PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:	WO 93/19741
A61K 9/28	A1	(43) International Publication Date:	14 October 1993 (14.10.93)

(21) International Application Number: PCT/DK93/00117

(22) International Filing Date: 30 March 1993 (30.03.93)

(30) Priority data:
PCT/DK92/00101 31 March 1992 (31.03.92) WO
(34) Country for which the regional or international application was filed: DK

(71) Applicant *(for all designated States except US)*: BENZON PHARMA A/S [DK/DK]; Helseholmen 1, DK-2650 Hvidovre (DK).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : BERTELSEN, Poul [DK/DK]; Duevej 42, DK-2000 Frederiksberg (DK). HANSEN, Nils, Gjerløv [DK/DK]; Strandboulevarden 75, DK-2100 Copenhagen Ø (DK). JØRGENSEN, Kim [DK/DK]; Jagtvej 14, 3.th., DK-2200 Copenhagen N (DK).

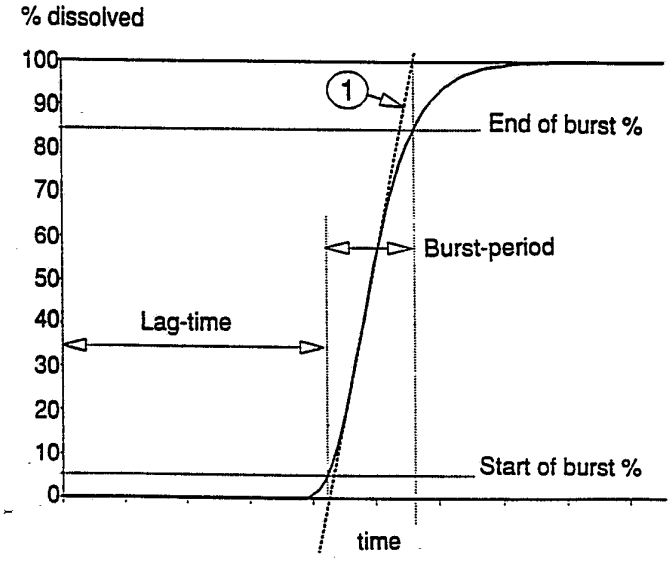
(74) Agent: PLOUGMANN & VINGTOFT A/S; Sankt Annæ Plads 11, P.O. Box 3007, DK-1021 Copenhagen K (DK).

(81) Designated States: AU, BG, BR, CA, CZ, FI, HU, JP, KR, KZ, NO, NZ, PL, RO, RU, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: A PHARMACEUTICAL FORMULATION

(57) Abstract



A pharmaceutical formulation for time-controlled release of an active substance, the formulation comprising a solid ingestible material adapted to oral administration, preferably containing an active drug substance and an erodable layer or a combination of erodable layers surrounding and covering the solid ingestible material, at least one of the erodable layers containing, as a major constituent, a water soluble cellulose derivative or a mixture of water soluble cellulose derivatives such as, e.g., hydroxypropylmethylcellulose, hydroxypropylcellulose or methylcellulose, the viscosity thereof being selected so that a test composition comprising a combination (C) of 1) a core containing an active substance in an inherently substantially freely releasable form as defined herein and 2) said erodable layer or combination of erodable layers, after a lag-time (A), defined as described herein, of at least 60 minutes during which at the most 30% by weight of the inherently substantially freely releasable active substance contained in the core is released, releases at least 70 % by weight of the inherently substantially freely releasable active substance contained in the core within a burst-period (B), defined as described herein, of at the most 45 minutes, the said releases being measured as mean data determined by dissolution testing in purified water at 37 °C and in 0.1 N hydrochloric acid at 37 °C in accordance with Ph.Eur. V.5.4. (1991 edition), using a dissolution apparatus equipped with baskets rotating at 100 rpm.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**FR**	France	**MR**	Mauritania
AU	Australia	**GA**	Gabon	**MW**	Malawi
BB	Barbados	**GB**	United Kingdom	**NL**	Netherlands
BE	Belgium	**GN**	Guinea	**NO**	Norway
BF	Burkina Faso	**GR**	Greece	**NZ**	New Zealand
BG	Bulgaria	**HU**	Hungary	**PL**	Poland
BJ	Benin	**IE**	Ireland	**PT**	Portugal
BR	Brazil	**IT**	Italy	**RO**	Romania
CA	Canada	**JP**	Japan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SK**	Slovak Republic
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SN**	Senegal
CM	Cameroon	**LI**	Liechtenstein	**SU**	Soviet Union
CS	Czechoslovakia	**LK**	Sri Lanka	**TD**	Chad
CZ	Czech Republic	**LU**	Luxembourg	**TG**	Togo
DE	Germany	**MC**	Monaco	**UA**	Ukraine
DK	Denmark	**MG**	Madagascar	**US**	United States of America
ES	Spain	**ML**	Mali	**VN**	Viet Nam
FI	Finland	**MN**	Mongolia		

