Sahlin model to investigate the effect of the polymer molecular weight and addition of impermeable coatings on the release rate of buflomedil pyridoxal phosphate from HPMC tablets. Case 0, uncoated matrix; case 1, one base of the cylinder covered; case 2, two bases of the cylinder covered; open triangles, Methocel K4M; open circles, Methocel K15M; and filled squares, Methocel K100M. (Reprinted from [74] with permission from Elsevier).

4.3. Other empirical and semi-empirical models

Another interesting model was developed by Peppas and Sahlin [73]:

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m} \tag{6}$$

where k_1, k_2 and m are constants. The first term on the right hand side represents the Fickian diffusional contribution, F, whereas the second term the case-II relaxational contribution, R. The ratio of both contributions can be calculated as follows:

$$\frac{R}{F} = \frac{k_2 t^m}{k_1} \tag{7}$$

Bettini et al. [74] applied these equations to investigate the effect of the molecular weight of the HPMC type used and the addition of partial impermeable coatings to HPMC matrix tablets containing buflomedil pyridoxal phosphate. No significant effect on the resulting R/F-ratios was found with the investigated different viscosity grades of HPMC, whereas the addition of the impermeable coatings significantly affected the governing release mechanism (Fig. 3). Uncoated matrix tablets showed very low, and partially coated systems much higher R/F-ratios. The authors concluded that the importance of the relaxational contribution for drug release is more pronounced in the case of partially coated HPMC matrix tablets.

5. Comprehensive mechanistic theories

Fu and co-workers [75] described an analytical solution of Fick's second law for cylindrical geometry, considering mass transfer in three dimensions:

$$\frac{M_t}{M_\infty} = 1 - \frac{8}{h^2 r^2} \sum_{m=1}^{\infty} \alpha_m^{-2} \exp(-D\alpha_m^2 t) \times \sum_{n=1}^{\infty} \beta_n^{-2} \exp(-D\beta_n^2 t) \tag{8}$$

with

$$J_0(r\alpha) = 0 \tag{9}$$

and

$$\beta_n = \frac{(2n+1)\pi}{2h} \tag{10}$$

Here, M_t and M_∞ are the amount of drug released at time t and infinite time, respectively; h denotes the half-length and r the radius of the cylinder. The constant diffusion coefficient is represented by D, t is the time, α and β are defined by the above given equations, with J_0 being a zero-order Bessel function; m and n are integers. This model is applicable to tablets that range from the shape of a flat disk (radius>thickness) to that of a cylindrical rod (radius<thickness), the drug being homogeneously distributed within the system. But they did not consider the volume expansion of the system and assumed constant diffusion coefficients.

Peppas et al. [76] presented a drug diffusion model for the case of diffusion of an initially uniformly distributed drug through a polymeric matrix. Drug diffusion from a single surface is analyzed for the case of countercurrent diffusion of a solvent which is thermodynamically compatible with the polymer. Due to swelling, considerable volume expansion is observed leading to a moving boundary diffusion problem. Drug concentration profiles within the polymer and drug release rates can be determined. The results are in good agreement with experimental data obtained for the system of KCl distributed in HPMC matrix tablets (Fig. 4). Singh and Fan [77] developed a generalized mathematical model for the simultaneous transport of a drug and a solvent in a planar glassy polymer matrix. The drug diffuses out of the matrix which is undergoing macromolecular chain relaxation and volume expansion due to solvent absorption from the environment into the matrix. The swelling behavior of the polymer is characterized by a stress-induced drift velocity term 'v' corresponding to the so-called case-II velocity. The change of volume due to the relaxation phenomenon is assumed instantaneous. The model incorporates convective transport of the two species induced by volume expansion and by stress gradient. However, it was developed for planar systems, not for cylindrical matrices. Cohen and Erneux [78,79] used free boundary problems to model swelling-controlled release. Drug release is achieved by countercurrent diffusion through a penetrant solvent with the release rate being determined by the rate of diffusion of the solvent into the polymer. But also their theory was developed for thin films, and not for cylindrical tablets.

Korsmeyer et al. [80,81] developed a model, describing the diffusion of a penetrant and a solute in a swellable polymer slab. The model was applied to the case of a hydrophilic polymer containing a water-soluble drug, in which the penetrant (water) is sorbed and the drug is desorbed. The model allows the incorporation of any appropriate form of the diffusion coefficients. A Fujita-type exponential dependence on penetrant concentration was chosen [82] and shown to be adequate for the prediction of a range of transport behavior. Dimensional changes in the sample are predicted by allowing each spatial increment to expand according to the amount of penetrant sorbed. During the initial period of drug release, the swelling is restricted to one dimension by the glassy core of the sample. At a later point in the process, when the center of the sample has sorbed enough penetrant to plasticize it, the sample relaxes to an isotropically swollen state; thereafter, swelling is three-dimensional. The process is modeled as a two-component diffusion in a continuous medium. For the penetrant (water, subscript 1), the following equations are applied:

$$\frac{\partial c_1}{\partial \tau} = \frac{\partial}{\partial \xi}\left(D_1 \frac{\partial c_1}{\partial \xi}\right) \tag{11}$$

where D_1 is the diffusion coefficient of the penetrant, and c_1 is the normalized concentration of the penetrant:

$$c_1 = \frac{c_w}{c_{w,e}} \tag{12}$$

Here, c_w is the penetrant concentration in the polymer, and $c_{w,e}$ is the equilibrium concentration of the penetrant in the polymer. Time t is scaled according to the diffusion coefficient of water in the fully swollen polymer, $D_{1,s}$, and the dry thickness of the slab, L_0:

$$\tau = \frac{tD_{1,s}}{L_0^2} \tag{13}$$

The spatial coordinate x is normalized with respect to the dry thickness of the slab:

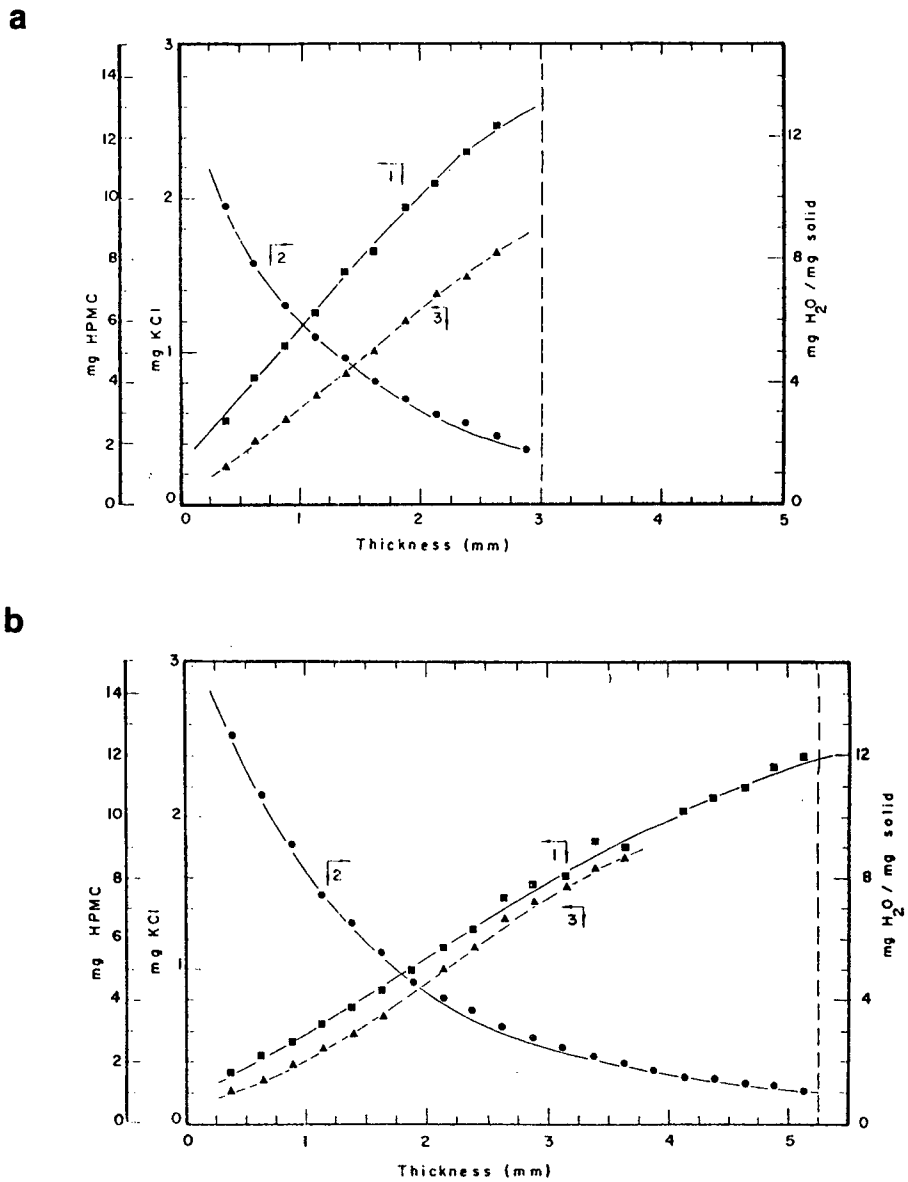

Fig. 4. Use of a comprehensive mechanistic diffusion model [76] to elucidate the involved transport processes from KCl-loaded HPMC tablets. Calculated (curves) and experimentally measured (symbols) concentration profiles of (1) KCl, (2) water, and (3) HPMC 2208 in the gel phase of swollen polymer tablets after (a) 5 h, and (b) 6 h, respectively. The vertical broken line corresponds to the swelling front (reprinted from [76], with permission from Elsevier).

$$\xi = \frac{x}{L_0} \tag{14}$$

To describe drug diffusion (subscript 2) through the polymer, the following equations are used:

$$\frac{\partial c_2}{\partial \tau} = \frac{\partial}{\partial \xi}\left(D_2 \frac{\partial c_2}{\partial \xi}\right) \tag{15}$$

where D_2 is the diffusion coefficient of the drug, and c_2 is the normalized concentration of the drug:

$$c_2 = \frac{c_s}{c_{s,i}} \tag{16}$$

Here, c_s is the drug concentration in the polymer, and $c_{s,i}$ denotes the initial concentration of the drug in the polymer. The following boundary conditions are applied:

$$c_1(0,\tau) = c_1(\xi,\tau) = 1 \tag{17}$$

and

$$c_2(0,\tau) = c_2(\xi,\tau) = 0 \tag{18}$$

where 0 and ξ are the two surfaces of the slab. It has to be emphasized that ξ describes the continuously moving outside surface of the slab. The initial conditions are:

$$c_1(\xi,0) = 0 \tag{19}$$

and

$$c_2(\xi,0) = 1 \tag{20}$$

These sets of differential equations are solved numerically. However, their theory was developed for thin films, not for cylindrical tablets.

A model for the prediction of the relative change in drug release rate as a function of formulation composition for HPMC tablets of adinazolam mesylate and alprazolam was developed by Gao et al. [83,84]. It is based on the steady state approximation to Fick's law for the release of drugs from solid matrices [52], modified by Lapidus and Lordi [57]:

$$M_t = M_0 \frac{S}{V}\left(\frac{D't}{\pi}\right)^{0.5} \tag{21}$$

where M_t denotes the amount of drug released at time t, M_0 is the initial amount of drug within the tablet; S represents the surface area and V the volume available for release, D' is the effective diffusion coefficient, defined by:

$$D' = \frac{D}{\tau} \tag{22}$$

Here, D is the true self-diffusion coefficient of the drug in the pure release medium and τ is the tortuosity of the diffusing matrix. However, the swelling of the system is not taken into account and the mathematical analysis reduced to one dimension.

Ju and co-workers [85–87] developed a comprehensive mathematical model to describe the swelling/dissolution behaviors and drug release from HPMC matrices. The major thrust of this model is to employ an important physical property of the polymer, the polymer disentanglement concentration, $\rho_{p,dis}$, the polymer concentration below which polymer chains detach of the gelled matrix. Furthermore, matrix dissolution is considered similar to the dissolution of an object immersed in a fluid. As a result, a diffusion layer separating the matrix from the bulk solution is incorporated into the transport regime. In addition, an anisotropic expansion model is introduced to account for the anisotropic expansion of the matrix, the surface area in the radial direction dominating over the surface area in the axial direction. They predicted that the overall tablet size and characteristic swelling time correlate with $\rho_{p,dis}$ qualitatively. Two scaling laws were established for the fractional polymer $[M_p(t)/M_p(\text{infinity})]$ and drug $[M_d(t)/M_d(\text{infinity})]$ released as $M_p(t)/M_p(\text{infinity}) \propto M^{-1.05}$ and $M_d(t)/M_d(\text{infinity}) \propto M^{-0.24}$, which is consistent with the limiting polymer molecular weight effect on drug release.

The mathematical analysis is based on the following equation:

$$\left(\frac{\partial \rho_i}{\partial t}\right) = -\frac{\partial \rho_i}{\partial r}\frac{dr}{dt} + \frac{1}{r}\frac{\partial}{\partial r}\left(rD_i\rho_t\frac{\partial w_i}{\partial r}\right) - \rho_i\frac{dV/V}{dt} \tag{23}$$

Here, ρ_i and D_i are the mass concentration and diffusivity of the species i; w_i represents the respective weight fraction, r and t radial position and time; V denotes the volume of the matrix. As can be seen, they restricted the mathematical analysis to radial mass transfer only, neglecting processes in axial direction. The first term on the right hand side is a convection term, arising from the moving boundary. It can also be considered as the interpolation term for calculating the concentrations at each new time step. Muray and Landis [88] assumed a grid point at r to move with a velocity dr/dt. The second term accounts for the Fickian diffusion of the species i, with the diffusivity D_i and the local overall mass concentration ρ_t. The presence of the second term also

implies that the time scale for drug dissolution is much faster than that for drug diffusion, e.g., diffusion (instead of dissolution) of drug molecules is the controlling mechanism of drug release. This assumption is only valid for water-soluble drugs. For poorly water-soluble drugs, a dissolution term needs to be incorporated into the governing equation. The third term is the source term, which considers concentration changes resulting from matrix volume changes. Based on NMR measurements of Gao and Fagerness [83], the following concentration dependencies of the diffusivities are assumed:

$$\frac{D_{s,w}}{D_{w,0}} = k'_w \exp(k_w w_w) \tag{24}$$

$$\frac{D_d}{D_{d,0}} = \exp(-k_{d,p} w_p - k_{d,1} w_1 - k_{d,d} w_d) \tag{25}$$

with $D_{s,w}$ and D_d being the self-diffusion coefficient of water and the mutual diffusion coefficient of the drug. The subscripts w, d and p refer to water, drug and polymer, respectively. The diffusivity of the species i in a dilute solution is denoted by D_{i0}; and k'_w, k_w, and $k_{d,i}$ are the prefactor, and the weighting factors, respectively. For water and polymer, the mutual diffusion coefficient, D_w, is related to the self-diffusion coefficient of water, $D_{s,w}$ and polymer, $D_{s,p}$, as follows [89]:

$$D_w = D_{s,w}\phi_p + D_{s,p}\phi_w \cong D_{s,w}\phi_p \tag{26}$$

where ϕ_i is the volume fraction of the species i. For HPMC they found the following relationship between the polymer disentanglement concentration, $\rho_{p,dis}$, and the polymer molecular weight, M:

$$\rho_{p,dis} = 0.05(M/96000)^{-0.8} \tag{27}$$

This relationship is also illustrated in Fig. 5. At lower polymer molecular weights the variation of $\rho_{p,dis}$ is much more pronounced than at higher molecular weights. For example, $\rho_{p,dis}$ decreases from 0.13 to 0.05 g/ml as the molecular weight increases from 30 to 100 kDa. However, a further increase in molecular weight from 100 to 300 kDa causes a decrease in $\rho_{p,dis}$ by only less than 0.03 g/ml. This observation suggests that the extend of polymer chain entanglement gradually reaches a limit at high polymer molecular weights. Rather

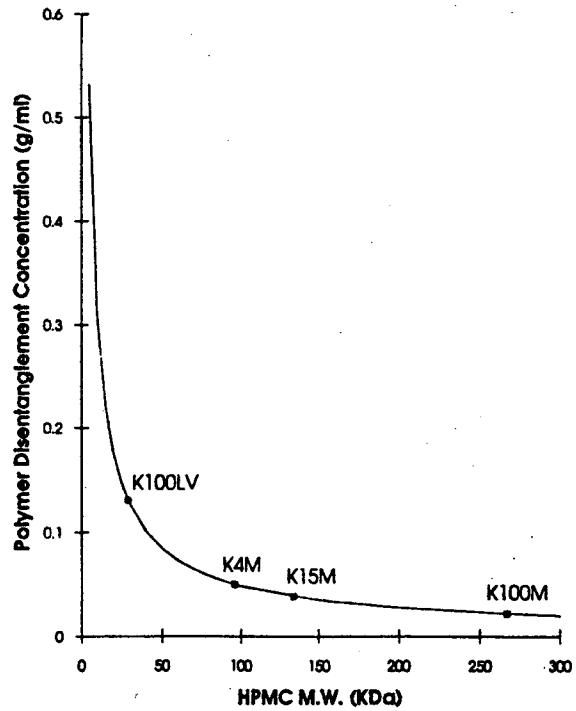

Fig. 5. Dependence of the polymer disentanglement concentration, $\rho_{p,dis}$, for HPMC on the molecular weight of the polymer, according to Ju and co-workers [86]. The filled circle corresponds to $\rho_{p,dis}$ for HPMC K100LV, while the filled squares correspond to $\rho_{p,dis}$ for HPMC K4M, K15M, and K100M, respectively (reprinted from [86], with permission from Wiley & Sons).

good agreement between model predictions for polymer and drug release and experimental data was found (within 15% error, Fig. 6). However, mathematical analysis of mass transport is restricted to radial processes only, ignoring axial transport phenomena.

Recently ([5,11,69,90]), a new comprehensive mathematical model has been developed describing drug release from HPMC-based matrix tablets, taking into account the diffusion of water and drug, non-constant diffusivities, moving boundary conditions, the swelling of the system, polymer and drug dissolution, and radial and axial mass transfer in cylindrical geometries. This model is valid for various kinds of HPMC types (even for derivatives, such as hydroxypropyl methylcellulose acetate succinate, HPMCAS [91]), freely and poorly water-soluble drugs and a wide range of initial drug loadings. It has successfully been used to describe the effect of

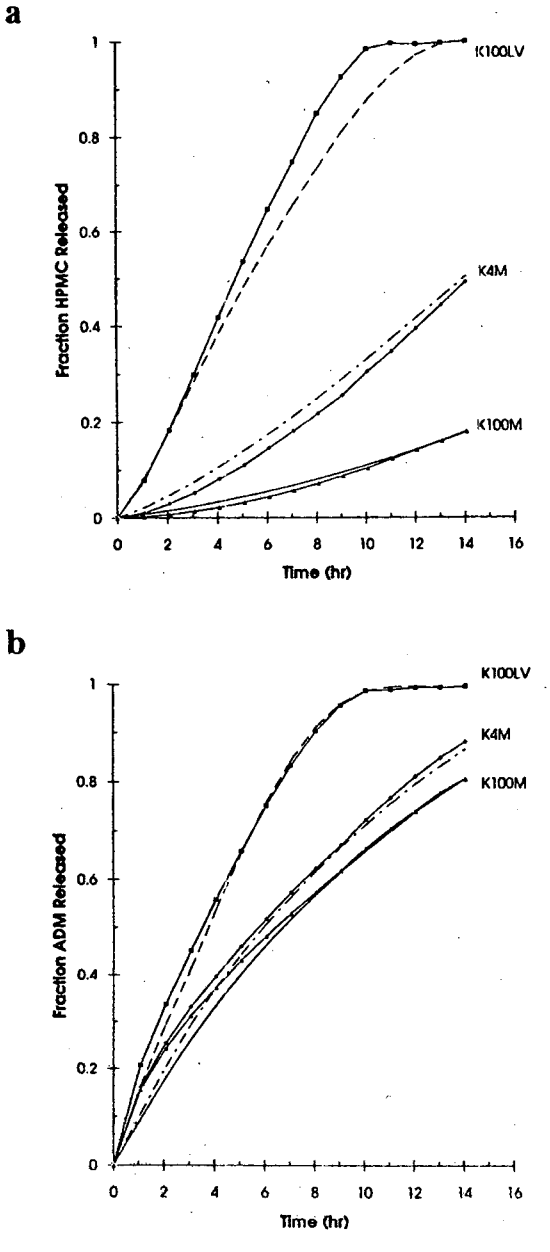

Fig. 6. Comparison of model predictions (broken curves) and experimental data (solid curves) for fractional (a) HPMC, and (b) adinazolam mesylate (ADM) release from HPMC-based matrices. Each tablet weights 500 mg, with a radius and thickness of 3.85 mm and 7.7 mm, respectively. The composition of each tablet is as follows: 35% HPMC, 62% lactose, 2.5% adinazolam mesylate, and 0.5% magnesium stearate (reprinted from [86], with permission from Wiley & Sons).

the design parameters of HPMC-based controlled release systems, such as size and shape of matrix tablets and composition of the device (type and amount of drug and type and amount of polymer).

Polymer dissolution is taken into account using the reptation theory [92–94]. Above a certain critical water concentration, c_{1crit}, the polymer chains at the surface of the system start to disentangle and diffuse through the unstirred layer into the bulk fluid. A dissolution rate constant, k_{diss}, is considered characterizing the polymer mass loss velocity normalized to the actual surface area of the system:

$$M_{pt} = M_{p0} - k_{diss} A_t t \tag{28}$$

Here, M_{pt} and M_{p0} are the dry polymer matrix mass at time t, and $t=0$, respectively; A_t denotes the surface area of the device at time t. Water and drug diffusion are described using Fick's second law of diffusion for cylindrical geometry, taking into account axial and radial mass transport and concentration-dependent diffusivities [7]:

$$\frac{\partial c_k}{\partial t} = \frac{1}{r}\left\{\frac{\partial}{\partial r}\left(rD_k\frac{\partial c_k}{\partial r}\right) + \frac{\partial}{\partial \theta}\left(\frac{D_k}{r}\frac{\partial c_k}{\partial \theta}\right) + \frac{\partial}{\partial z}\left(rD_k\frac{\partial c_k}{\partial z}\right)\right\} \tag{29}$$

Here, c_k and D_k are the concentration and diffusion coefficient of the diffusing species ($k=1$ for water, $k=2$ for the drug), respectively; r denotes the radial coordinate, z is the axial coordinate, θ is the angular coordinate, and t represents time (Fig. 7). According to the free volume theory of diffusion, a Fujita-type [82] exponential dependence of the diffusion coefficients on the water content of the system is taken into account:

$$D_k = D_{kcrit}\exp\left\{-\beta_k\left(1-\frac{c_1}{c_{1crit}}\right)\right\} \tag{30}$$

where β_1 and β_2 are dimensionless constants characterizing this concentration-dependence. Also D_{1crit} and D_{2crit} denote the diffusion coefficients of water and drug at the interface matrix/release medium, where polymer chain disentanglement occurs [85,86,92–94]. Ideal mixing is assumed (no volume contraction upon mixing drug, polymer and water), and the total volume of the system at any instant is given by the sum of the volumes of the single

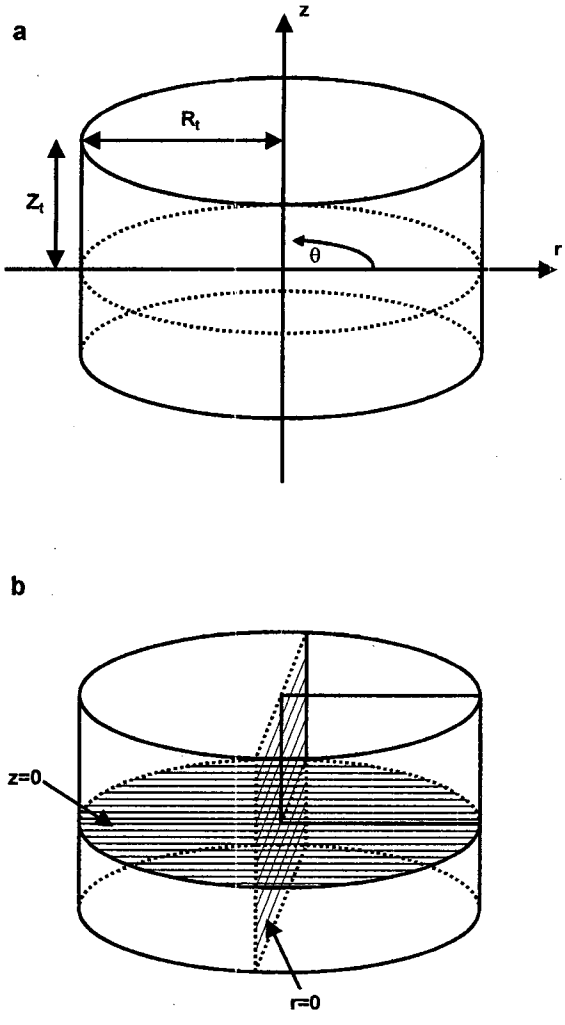

Fig. 7. (a) Schematic of an HPMC matrix tablet for the mathematical analysis of a comprehensive mechanistic model [5,11,69,90], with (b) symmetry planes in axial and radial direction for the water and drug concentration profiles (R_t and Z_t represent the time-dependent radius and half-height of the cylindrical matrices, respectively).

components. The calculation of the new matrix dimensions is based on a mass balance considering drug, polymer and water. The initial conditions reflect the fact that the matrix is dry and the drug uniformly distributed throughout the device at $t=0$. For the definition of the boundary conditions the water concentration at the surface of the matrix, c_{1crit}, is calculated from the polymer disentanglement concentration [85,86,92–94], and the drug concentration at the surface of the matrix is assumed to be equal to zero (perfect sink condition). To minimize computation time, the origin of the coordinate system is placed at the center of the matrix, resulting in two symmetry planes for the drug and water concentration profiles (Fig. 7). Thus, only the concentration profiles within a quarter of the cylindrical matrix have to be calculated. Owing to the concentration dependence of the diffusion coefficients and to the time-variant composition and dimensions of the system, the described set of partial differential equations is solved numerically, using finite differences.

A practical application of this model is shown in Fig. 8. The effect of the initial theophylline loading on the resulting absolute and relative release rates from HPMC tablets is illustrated in phosphate buffer pH 7.4 (Figs. 8a and c), and 0.1 N HCl (Figs. 8b and d), respectively. With increasing initial drug loading the relative release rate first decreases and then increases, whereas the absolute release rate monotonically increases in both media. This phenomenon can be explained as follows. With increasing initial drug loading the porosity of the matrix upon drug depletion increases. Thus, the resistance for further drug diffusion decreases. This effect leads to increased absolute drug transfer rates. However, another phenomenon also has to be taken into account. When the amount of drug present at a certain position within the matrix exceeds the amount of drug soluble under the given conditions, the excess of drug has to be considered as non-dissolved and thus not available for diffusion. The solid drug remains within the tablet. When increasing the initial drug loading of poorly water-soluble drugs this excess of drug remaining within the matrix increases, whereas the resulting drug concentration gradient (being the driving force for diffusion) not increases. Thus, the absolute amount of drug released within a certain time period remains constant, while the 100%-reference value increases. In consequence, the relative drug release rate decreases. This non-dissolved drug effect can overcompensate the above described porosity effect, as illustrated in Figs. 8a and b. These phenomena are not straightforward and have to be accurately taken into account when designing new controlled drug delivery systems. It is a crucial point for the practical importance of a

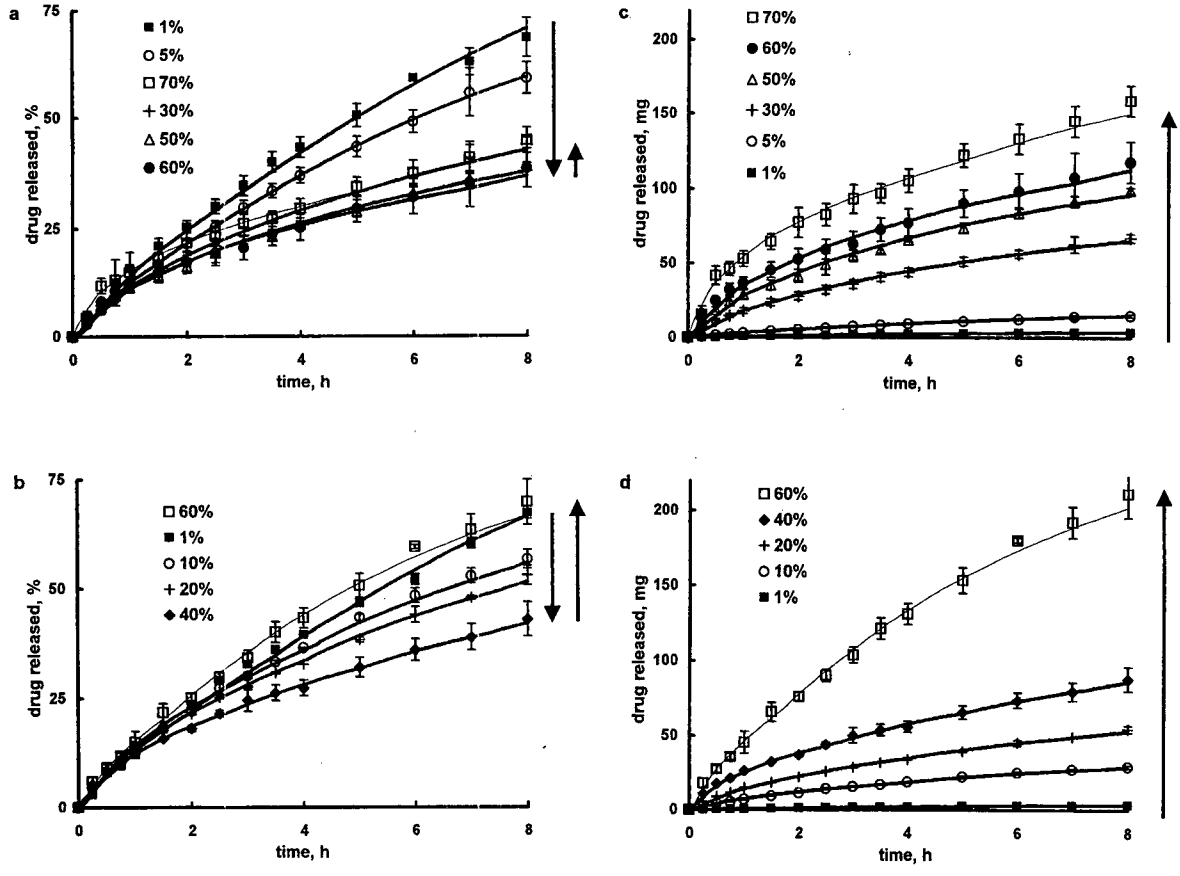

Fig. 8. Practical application of a comprehensive mechanistic model to experimental drug release data. Effect of the initial theophylline loading on the resulting release kinetics from HPMC tablets in (a) phosphate buffer (pH 7.4), relative values (■ 1%, ○ 5%, □ 70%, + 30%, △ 50%, ● 60%), (b) 0.1 N HCl, relative values (□ 60%, ■ 1%, ○ 10%, + 20%, ♦ 40%), (c) phosphate buffer (pH 7.4), absolute values (□ 70%, ● 60%, Δ 50%, + 30%, ○ 5%, ■ 1%), (d) 0.1 N HCl, absolute values (□ 60%, ♦ 40%, + 20%, ○ 10%, ■ 1%) (500 mg tablets, initial radius = 0.6 cm, 37°C, curves: calculated values, symbols: experimental results).

mathematical model to consider these aspects and to predict precisely the resulting drug release rates.

6. Conclusions

A large spectrum of mathematical models describing drug release from HPMC-based controlled release devices has been developed. The choice of the appropriate model for a particular purpose depends on various aspects. Of course, certain device design parameters, such as the geometry of the system or the amount and water-solubility of the incorporated drug already exclude some of the models. But probably the most important aspect when developing new pharmaceutical products or elucidating drug release mechanisms is the desired/required predictive ability and accuracy of the model. In many cases, the use of simple empirical or semi-empirical models is fully sufficient. However, when reliable, detailed information are required, more complex, mechanistic theories must be applied.

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Display Settings: Abstract

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Role of cellulose ether polymers on ibuprofen release from matrix tablets.

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Abstract

Cellulose derivatives are the most frequently used polymers in formulations of pharmaceutical products for controlled drug delivery. The main aim of the present work was to evaluate the effect of different cellulose substitutions on the release rate of ibuprofen (IBP) from hydrophilic matrix tablets. Thus, the release mechanism of IBP with methylcellulose (MC25), hydroxypropylcellulose (HPC), and hydroxypropylmethylcellulose (HPMC K15M or K100M) was studied. In addition, the influence of the diluents lactose monohydrate (LAC) and beta-cyclodextrin (beta-CD) was evaluated. Distinct test formulations were prepared containing: 57.14% of IBP, 20.00% of polymer, 20.29% of diluent, 1.71% of talc lubricants, and 0.86% of magnesium stearate as lubricants. Although non-negligible drug-excipient interactions were detected from DSC studies, these were found not to constitute an incompatibility effect. Tablets were examined for their drug content, weight uniformity, hardness, thickness, tensile strength, friability, porosity, swelling, and dissolution performance. Polymers MC25 and HPC were found to be unsuitable for the preparation of this kind of solid dosage form, while HPMC K15M and K100M showed to be advantageous. Dissolution parameters such as the area under the dissolution curve (AUC), the dissolution efficiency (DE(20 h)), dissolution time (t 50%), and mean dissolution time (MDT) were calculated for all the formulations, and the highest MDT values were obtained with HPMC indicating that a higher value of MDT signifies a higher drug retarding ability of the polymer and vice-versa. The analysis of the drug release data was performed in the light of distinct kinetic mathematical models-Kosmeyer-Peppas, Higuchi, zero-, and first-order. The release process was also found to be slightly influenced by the kind of diluent used.

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31

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Different HPMC viscosity grades as coating agents for an oral time and/or site-controlled delivery system: a study on process parameters and in vitro performances.

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Abstract

Currently, delayed/pulsatile release and colon delivery represent topics of remarkable interest. The present paper deals with the study and development of an oral dosage form devised to release drugs following a programmed time period after administration or, when opportune design modifications are introduced, to target the colon. The system is composed of a drug-containing core and a hydrophilic swellable polymeric coating capable of delaying drug release through slow interaction with aqueous fluids. An optional external gastroresistant film is applied to overcome gastric emptying variability, thus allowing colon delivery to be pursued according to the time-dependent approach. The aim of this work was to evaluate different hydroxypropyl methylcellulose (HPMC) viscosity grades as possible materials for the attainment of the system retarding hydrophilic layer. Both the relevant suitability for application onto tablet cores by aqueous spray-coating in fluid bed and capability of delaying drug release for a programmable period were explored and compared. Methocel E50 was found to afford the best balance among different important items, i.e. process time, retarding ability, dimensions of the coated units and possibility of finely tuning the delay duration. Further results pointed out the robustness of Methocel E50-based systems, which have shown to be practically unaffected by the concentration of the employed coating solution and the pH of the release medium, as well as only poorly influenced by ionic strength, at least with regard to values encompassed in the physiological range for gastrointestinal fluids.

PMID: 15265517 [PubMed - indexed for MEDLINE]

United States Patent [19]

Lui

[11] **Patent Number: 5,009,895**

[45] **Date of Patent: Apr. 23, 1991**

[54] **SUSTAINED RELEASE WITH HIGH AND LOW VISCOSITY HPMC**

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[73] Assignee: **Merck & Co., Inc.**, Rahway, N.J.

[21] Appl. No.: **473,801**

[22] Filed: **Feb. 2, 1990**

[51] **Int. Cl.**[5] **A61K 9/20**

[52] **U.S. Cl.** **424/465**; 424/494; 424/480

[58] **Field of Search** 424/465, 494, 480

[56] **References Cited**

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[57] **ABSTRACT**

Sustained release formulations are disclosed which contain a therapeutically active medicament and a high and low viscosity HPMC and which exhibit a zero order release profile.

11 Claims, No Drawings

SUSTAINED RELEASE WITH HIGH AND LOW VISCOSITY HPMC

BACKGROUND OF THE INVENTION

Sustained release formulations containing a pharmacologically active agent and exhibiting a zero order release rate are particularly useful.

Ibuprofen is a well-known analgesic which has been used to treat chronic pain such as that associated with arthritic and rheumatic conditions. In such cases the analgesic is best administered so as to sustain its action over a period of time and to have a uniform level of analgesic action over this extended time period. This objective can partly be achieved by the repeated administration of a rapid release dosage. However, this procedure clearly has patient acceptability problems as well as a repeated raising and lowering of the blood levels of analgesic.

Generally, the release profiles in controlled release formulations follow a classical square root of time relationship, i.e., the release rate decreases with time. In a zero order composition a plot of the rate of release of drug vs. time shows a straight horizontal line, i.e., the release rate is independent of time. Zero order sustained release compositions provide a more uniform delivery of the therapeutic agent over long periods of time.

Sustained release formulations for ibuprofen have been disclosed in EP publication No. 255,404, however the formulations disclosed do not provide for a zero order release rate. In WO No. 87/00044 a sustained release formulation, exhibiting a bimodal controlled release, is disclosed. The carrier base is composed of a bimodal hydroxypropylmethylcellulose (HPMC) and the medicament selected from an antiflammatory group such as flurbiprofen. The publication is silent on the formulation of zero order release compositions. The Boots Company PLC, EP No. 234,670 has disclosed a sustained release composition containing xanthan gum wherein the medicament may be ibuprofen. The Boots formulation does not solve the problem of a zero order release rate.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a carrier base material for therapeutically active medicaments in a solid dosage formulation wherein the carrier base comprises:

(a) a high viscosity HPMC; and

(b) a low viscosity HPMC wherein the high and low viscosity HPMC are in a ratio yielding a zero order release profile for the medicament.

In the present invention it has unexpectedly been found that a zero-order release profile can be obtained by controlling the ratio of high to low viscosity HPMC in a carrier base formulation.

A high viscosity HPMC is defined as one having a molecular weight of 60,000 or greater. A low viscosity HPMC is defined as one having a molecular weight of 50,000 or less.

The preferred low viscosity HPMC are available as Dow Methocel cellulose ethers E5, E15LV, E50LV, AND K100LV. The preferred high viscosity HPMC are available as Dow Methocel cellulose ethers E4M CR, E10M CR, K4M, K15M, AND K100M.

The methocel cellulose ethers are characterized by their methoxy and hydroxypropyl content and viscosity as shown in the following table:

	Methocel Cellulose Ethers								
	E5	E15LV	E50LV	K100LV	E4M	E10M	K4M	K15M	K100M
Methoxyl %	28-30	28-30	28-30	19-24	19-24	28-30	19-24	19-24	19-24
Hydroxypropyl %	7-12	7-12	7-12	7-12	7-12	7-12	7-12	7-12	7-12
Viscosity cps (2% in water)	4-6	12-18	40-60	100	4000	10,000	4000	15,000	100,000

The medicament in the present invention may be selected from ibuprofen, or salts of ibuprofen. Most preferably the medicament is ibuprofen lysine which should be taken to mean all stereoisomeric configurations including racemic ibuprofen lysine and (S)-ibuprofen-(S)-lysine; i.e. the salt formed from (S)-ibuprofen and (S)-lysine.

It should be appreciated that a zero order release profile is obtained only with a certain relative range of high to low viscosity HPMC. This may be illustrated by the combination of 1 part high viscosity E10M CR and a varying amount of any of the preferred low viscosity HPMC wherein a zero order release was found, for example:

(i) 1 part E10M CR: 3 parts E5;
(ii) 1 part E10M CR: 2 to 4 parts E15LV;
(iii) 1 part E10M CR: 3 to 9 parts E50LV;
(iv) 1 part E10M CR: 3 to 9 parts K100LV.

These ranges are not limited to combinations where the high viscosity HPMC is E10M CR but are to be expected with any of the other preferred high viscosity HPMC.

The medicament, preferably ibuprofen lysine is mixed with Povidone USP (PVP) which functions as a binding agent. Typically the ratio of drug to PVP is 20:1.

The percent of drug/PVP granules in the pharmaceutical composition is 33.3 to 83%.

The range of ibuprofen in this invention is preferably 100 to 600 mg per tablet.

Where the medicament is ibuprofen lysine the weight range is 100 to 600 mg measured in mg ibuprofen.

The percent range of HPMC carrier base is 17-66%.

An example of the composition and processing of the controlled release dosage form is provided below:

Composition:	
Ibuprofen Lysine	61.8%
PVP	3.0%
Carrier Base	34.1%
Magnesium Stearate	1.0%
Total	99.9%

Fillers such as Avicel, lactose, manitol, dicalcium phosphate, starch or pregelatin starch 1500 may be added to the composition. Binders such as corn starch, pregelatin starch 1500, Klucel LF, methocel E3, E5, gelatin or acacia may be added as necessary by those skilled in the art. Besides magnesium stearate, other

lubricants such as stearic acid, sodium stearate fumerate or calcium stearate may be employed.

Processing

A batch of ibuprofen lysine granules containing PVP was prepared. An appropriate amount of granules, typically 3.21 grams was removed and mixed in a V-blender for 10 minutes with a carrier base, usually 1.71 grams, chosen from the preferred high viscosity and low viscosity HPMC. The resultant mixture was then mixed in a V-blender for three minutes with magnesium stearate, which had previously been sieved through a #60 mesh screen. Tablets of about 980 mg were compressed on an F-press.

Tables I-V provide release profiles for controlled release tablets prepared following the processing described above and containing 600 mg Ibuprofen Lysine and 330 mg carrier base. Dissolution determinations were conducted using an automated dissolution testing unit such as a Beckman Spectrophotometer, model DU65, connected with a Vanderkamp 600 six-spindle dissolution tester. Samples were taken every hour for at least 12 to 24 hours and absorbance was read spectrophotometrically at 260 nm.

All the HPMC polymers described are available from the Dow Chemical Company. Racemic ibuprofen lysine may be prepared following the description in U.S. Pat. No. 4,279,926. (S)-ibuprofen-(S)-lysine is prepared as described in copending application Ser. No. 422,466 filed Oct. 18, 1989.

TABLE I

Release Profiles of Ibuprofen Lysine Using 25% E4MCR and 75% of a Low Viscosity HPMC

Time [hr]	75% E15LV MEAN ABSORBANCE	75% E50 MEAN ABSORBANCE	75% K100LV MEAN ABSORBANCE
0	0.0000	0.0000	0.0000
1	0.1125	0.1160	0.0820
2	0.1885	0.1935	0.1400
3	0.2570	0.2615	0.1940
4	0.3180	0.3230	0.2440
5	0.3735	0.4080	0.2920
6	0.4265	0.5290	0.3375
7	0.4945	0.6265	0.3860
8	0.5975	0.6820	0.4445
9	0.6855	0.7190	0.5045
10	0.7280	0.7405	0.5750
11	0.7520	0.7555	0.6350
12	0.7540	0.7620	0.6845
13	0.7500	0.7675	0.7225
14	0.7445	0.7680	0.7515
15	0.7405	0.7670	0.7695
16			0.7785
17			0.7825
18			0.7835
19			
20			
21			
22			
23			
24			

TABLE II

Release Profiles of Ibuprofen Lysine Using Various Ratios of E10MCR and a Low Viscosity HPMC

Time [hr]	25% E10MCR: 75% E5 MEAN ABSORBANCE	33.3% E10MCR: 66.7% E15LV MEAN ABSORBANCE	20% E10MCR: 80% E15LV MEAN ABSORBANCE	25% E10MCR 75% E50 MEAN ABSORBANCE	10% E10MCR 90% E50LV MEAN ABSORBANCE	25% E10MCR 75% K100LV MEAN ABSORBANCE	10% E10MCR 90% K100LV MEAN ABSORBANCE
0	0.0000	0.0010	0.0010	0.0000	0.0005	0.0000	0.0005
1	0.0985	0.1140	0.1615	0.1095	0.1250	0.0790	0.1120
2	0.1670	0.1720	0.2420	0.1855	0.1960	0.1360	0.1775
3	0.2335	0.2210	0.3130	0.2570	0.2540	0.1845	0.2325
4	0.3055	0.2630	0.3760	0.3220	0.3065	0.2300	0.2845
5	0.3960	0.3050	0.4345	0.3870	0.3580	0.2715	0.3325
6	0.4800	0.3450	0.5265	0.4505	0.4110	0.3125	0.3825
7	0.5630	0.3840	0.5975	0.5140	0.4810	0.3525	0.4360
8	0.6505	0.4220	0.6525	0.5780	0.5475	0.3905	0.4900
9	0.6875	0.4600	0.7095	0.6220	0.5990	0.4305	0.5595
10	0.7165	0.4970	0.7475	0.6645	0.6525	0.4730	0.6235
11	0.7235	0.5345	0.7565	0.7020	0.6885	0.5210	0.6785
12	0.7255	0.5835	0.7590	0.7255	0.7080	0.5685	0.7170
13	0.7260	0.6410	0.7600	0.7395	0.7200	0.6045	0.7365
14	0.7245	0.6915	0.7575	0.7510	0.7275	0.6415	0.7390
15	0.7240	0.7230	0.7530	0.7560	0.7310	0.6715	0.7370
16	0.7240	0.7395	0.7525	0.7600	0.7290	0.6905	0.7360
17	0.7240	0.7425	0.7520	0.7630	0.7260	0.7080	0.7340
18	0.7245	0.7435	0.7520	0.7650	0.7260	0.7225	0.7360
19	0.7255	0.7455		0.7670		0.7345	
20	0.7265	0.7440		0.7680		0.7395	
21	0.7275	0.7420		0.7700		0.7440	
22	0.7290	0.7420		0.7725		0.7450	
23	0.7290	0.7410		0.7740			
24	0.7310	0.7395		0.7755			

TABLE III

Release Profiles of Ibuprofen Lysine Using Various Ratios of K4M and a Low Viscosity HPMC

Time [hr]	50% K4M 50% E5 MEAN ABSORBANCE	25% K4M 75% E15LV MEAN ABSORBANCE	25% K4M 75% E5 MEAN ABSORBANCE	25% K4M 75% K100LV MEAN ABSORBANCE
0	0.0000	0.0000	0.0000	0.0000
1	0.1155	0.1010	0.0995	0.0815

TABLE III-continued

Release Profiles of Ibuprofen Lysine Using Various Ratios of K4M and a Low Viscosity HPMC

Time [hr]	50% K4M 50% E5 MEAN ABSORBANCE	25% K4M 75% E15LV MEAN ABSORBANCE	25% K4M 75% E5 MEAN ABSORBANCE	25% K4M 75% K100LV MEAN ABSORBANCE
2	0.1795	0.1700	0.1565	0.1390
3	0.2315	0.2335	0.2110	0.1895
4	0.2815	0.2905	0.2630	0.2365
5	0.3655	0.3490	0.3130	0.2815
6	0.4095	0.4360	0.4395	0.3260
7	0.4465	0.5510	0.5270	0.3705
8	0.4925	0.6430	0.5815	0.4225
9	0.5695	0.6990	0.6305	0.4850
10	0.6550	0.7405	0.6580	0.5435
11	0.7045	0.7560	0.6775	0.6000
12	0.7235	0.7565	0.6950	0.6500
13	0.7360	0.7515	0.7060	0.6740
14	0.7400	0.7445	0.7175	0.6920
15	0.7460	0.7415	0.7245	0.7040
16	0.7535	0.7450	0.7260	0.7220
17	0.7525	0.7435	0.7275	0.7315
18	0.7555	0.7415	0.7270	0.7380
19	0.7605	0.7405	0.7305	
20	0.7605	0.7400	0.7305	
21	0.7650	0.7425	0.7320	
22	0.7635		0.7310	
23	0.7660	24		

TABLE IV

Release Profiles of Ibuprofen Lysine Using Various Ratios of K15M and a Low Viscosity HPMC

Time [hr]	25% K15M 75% E5 MEAN ABSORBANCE	25% K15M 75% E15LV MEAN ABSORBANCE	25% K15M 75% E50 MEAN ABSORBANCE	25% K15M 75% K100LV MEAN ABSORBANCE
0	0.0000	0.0000	0.0000	0.0000
1	0.1280	0.0935	0.0855	0.0950
2	0.2110	0.1540	0.1425	0.1640
3	0.2830	0.2085	0.1915	0.2225
4	0.3640	0.2590	0.2390	0.2740
5	0.4350	0.3070	0.2810	0.3215
6	0.5060	0.3530	0.3265	0.3665
7	0.6475	0.3980	0.3970	0.4120
8	0.7215	0.4470	0.4890	0.4575
9	0.7360	0.5505	0.5535	0.5040
10	0.7415	0.6200	0.5945	0.5485
11	0.7410	0.6655	0.6125	0.5910
12	0.7395	0.6815	0.6400	0.6245
13	0.7435	0.6850	0.6590	0.6490
14	0.7475	0.7040	0.6910	0.6650
15	0.7490	0.7250	0.7085	0.6845
16	0.7520	0.7365	0.7295	0.7035
17	0.7505	0.7395	0.7395	0.7160
18	0.7515	0.7390	0.7400	0.7235
19	0.7485	0.7405	0.7330	0.7305
20	0.7525	0.7405	0.7355	0.7345
21	0.7500	0.7360	0.7255	0.7385
22				0.7415

TABLE V

Release Profiles of Ibuprofen Lysine Using 25% K100M and 75% of a Low Viscosity HPMC.

Time [hr]	75% E15LV MEAN ABSORBANCE	75% E50 MEAN ABSORBANCE
0	0.0000	0.0000
1	0.0820	0.1005
2	0.1330	0.1615
3	0.1800	0.2180
4	0.2225	0.2680
5	0.2630	0.3150
6	0.3025	0.3630
7	0.3405	0.4230
8	0.3805	0.4950
9	0.4240	0.5465

TABLE V-continued

Release Profiles of Ibuprofen Lysine Using 25% K100M and 75% of a Low Viscosity HPMC.

Time [hr]	75% E15LV MEAN ABSORBANCE	75% E50 MEAN ABSORBANCE
10	0.4880	0.5940
11	0.5510	0.6350
12	0.5945	0.6715
13	0.6335	0.7000
14	0.6650	0.7215
15	0.6950	0.7370
16	0.7195	0.7485
17	0.7395	0.7575
18	0.7530	0.7655
19	0.7680	0.7710

TABLE V-continued

Release Profiles of Ibuprofen Lysine Using 25% K100M and 75% of a Low Viscosity HPMC.

Time [hr]	75% E15LV MEAN ABSORBANCE	75% E50 MEAN ABSORBANCE
20	0.7740	0.7755
21	0.7795	0.7770
22	0.7825	0.7785
23		0.7800
24		0.7820

What is claimed is:

1. A carrier base material combined with a therapeutically active medicament and shaped and compressed to a solid sustained release pharmaceutical dosage form having a zero order release profile upon administration, carrier base material comprising:

(a) a high viscosity HPMC; having a molecular weight of 60,000 or greater; and

(b) a low viscosity HPMC, having a molecular weight of 50,000 or less, wherein the high and low viscosity HPMC are in a ratio yielding a zero order release profile.

2. A zero order release pharmaceutical formulation according to claim 1 in which the high viscosity HPMC is selected from a methocel cellulose ether wherein:

(a) % methoxy=19-24, % hydroxypropyl=7-12, viscosity=4000 cps;

(b) % methoxy=28-30, % hydroxypropyl=7-12, viscosity=10,000;

(c) % methoxy=19-24, % hydroxypropyl=7-12, viscosity=4,000;

(d) % methoxy=19-24, % hydroxypropyl=7-12, viscosity=15,000;

(e) % methoxy=19-24, % hydroxypropyl=7-12, viscosity=100,000;

and the low viscosity HPMC is selected from a methocel cellulose ether wherein:

(a) % methoxy=28-30, % hydroxypropyl=7-12, viscosity=4-6;

(b) % methoxy=28-30, % hydroxypropyl=7-12, viscosity=12-18;

(c) % methoxy=28-30, % hydroxypropyl=7-12, viscosity=40-60;

(d) % methoxy=19-24, % hydroxypropyl=7-12, viscosity=100.

3. A zero order release pharmaceutical formulation according to claim 2 wherein the high viscosity HPMC is 1 part methocel cellulose ether wherein % methoxy=28-30, % hydroxypropyl=7-12 and viscosity=10,000 and wherein the low viscosity HPMC is selected from;

(a) 3 parts wherein % methoxy=28-30, % hydroxypropyl=7-12, and viscosity=4-6;

(b) 2 to 4 parts wherein % methoxy=28-30, % hydroxypropyl=7-12, and viscosity=12-18;

(c) 3 to 9 parts wherein % methoxy=28-30, % hydroxypropyl=7-12, and viscosity=40-60; or

(d) 3 to 9 parts wherein % methoxy=19-24, % hydroxypropyl=7-12, and viscosity=100.

4. A zero order release pharmaceutical formulation according to claim 2 wherein the high viscosity HPMC is 1 part wherein % methoxy=19-24, % hydroxypropyl=7-12, and viscosity=4,000 and wherein the low viscosity HPMC is selected from:

(a) 2 to 4 parts wherein % methoxy=28-30, % hydroxypropyl=7-12, and viscosity=12-18;

(b) 3 to 9 parts wherein % methoxy=28-30, % hydroxypropyl=7-12, and viscosity=40-60;

(c) 3 to 9 parts wherein % methoxy=19-24, % hydroxypropyl=7-12, and viscosity=100.

5. A zero order release pharmaceutical formulation according to claim 2 wherein the high viscosity HPMC is 1 part wherein % methoxy=19-24, % hydroxypropyl=7-12, and viscosity=4,000 and wherein the low viscosity HPMC is selected from:

(a) 1 part wherein % methoxy=28-30, % hydroxypropyl=7-12, and viscosity=4-6;

(b) 2 to 4 parts wherein % methoxy=28-30, % hydroxypropyl=7-12, and viscosity=12-18;

(c) 3 to 9 parts wherein % methoxy=28-30, % hydroxypropyl=7-12, and viscosity=40-60;

(d) 3 to 9 parts wherein % methoxy=19-24, % hydroxypropyl=7-12, and viscosity=100.

6. A zero order release pharmaceutical formulation according to claim 2 wherein the high viscosity HPMC is one part wherein % methoxy=19-24, % hydroxypropyl=7-12, and viscosity=15,000 and wherein the low viscosity HPMC is selected from:

(a) 1 to 3 parts wherein % methoxy=28-30, % hydroxypropyl=7-12, and viscosity=4-6;

(b) 1 to 3 parts wherein % methoxy=28-30, % hydroxypropyl=7-12, and viscosity=12-18;

(c) 1 to 3 parts wherein % methoxy=28-30, % hydroxypropyl=7-12, and viscosity=40-60;

(d) 3 to 9 parts wherein % methoxy=19-24, % hydroxypropyl=7-12, and viscosity=100.

7. A zero order release pharmaceutical formulation according to claim 2 wherein the high viscosity HPMC is 1 part wherein % methoxy=19-24, % hydroxypropyl=7-12 and viscosity=100,000 and wherein the low viscosity HPMC is selected from:

(a) 1 to 3 parts wherein % methoxy=28-30, % hydroxypropyl=7-12, and viscosity=12-18;

(b) 1 to 3 parts wherein % methoxy=28-30, % hydroxypropyl=7-12, and viscosity=40-60.

8. A zero order release pharmaceutical formulation according to claim 2 wherein the medicament is selected from:

(a) ibuprofen; or

(b) salts of ibuprofen

9. A formulation according to claim 8 wherein the medicament is ibuprofen lysine.

10. A formulation according to claim 9 wherein the medicament is (S)-ibuprofen-(S)-lysine.

11. A formulation according to claim 10 wherein the amount of medicament as ibuprofen is 100 to 600 mg.

* * * * *

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(57) Abstract

By combining the same active ingredient in a form which is readily soluble in water or aqueous liquids and in a delayed and programmable release form in the same solid pharmaceutical form for oral administration, preferably in the form of a double-layered tablet, high plasma levels are obtained immediately after administration which lead to a consequently rapid therapeutic effect and the maintenance of high plasma levels over a prolonged period after administration. The two forms of active ingredient are accompanied by suitable adjuvants and excipients which are capable of causing the rapid disintegration of the layer containing the active ingredient in a readily soluble form and the delayed release of the active ingredient in the delayed release form.

CLAIMS

1. Solid pharmaceutical form for the oral administration of at least one active ingredient, with release of the latter at successive times and at different rates, characterised in that it comprises at least two fractions, of which:

(a) in the first fraction, the active ingredient is contained in the form of a soluble derivative together with technological excipients and adjuvants enabling the mass to be compressed and/or processed and ensuring an immediate release of the active ingredient (or active ingredients if more than one) contained in that fraction;

(b) in the second fraction, the same active ingredient is contained in non-derivative form, characterised by a substantially lower solubility in water and/or aqueous liquids, together with technological excipients and adjuvants which, in this case too, enable the mass to be compressed but which are such that they modulate, in accordance with accurately programmable kinetics and rates, the release of the active ingredient(s) contained in that fraction.

2. Solid pharmaceutical form according to Claim 1, characterised in that the said at least one active ingredient is selected from:

(i) steroidal and non-steroidal anti-inflammatory drugs;

(ii) sleep-inducing and tranquillising substances;

(iii) substances active in the prevention of angina attacks and hypertension attacks;

(iv) anti-histamine and anti-asthmatic substances.

3. Solid pharmaceutical form according to Claim 2, characterised in that the anti-inflammatory drug is selected from ibuprofen, ketoprofen, acetylsalicylic acid, mefenamic acid, flufenamic acid, tiprofenic acid, tolfenamic acid, diflunisal, piroxicam, naproxen, flurbiprofen, sodium diclofenac and indomethacin.

4. Solid pharmaceutical form according to Claim 2, characterised in that the salts of sodium, potassium or inorganic or organic bases of the anti-inflammatory compounds are used as the soluble derivatives of those compounds.

5. Solid pharmaceutical form according to Claim 4, characterised in that the derivatives are glycine, betaine, histidine, lysine, arginine, ornithine, leucine, tyrosine salts either in racemic form or in optically active form.

6. Solid pharmaceutical form according to Claim 2, characterised in that the sleep-inducing and tranquillising substance is selected from diazepam, nitrazepam, clonazepam and oxazepam.

7. Solid pharmaceutical form according to Claim 2, characterised in that the anti-angina and anti-hypertensive substance is selected from diltiazem, urapidil, trapidil benziodaron and dipiridamol.

8. Solid pharmaceutical form according to Claim 2, characterised in that the anti-histamine or anti-asthmatic substance is selected from terfenadin, chlorpheniramine, terbutaline and combinations thereof.

9. Solid pharmaceutical form according to Claim 1, characterised in that the adjuvant substances contained in the first component fraction are selected from the group of the natural and/or synthetic and/or semi-synthetic polymers belonging to the class of the disintegrators and/or super-disintegrators.

10. Solid pharmaceutical form according to Claim 9, characterised in that the polymers are selected from crosslinked polyvinylpyrrolidone, crosslinked sodium carboxymethylcellulose, carboxymethyl starch, a copolymer of potassium methacrylate and divinylbenzene, polyvinyl alcohols, starches and their derivatives, microcrystalline cellulose and derivatives of cellulose, beta-cyclodextrin and derivatives of dextrin in general.

11. Solid pharmaceutical form according to Claim 10, characterised in that the polymers are present in the first fraction in an amount of from 1.0 to 90% by weight based on the weight of the fraction.

12. Solid pharmaceutical form according to Claim 11, characterised in that the polymers are present in the first fraction in an amount of from 20 to 70% by weight based on the weight of the fraction.

13. Solid pharmaceutical form according to Claim 1, characterised in that the adjuvant substances acting as diluents are selected, depending on the hydrophilic characteristics of the active ingredient, from the group consisting of starch, pregelled starch, calcium phosphate, mannitol, lactose, saccharose, glucose, sorbitol and microcrystalline cellulose.

14. Solid pharmaceutical form according to Claim 1, characterised in that the adjuvant substances acting as agglutinants are selected from the group of polymers having a binding power.

15. Solid pharmaceutical form according to Claim 14, characterised in that the polymers are selected from gelatin, polyvinylpyrrolidone, methylcellulose, sizing starch, ethylcellulose, gum arabic and gum tragacanth.

16. Solid pharmaceutical form according to Claim 1, characterised in that the adjuvant substances having the function of promoting the wettability and the solubilisation of the active ingredient are selected from the group consisting of ionic and non-ionic surfactants, saponins and sterols.

17. Solid pharmaceutical form according to Claim 16, characterised in that the substance promoting the wettability and solubilisation of the active ingredient is contained in a percentage of from 0.01 to 25% by weight based on the active ingredient.

18. Solid pharmaceutical form according to Claim 1, characterised in that the adjuvant substances acting as lubricants and anti-adherents are selected from the group consisting of magnesium stearate, stearic acid, colloidal silica, glyceryl monostearate, polyoxyethylene glycols having a molecular weight of from 400 to 50000, hydrogenated castor oil, waxes and mono-, di- and tri-substituted glycerides.

19. Solid pharmaceutical form according to Claim 1, characterised in that the adjuvant substances have an effervescent effect and are selected from the group consisting of carbonate of sodium and/or other alkali metals and/or alkaline earth metals, sodium bicarbonate, sodium carbonate glycocoll and other pharmaceutically acceptable salts capable of producing effervescence in an acid medium, citric acid, tartaric acid and fumaric acid.

20. Solid pharmaceutical form according to Claim 1, characterised in that the adjuvant substances producing effervescence are selected from citric acid, tartaric acid and fumaric acid.

21. Solid pharmaceutical form according to Claims 19 and 20, characterised in that the adjuvant substances having an effervescent effect are present in an amount of from 3 to 40% by weight of the weight of the first fraction.

22. Solid pharmaceutical form according to Claim 1, characterised in that the second fraction contains natural and/or synthetic or semi-synthetic biocompatible polymeric materials belonging to the class of the so-called gelling and/or erodible hydrophilic polymers capable of slowing down the release of the active ingredient from the second fraction.

23. Pharmaceutical form according to Claim 22, characterised in that the hydrophilic polymers are selected from the class consisting of hydroxypropylmethylcellulose having a molecular weight of from 1000 to 2,000,000 Daltons, carboxyvinyl polymer, polyvinyl alcohols, glucans, xanthans, mannans, galactomannans, scleroglucans, alginates, pectin, amylose having different degrees of crosslinking, carboxymethylcellulose and its derivatives, methylcellulose, ethylcellulose and their salts and/or derivatives.

24. Pharmaceutical form according to Claims 22 and 23, characterised in that the polymeric substances may be present in a percentage varying from 5 to 90% relative to the total weight of the slow-release fraction.

25. Pharmaceutical form according to Claims 22 and 23, characterised in that the polymeric substances may be present in a percentage varying from 30 to 75% relative to the total weight of the slow-release fraction.

26. Solid pharmaceutical form according to Claim 1, characterised in that it is in the form of a double-layered tablet of which each layer constitutes one of the component fractions.

27. Solid pharmaceutical form according to Claim 26, characterised in that it contains from 1 to 90% by weight of active ingredient.

28. Solid pharmaceutical form according to Claim 26, characterised in that it contains ibuprofen as the active ingredient, with a dimensional distribution of less than 20 microns.

29. Solid pharmaceutical form according to Claim 26, characterised in that it contains sodium lauryl sulphate as the surfactant substance.

30. Solid pharmaceutical form according to Claim 1, characterised in that it is in the form of a hard gelatin capsule which contains one or more tablets containing at least one active ingredient in a form soluble in water and aqueous liquids and one or more

tablets containing the same at least one active ingredient in delayed and programmed release form.

31. Solid pharmaceutical form according to Claim 1, characterised in that it is in the form of a hard gelatin capsule which contains one or more double-layered tablets according to Claim 26.

32. Solid pharmaceutical form according to Claim 1, characterised in that it is in the form of a hard gelatin capsule which contains at least two different granulates of which at least one contains at least one active ingredient in a form readily soluble in water or aqueous liquids and at least one contains the same at least one active ingredient in a delayed and programmed release form.

33. Solid pharmaceutical form according to Claim 32, characterised in that the granulates are in pelletised form.

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Sherwood et al.

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[54] **PHARMACEUTICAL EXCIPIENT HAVING IMPROVED COMPRESSIBILITY**

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[52] **U.S. Cl.** **424/49**; 424/464; 424/489; 424/494; 424/495; 424/496; 424/497; 106/154.51

[58] **Field of Search** 424/489, 494, 424/468, 490, 487, 486, 78.1, 461, 49, 495–497, 464; 106/154.51

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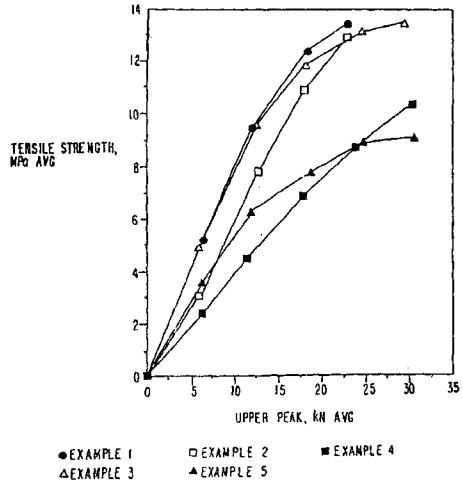
[57] **ABSTRACT**

A microcrystalline cellulose-based excipient having improved compressibility, whether utilized in direct compression, dry granulation or wet granulation formulations, is disclosed. The excipient is an agglomerate of microcrystalline cellulose particles and from about 0.1% to about 20% silicon dioxide particles, by weight of the microcrystalline cellulose, wherein the microcrystalline cellulose and silicon dioxide are in intimate association with each other. The silicon dioxide utilized in the novel excipient has a particle size from about 1 nanometer to about 100 microns. Most preferably, the silicon dioxide is a grade of colloidal silicon dioxide.

83 Claims, 5 Drawing Sheets



well below that provided by colloidal SiO_2 having surface areas of about 200 m^2/g. In fact, MCC coprocessed with silica gel demonstrates compressibility properties about the same as off-the-shelf MCC in wet granulation formulations.

EXAMPLES 20–22

HS-5 Grade Silicon Dioxide

In these examples, the coprocessing method described in example 1 was repeated using HS-5 grade SiO_2 surface area 325 m^2/g (Cabot Corp., Tuscola, Ill.).

Example	Silica Gel (wt %)
20	2
21	1
22	0.5

The resultant granulates prepared according to Example 1B were tabletted according to the same method described in Example 6 and evaluated for tensile strength. The products of inventive Example 3 (MCC-SiO_2 2% w/w) and Example 5 (off-the-shelf MCC) were included in FIG. **5** for comparison purposes.

Referring now to FIG. **5**, the retention of compressibility afforded by coprocessing with HS-5 is comparable to that obtained using SiO_2 having surface areas of about 200 m^2/g.

While there have been described what are presently believed to be the preferred embodiments of the invention, those skilled in the art will realize that changes and modifications may be made thereto without departing from the spirit of the invention. It is intended to claim all such changes and modifications that fall within the true scope of the invention.

What is claimed is:

1. An aqueous slurry useful in the preparation of a compressible pharmaceutical excipient, comprising a mixture of microcrystalline cellulose in the form of a wet cake and from about 0.1 % to about 20% by weight silicon dioxide based on the weight of said microcrystalline cellulose, said silicon dioxide having an average primary particle size from about 1 nm to about 100 μm, the solids content of said aqueous slurry being from about 0.5% to about 25% by weight, said silicon dioxide being present in an amount from about 0.5% to about 10%, by weight, based on the weight of said microcrystalline cellulose.

2. The slurry of claim **1**, wherein said silicon dioxide is present in an amount from about 1.25% to about 5%, by weight, based on the weight of said microcrystalline cellulose.

3. The slurry of claim **1**, which has a solid content from about 15% to about 20%.

4. The slurry of claim **3**, which has a solid content from about 17% to about 19%.

5. The Slurry of claim **1**, which has been pH-adjusted with a member of the group consisting of ammonium hydroxide, sodium hydroxide and mixtures thereof.

6. The slurry of claim **1**, further comprising a member of the group consisting of non-silicon metal oxides, starches, starch derivatives, surfactants, polyalkylene oxides, celluloses, cellulose ethers, cellulose esters and mixtures thereof.

7. A method of enhancing the compressibility of microcrystalline cellulose in wet granulation products, comprising:

(i) forming an aqueous slurry containing a mixture of microcrystalline cellulose in the form of a wet cake and silicon dioxide having an average primary particle size from about 1 nm to about 100 μm, the amount of silicon dioxide being from about 0.1% to about 20% relative to the amount of microcrystalline cellulose, by weight, wherein said slurry comprises from about 0.5% to about 25% by weight microcrystalline cellulose; and

(ii) drying said slurry to obtain an excipient comprising a plurality of agglomerated particles of microcrystalline cellulose in intimate association with said silicon dioxide.

8. The method of claim **7**, wherein said slurry contains from about 15% to about 20% microcrystalline cellulose.

9. The method of claim **7**, wherein said slurry contains from about 17% to about 19% microcrystalline cellulose.

10. The method of claim **7**, wherein said silicon dioxide is colloidal silicon dioxide.

11. The method of claim **7**, further comprising drying said slurry of microcrystalline cellulose and silicon dioxide by a method selected from the group consisting of flash drying, ring drying, spray drying, and micron drying.

12. The method of claim **7**, further comprising drying said slurry of microcrystalline cellulose and silicon dioxide by spray drying.

13. The method of claim **7**, further comprising drying said slurry such that the resultant excipient particles have an average particle size from about 10 μm to about 1,000 μm.

14. The method of claim **7**, further comprising drying said slurry such that the resultant excipient particles have a particle size of from about 10 μm to about 500 μm.

15. The method of claim **12**, further comprising drying said slurry such that the resultant excipient particles have a particle size of from about 30 μm to about 250 μm.

16. The method of claim **7**, further comprising drying said slurry such that the resultant excipient particles have a moisture content of from about 0.5 to about 15%.

17. The method of claim **7**, wherein said slurry further comprises a member of the group consisting of non-silicon metal oxides, starches, starch derivatives, surfactants, polyalkylene oxides, cellulose, celluloses, celluloses ethers, and mixtures thereof.

18. The microcrystalline cellulose-based excipient particles prepared by the process of claim **7**.

19. The microcrystalline cellulose-based excipient particles prepared by the process of claim **15**.

20. A method of preparing a solid dosage form, comprising:

(a) forming an aqueous slurry containing a mixture of microcrystalline cellulose in the form of a wet cake and silicon dioxide having a particle size from about 1 nm to about 100 μm, the amount of silicon dioxide being from about 0.1% to about 20% relative to the amount of microcrystalline cellulose, by weight;

(b) drying said slurry to obtain an excipient comprising a plurality of agglomerated particles of microcrystalline cellulose in intimate association with said silicon dioxide;

(c) mixing an active ingredient with said excipient in a ratio from about 1:99 to about 99:1;

(d) incorporating said mixture obtained in step (c) into a plurality of solid unit doses.

21. The method of claim **20**, wherein said silicon dioxide is colloidal silicon dioxide, further comprising wet granulating said mixture obtained in step (c) prior to incorporating said mixture into said solid unit doses.

22. The method of claim 22, wherein said aqueous slurry prepared in step (a) comprises from about 0.5% to about 25% by weight microcrystalline cellulose.

23. The method of claim 20, wherein said drying of step (b) is accomplished by spray drying such that the resultant excipient particles have an average particle size from about 10 μm to about 1,000 μm.

24. The method of claim 20, wherein said drying of step (b) is accomplished by spray drying such that the resultant excipient particles have an average particle size from about 30 μm to about 250 μm.

25. The method of claim 20, wherein the resultant excipient particles have a bulk density from about 0.2 g/ml to about 0.6 g/ml.

26. The method of claim 21, wherein the resultant excipient particles have a bulk density of from about 0.35 g/ml to about 0.55 g/ml.

27. The method of claim 21, further comprising wet granulating the mixture of step (c), adding a further amount of excipient obtained in step (b) to said granulation, and thereafter incorporating the mixture into a solid dosage form.

28. The method of claim 21, further comprising wet granulating the mixture of step (b) prior to mixing said excipient with said active ingredient in step (c).

29. The method of claim 28, further comprising adding a further amount of excipient obtained in step (b) to the mixture of said granulation and said active ingredient, and thereafter compressing the mixture into a solid dosage form.

30. The method of claim 21, further comprising wet granulating the mixture of step (c), adding a further amount of a pharmaceutically acceptable excipient to said granulation, and thereafter compressing the mixture into a solid dosage form.

31. The method of claim 28, further comprising adding a further amount of pharmaceutically acceptable excipient to the mixture of said granulation and said active ingredient, and thereafter compressing the mixture into a solid dosage form.

32. A solid dosage form of a compressed mixture of from about 1% to about 99% of an excipient comprising a particulate agglomerate of coprocessed microcrystalline cellulose and from about 0.1% to about 20% by weight silicon dioxide, the microcrystalline cellulose and silicon dioxide being in intimate association with each other, said silicon dioxide portion of said agglomerate being derived from a silicon dioxide having an average primary particle size from about 1 nm to about 100 μm, and from about 99% to about 1% of a systemically active therapeutic agent.

33. The solid dosage form of claim 32, wherein the active agent is an antihistamine.

34. The solid dosage form of claim 33, wherein the antihistamine is selected from the group consisting of dimenhydrinate, diraenhydramine, chlorpheniramine, and dexchlorpheniramine.

35. The solid dosage form of claim 32, wherein the active agent is an analgesic.

36. The solid dosage form of claim 32, wherein the analgesic is selected from the group consisting of aspirin, codene, morphene, dihydromorphone, and oxycodone.

37. The solid dosage form of claim 32, wherein the active agent is a non-steroidal anti-inflammatory agent.

38. The solid dosage form of claim 37, wherein the non-steroidal anti-inflammatory agent is selected form the group consisting of naproxyn, diclofenac, indomethacin, ibuprofen, and sulindac.

39. The solid dosage form of claim 32, wherein the active agent is an anti-emetic.

40. The solid dosage form of claim 39, wherein the anti-emetic is metoclopramide.

41. The solid dosage form of claim 32, wherein the active agent is an anti-epileptic.

42. The solid dosage form of claim 41, wherein the anti-epileptic is selected from the group consisting of phenytoin, meprobamate and nitrezepam.

43. The solid dosage form of claim 32, wherein the active agent is a vasodilator.

44. The solid dosage form of claim 43, wherein the vasodilator is selected from the group consisting of nifedipine, papaverine, diltiazem and nicardirine.

45. The solid dosage form of claim 32, wherein the active agent is an anti-tussive agent.

46. The solid dosage form of claim 32, wherein the active agent is an expectorant.

47. The solid dosage form of claim 32, wherein the active agent is an anti-asthmatic.

48. The solid dosage form of claim 32, wherein the active agent is an antacid.

49. The solid dosage form of claim 32, wherein the active agent is an anti-spasmodic.

50. The solid dosage form of claim 32, wherein the active agent is an antidiabetic.

51. The solid dosage form of claim 32, wherein the active agent is a diuretic.

52. The solid dosage form of claim 32, wherein the active agent is an antihypotensive.

53. The solid dosage form of claim 32, wherein the active agent is an antihypertensive.

54. The solid dosage form of claim 32, wherein the active agent is a bronchodilator.

55. The solid dosage form of claim 32, wherein the active agent is a steroid.

56. The solid dosage form of claim 55, wherein the steroid is selected from the group consisting of hydrocortisone, triamcinolone, and prednisone.

57. The solid dosage form of claim 32, wherein the active agent is an antibiotic.

58. The solid dosage form of claim 32, wherein the active agent is selected from the group consisting of antihemorrhoidals, hypnotics, psychotropics, antidiarrheals, mucolytics, sedatives, decongestants, laxatives, vitamins, and stimulants.

59. The solid dosage form of claim 32, prepared by a process comprising the steps of

(a) forming an aqueous slurry containing a mixture of microcrystalline cellulose in the form of a wet cake and silicon dioxide having a particle size from about 1 nm to about 100 μm, the amount of silicon dioxide being from about 0.1% to about 20% relative to the amount of microcrystalline cellulose, by weight;

(b) drying said slurry to obtain an excipient comprising a plurality of agglomerated particles of microcrystalline cellulose in intimate association with said silicon dioxide;

(c) mixing the active agent with said excipient in a ratio from about 1:99 to about 99:1;

(d) incorporating said mixture obtained in step (c) into a plurality of solid dosage forms.

60. The solid dosage form of claim 32, wherein the solid dosage form provides a sustained-release of the systemically active therapeutic agent.

61. The solid dosage form of claim 32, the solid dosage form provides a sustained-release of the systemically active therapeutic agent over a period of at least 12 hours.

62. The solid dosage form of claim 32, wherein the solid dosage form provides an immediate release of the systemically active therapeutic agent.

63. The solid dosage form of claim 32, further comprising a coating of a hydrophobic polymer.

64. The solid dosage form of claim 63, wherein the solid dosage form includes a sufficient amount of the hydrophobic polymer coating to provide a sustained release of the active agent over a predetermined period.

65. The solid dosage form of claim 63, wherein the coating further includes an enteric coating material.

66. The solid dosage form of claim 32, further comprising a coating of an enteric coating material.

67. The solid dosage form of claim 66, wherein the enteric coating material is selected from a group consisting of cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinylacetate phthalate, methacrylic acid copolymer, shellac, hydroxypropylmethylcellulose succinate, cellulose acetate trimellitate, and mixtures thereof.

68. The solid dosage form of claim 63, wherein the coating further includes a hydrophilic material.

69. The solid dosage form of claim 32, further comprising a coating of a hydrophilic material.

70. The solid dosage form of claim 66, wherein the solid dosage form includes a sufficient amount of the coating to provide a sustained release of the active agent over a predetermined period.

71. The solid dosage form of claim 64, wherein the predetermined period is 12 hours.

72. The solid dosage form of claim 64, wherein the predetermined period is 24 hours.

73. The solid dosage form of claim 69, wherein the hydrophilic material is hydroxypropylmethylcellulose.

74. The solid dosage form of claims 32, further comprising a coating of an additional amount of the active agent.

75. The solid dosage form of claim 63, wherein the coating further includes an additional amount of the active agent.

76. The solid dosage form of claim 32, further comprising at least a partial coating of a support platform.

77. A solid dosage form of a compressed mixture of from about 1% to about 99% of an excipient comprising a particulate agglomerate of coprocessed microcrystalline cellulose and from about 0.1% to about 20% by weight silicon dioxide, the microcrystalline cellulose and silicon dioxide being in intimate association with each other, said silicon dioxide portion of said agglomerate being derived from a silicon dioxide having an average primary particle size from about 1 nm to about 100 μm, and from about 99% to about 1% of a locally active therapeutic agent.

78. The solid dosage form of claim 77, wherein the locally active therapeutic agent is selected from a group consisting of antifungal agents, antibiotic agents, antiviral agents, breath fresheners, antitussive agents, anti-cariogenic compounds, analgesic agents, local anesthetics, oral antiseptics, anti-flammatory agents, hormonal agents, anti-plaque agents, acidity reducing agents, and tooth desensitizers.

79. The solid dosage form of claim 77, wherein the solid dosage form provides a sustained-release of the locally active therapeutic agent.

80. The solid dosage form of claims 69, wherein the solid dosage form includes a sufficient amount of the coating to provide a sustained release of the active agent over a predetermined period.

81. The solid dosage form of claim 70, wherein the predetermined period is 12 hours.

82. The solid dosage form of claim 70, wherein the predetermined period is 24 hours.

83. The solid dosage form of claim 66, wherein the coating further includes an additional amount of the active agent.

* * * * *

blecen que al menos un 75% del fármaco debe disolverse en 45 minutos. Con objeto de reducir la variabilidad interlaboratorio en los test de disolución, la USP sugiere el uso de discos estándares de ácido salicílico y prednisona como calibradores del equipo de disolución.

2.2.11. Comprimidos especiales

Se incluye dentro de esta categoría a aquellos comprimidos que presentan alguna característica farmacotécnica diferente de las descritas para los comprimidos convencionales. Los comprimidos especiales de mayor utilización (sublinguales y bucales, masticables, efervescentes, multicapa, vaginales, de implantación, de liberación sostenida y recubiertos) se describen a continuación.

A) Comprimidos sublinguales y bucales

Son comprimidos destinados a situarse bajo la lengua (sublinguales) o a mantenerse en la cavidad oral (bucales), donde se disuelven lentamente liberando el principio activo para producir un efecto local o ser absorbidos a través de la mucosa y ejercer un efecto sistémico. En general, presentan pequeño tamaño y una forma plana u oval. Los comprimidos bucales deben disolverse con lentitud, para lo cual en su formulación se evita la presencia de agentes disgregantes y se incorporan aglutinantes enérgicos (gelatina, goma arábiga, carboximetilcelulosa...) y lubricantes de acción hidrofóbica, del tipo del estearato magnésico, que contribuyen a aumentar el tiempo de disgregación. Además, se utilizan fuerzas elevadas de compresión para obtener comprimidos duros. Se pueden administrar de esta forma hormonas como la metiltestosterona, el citrato de oxitocina, la progesterona, antisépticos y antibióticos, etc.

Los comprimidos sublinguales suelen contener fármacos que serían destruidos o inactivados a su paso por el tracto gastrointestinal. En general, están concebidos para que el principio activo se ceda lentamente, de manera que la velocidad de liberación sea del mismo orden de magnitud que la de absorción para asegurar el máximo aprovechamiento de la dosis administrada. Si la liberación se produjera muy rápidamente, la mucosa no estaría en situación de absorber toda la cantidad de fármaco disuelta, por lo que una parte de éste sería deglutida junto con la saliva. Por el contrario, en ciertos casos especiales, cuando se recurre a esta forma de administración para el tratamiento de situaciones urgentes, como la angina de pecho o el asma, los comprimidos sublinguales deben disolverse fácilmente, permitiendo una rápida absorción del fármaco, por lo que para su obtención se emplean bajas fuerzas de compresión y se les dota de una forma lenticular y de gran superficie. De este modo se administran fármacos tales como la nitroglicerina, el clorhidrato de isoproterenol, el sulfato de isoprenalina, el dinitrato de isosórbida, la ketanserina, etc.

F) Comprimidos de implantación

Los comprimidos de implantación están diseñados para ser depositados b la piel. Su objetivo es conseguir una acción prolongada (la duración del efecto os la entre un mes y un año); deben, pues, presentar bajas velocidades de disgre ción y disolución en los fluidos tisulares. Ello se consigue utilizando una eleva presión de compresión o recurriendo a la fusión conjunta del principio activo c ciertos coadyuvantes grasos (grasas hidrogenadas o polietilenóxido 6000). En ge ral, si es posible, se prefiere su fabricación sin la adición de excipientes; en el c de ser precisos, éstos deben ser totalmente solubles. Otros requisitos de los co primidos de implantación son un reducido tamaño (2-3 mm de diámetro), la fab cación en condiciones de asepsia y el envasado en recipientes estériles. La ad nistración de este tipo de comprimidos debe realizarse mediante técnicas quirúrgic o utilizando inyectores especiales (inyector de Kern). Su utilización en el hom ha caído en desuso; han sido sustituidos por otras formas de dosificación, como tubos de silicona de difusión controlada. No obstante, aunque su empleo está pr ticamente restringido a la administración de hormonas estimulantes del crecimie animal, un ejemplo característico del uso de este tipo de comprimidos en se humanos lo constituye el disulfiram (Esperal R®, 100 mg), utilizado en el tra miento crónico del alcoholismo.

G) Comprimidos de liberación controlada

Los comprimidos se pueden formular para liberar el principio activo de ma ra que se alcancen en el organismo concentraciones mantenidas, durante perío prolongados de tiempo. Existen diversos tipos entre los que se incluyen los co *primidos de liberación retardada*, en los que el principio activo no se libera ha un tiempo después de la administración o hasta que existan ciertas condicio fisiológicas; los *de acción repetida*, que liberan periódicamente una dosis com ta del fármaco en los líquidos gastrointestinales, y los *de liberación sostenida* liberan de forma continua una cantidad de fármaco. Estos comprimidos pue obtenerse por distintos métodos. Uno de los más simples es la incorporación principio activo en una matriz de naturaleza polimérica que forme una barr mucilaginosa que controle la difusión del principio activo o que se erosione le mente permitiendo la liberación gradual del mismo. Otra forma de control liberación consiste en el recubrimiento de los comprimidos con cubiertas espe les que permiten la cesión del fármaco por difusión, ósmosis, etc. Estos compri dos requieren la realización de ensayos de disolución adecuadamente adapta que permitan demostrar si la liberación del principio activo se realiza de acue con la cinética prevista en su diseño. Este tipo de fármacos, dado su creciente in rés, será revisado en detalle en otro capítulo.

3. Formulaciones pH-independientes

Puesto que el valor del pH varía de forma considerable a lo largo del tracto gastrointestinal, las formulaciones pH-independientes se presentan como una alternativa muy interesantes para su uso por vía oral. Estas formulaciones se obtienen mezclando un principio activo, ácido o base, con agentes *buffer* (sales de ácido cítrico) y excipientes que permiten obtener unos gránulos que se recubren con derivados de la celulosa que dan lugar a cubiertas semipermeables. Cuando los gránulos se encuentran en el aparato digestivo, penetra fluido a su interior y, por efecto del sistema *buffer,* el pH adquiere un valor adecuado, según el tipo de principio activo, se disuelve éste y difunde a través de la membrana polimérica a velocidad constante.

4. Matrices hidrofílicas

La formulación de principios activos en cápsulas gelatinosas o en comprimidos, utilizando polímeros hidrofílicos con elevada capacidad gelificante como excipientes base, representa una alternativa de indudable interés en el campo de la liberación controlada oral. Cuando estas formulaciones entran en contacto con un medio acuoso se produce una rápida hidratación de las macromoléculas situadas en la interfaz sólido-líquido, seguida de la formación de un lecho viscoso. Tal como se recoge en la figura 8.16, a medida que el agua va penetrando en el sistema con una velocidad que depende en gran medida de la naturaleza del polímero, la capa de gel experimenta una expansión progresiva que externamente se manifiesta en un incremento de su espesor. Al mismo tiempo, los estratos exteriores ya completamente hidratados se van dispersando en un proceso de erosión que lleva consigo la posibilidad de que el proceso de penetración de agua se prolongue hasta la total dispersión del sistema.

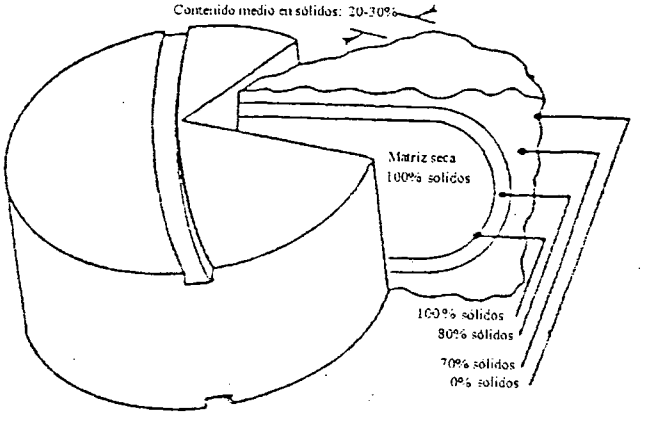


FIGURA 8.16. Representación esquemática del proceso de hidratación de un comprimido de matriz hidrofílica.

La liberación del principio activo a partir de un sistema matricial hidrofílico puede producirse por dos procesos simultáneos, tal como se recoge en la figura 8.17.

— Erosión o desgaste de las capas más externas y de menor consistencia del gel.
— Disolución del principio activo en el medio líquido y difusión a través del gel barrera, una vez que éste se ha formado.

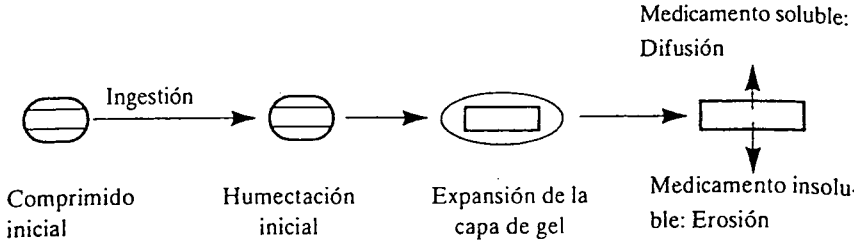


FIGURA 8.17. Liberación de un principio activo a partir de una matriz hidrofílica.

El predominio de uno u otro mecanismo está directamente relacionado con la hidrosolubilidad del principio activo. Si ésta es reducida, las posibilidades de cesión por difusión serán prácticamente nulas y la liberación se producirá casi exclusivamente por erosión superficial, con lo que se obtendrán perfiles característicos de la cinética de orden 0. En cambio, si el principio activo es moderada o marcadamente hidrosoluble, el mecanismo implicado en la liberación será la difusión; en este último caso, pueden distinguirse tres etapas en el proceso global de liberación:

— En la fase inicial el agua disuelve el principio activo que se encuentra en la superficie, lo que provoca su liberación inmediata. El agua penetra en la matriz a través de los poros y se produce la gelificación del polímero. En esta primera etapa la velocidad de penetración del líquido depende de la porosidad del sistema y la capa de gel no constituye necesariamente una capa de gel continua, especialmente cuando las partículas son relativamente grandes.
— En la segunda etapa o estacionaria, que abarca del 60 al 70% del proceso, el frente de agua penetra de forma continua en el sistema, al tiempo que se produce la expansión de la capa de gel. Durante la misma, la liberación del principio activo está controlada por el proceso de difusión y no por el de disolución del principio activo o por la velocidad de penetración del agua en el sistema.
— El período final o de agotamiento comienza cuando el frente ha alcanzado el centro del sistema y la concentración de principio activo ha caído por

debajo de su coeficiente de solubilidad. Esta etapa se caracteriza por una reducción gradual de la velocidad de liberación del principio activo.

Como polímeros que se pueden utilizar en la elaboración de matrices hidrofílicas se pueden considerar los siguientes:

— *Polímeros naturales o semisintéticos.* Son productos de origen vegetal (agar-agar, alginatos, etc.) o bien transformados mediante procesos físicos o de semisíntesis (chitosanos, almidones modificados, etc.).
— *Éteres de la celulosa.* Este grupo de derivados semisintéticos de la celulosa es el que ha encontrado mayor aplicación en el campo de las matrices hidrofílicas. Se obtienen substituyendo algunos átomos de hidrógeno de los grupos hidróxilo de la celulosa, de las unidades de glucosa, por grupos metilo, hidróxietilo, hidroxipropilo o carboximetilo. Las propiedades físicas y fisicoquímicas de los éteres de la celulosa están determinadas por el tipo, proporción y, en su caso, variedad de los grupos substituyentes. Esto sucede, por ejemplo, con la viscosidad de las dispersiones acuosas, aspecto de gran importancia en relación con muchas de las aplicaciones de estos excipientes.
— *Polímeros del ácido acrílico.* Integrados en el grupo de los carbomer y comercializados bajo el nombre de Carbopol®, constituyen actualmente unos polímeros con variedades que difieren en su peso molecular y en su capacidad viscosizante.

Los carbomer han encontrado interesantes aplicaciones en el campo de las formas orales de liberación controlada y con su empleo pueden conseguirse básicamente tres tipos de sistemas:

— *Sistemas de inclusión* en los que las moléculas se alojan en los espacios abiertos en la red molécular del polímero, tras provocar la floculación de éste en medio acuoso mediante una modificación controlada del pH. Finalmente, el aducto así formado se separa por filtración, se deseca y se comprime.
— *Sistemas megaloporosos.* Están constituidos por dos fases: una fase continua denominada "hospedadora", que controla la velocidad de penetración del líquido en el sistema, y otra en la que se encuentra el principio activo y que se encarga del control de su liberación durante un tiempo prolongado. Cuando uno de estos sistemas, obtenido por compresión de una mezcla de granulados de una y otra fase, se pone en contacto con un medio acuoso, el líquido penetra en la fase hospedadora debido a la presencia de cantidades importantes de componentes solubles, provocando la formación de grandes poros en el sistema. A medida que el líquido va penetrando en las partes internas del dispositivo, una parte cada vez mayor de la superficie de la fase responsable del control de la liberación se pone en disposición de ceder prin-

cipio activo al líquido de los poros. Puesto que la velocidad con que aumenta la superficie útil para liberar principio activo a los megaloporos disminuye, mientras que aumenta la superficie total de los poros expuesta al líquido, los sistemas megaloporosos pueden proporcionar velocidades de liberación sensiblemente constantes.

— *Matrices hidrofílicas.* La capacidad gelificante de los carbomer los convierte en productos potencialmente útiles en la formulación de sistemas matriciales de carácter hidrofílico. La mayoría de las publicaciones se centran en la utilización de la variedad 934 y persiguen, como objetivo fundamental, la obtención de una formulación adecuada para el principio activo seleccionado en cada caso. Para ello se acude a modificaciones en las condiciones de elaboración y, en algunas ocasiones, a la incorporación de otros excipientes de diferente naturaleza.

5. Matrices lipídicas

Las matrices lipídicas constituyen una interesante alternativa para la obtención de niveles sostenidos en plasma de un principio activo administrado por vía oral. La base de estos sistemas matriciales está constituida por compuestos de tipo graso o lipídico que, en contacto con los fluidos gastrointestinales, sufren un gradual proceso de erosión, liberando lentamente el principio activo al medio. Sin embargo, las matrices lipídicas presentan generalmente problemas de estabilidad en las condiciones habituales de almacenamiento, ya que las grasas naturales y los compuestos lipídicos suelen sufrir con el tiempo transiciones polimórficas o amorfo-cristalinas que dan lugar a un endurecimiento y, en consecuencia, a una disminución de la velocidad de cesión del principio activo.

Entre los procedimientos utilizados para dispersar el principio activo en el material graso, se puede citar el consistente en adicionar una solución o dispersión del principio activo y aditivos en la grasa fundida y posteriormente eliminar el disolvente por evaporación. Otra alternativa consiste en incorporar directamente el principio activo y los aditivos a la matriz grasa, previamente fundida a una temperatura ligeramente superior a su punto de fusión.

La liberación de principios activos a partir de matrices lipídicas está controlada por los mecanismos de difusión y erosión, y prevalece uno u otro según las características del principio activo y del propio excipiente lipídico. Las matrices lipídicas presentan un cierto grado de porosidad que permite la penetración inicial del medio de disolución y, en consecuencia, la disolución y difusión del principio activo en el mismo. Paralelamente, se producirá una gradual erosión de la matriz por lipólisis enzimática, simple hidrólisis o solubilización por ionización. Así, la velocidad de liberación y, consecuentemente, la absorción de un principio activo a partir de una matriz lipídica dependen en gran medida de la composición de los fluidos digestivos. Las variaciones de pH y el contenido enzimático del tracto gas-