A PHARMACEUTICAL FORMULATION

FIELD OF THE INVENTION

The present invention relates to a pharmaceutical formulation in the form of a coated solid ingestible material adapted to oral administration, in which the coating constitutes a barrier delaying the direct exposure of the solid material to gastrointestinal fluids; i.e. a solid substrate on which has been deposited a coating which is such that when such a coated material is swallowed by a human, it will be substantially unaffected by the pH prevailing in the stomach and in the other parts of the gastrointestinal tract, but will erode or dissolve or otherwise disintegrate within the gastrointestinal tract of the human in question, thereby first after a certain lag-time of, e.g., at least 60 minutes exposing the solid material itself to gastrointestinal fluids. Such formulations, which may be in the form of single-unit dosage forms or multiple-unit dosage forms such as, e.g., in the form of tablets or capsules, may also be denoted, e.g., as "burst", "pulsed", "time-controlled", "lag-time controlled" or "programmed" release pharmaceutical formulations.

The invention also relates to a method for preparing the coated solid ingestible material.

BACKGROUND OF THE INVENTION

In general, an aim of medicinal treatment of a particular disease or condition is to deliver the minimum required amount of a drug substance to the particular target site within the body and to avoid the presence or the accumulation of drugs at non-target sites. Another aim is to maintain the necessary therapeutic concentration of the drug substance at the target site for some desirable period of time, after which the drug substance is eliminated from the body without adverse effects or formation of any toxic metabolites.

Various controlled-release drug delivery systems (sometimes also known as "sustained release", "prolonged release", "retard" or "mediated release" systems) have been developed mainly with the

purpose of prolonging the residence time of the drug substance in the body after administration of the drug substance in form of an appropriate pharmaceutical formulation and at the same time avoiding excessively high or low levels (peak or valley levels) of the drug substance in the body. An excessively high level may give rise to a drug concentration in the blood which is so high that adverse effects become apparent. On the other hand, an excessively low concentration may lead to drug concentrations in the blood which are below the therapeutically effective level.

Controlled-release drug delivery systems may advantageously be used in the administration of drug substances having very short biological half-lives, or in situations where the margin between toxic and therapeutic concentration is very narrow.

However, in a number of situations, it is believed that beneficial therapeutic effects can be achieved if drug substances are administered in such a manner that the optimal effect of the drug substance is achieved by matching drug delivery to variations in bodily response and symptoms or severity of the disease. Furthermore, it is known that the blood concentration of many physiologically active substances varies during the day, although the importance thereof has not yet been fully recognized. This knowledge has until now manifested itself in asymmetric administration of the drugs and has been used as an argument against the attainment of the constant plasma levels aimed at by most of the presently employed controlled-release dosage forms.

The provision of a drug formulation adapted to release the drug substance after a predetermined period of time (lag-time) is important, or at least highly desirable, in a number of situations, some of which are:

1. attempting to match drug delivery to variations in bodily response (*vide supra*) in order to obtain an improved therapeutic effect,
2. reducing the dose frequency in order to, e.g., obtain better patient compliance,

3. administering the drug substance at a time which is convenient for the patient, and
4. obtaining therapeutic benefit of the drug substance at the outbreak of disease symptoms.

In the following is given a brief review of patent literature relating to various approaches which have been employed in an attempt to solve the problem of administering a drug substance in a delivery system capable of releasing the active drug substance at a predetermined point in time. However, the formulations described are contemplated to have a number of disadvantages such as, e.g., i) only being suitable for a specific drug substance, ii) releasing a relatively high amount of drug substance during the lag-time, iii) having a lag-time which is pH-dependent, or iv) releasing drug substance during a relatively long burst-period:

JP 63-215620 (Nippon Soda) describes a sustained release preparation having a nucleus composed of a mold which is substantially formed of water soluble high molecular substances and which contains an active substance. The nucleus is provided with a coating substantially formed of the same kind of water soluble high molecular substance as in the mold. Examples of water soluble high molecular substances which are capable of gelling or swelling, are, e.g., hydroxypropylcellulose and hydroxypropylmethylcellulose of a relatively high viscosity. The preparation is said to be capable of controlling the releasing start-up time of a sparingly water soluble drug substance and performing a zero-order functional release.

JP 62-246512 (Fujisawa) describes a drug preparation having repeating action comprising a rapidly dissolving part containing a principal drug; a slow-releasing part containing a disintegrant and wax or containing a water-soluble polymeric substance; and a repeating action part containing a principal drug.

EP 306699 (Bayer AG) describes dihydropyridine formulations comprising a core containing a relatively sparingly water soluble dihydropyridine compound such as, e.g., nifedipine or nitrendipine, which is surrounded by a layer which slowly dissolves in an aqueous

environment and thus delays the release of the dihydropyridine in the core, the formulation optionally being provided with a rapidly releasable initial dose of dihydropyridine. As will be evident from the Examples given herein in the experimental section below, a suitable lag-time followed by a relatively rapid burst-release of the drug substance cannot be obtained in those cases where an inherently freely releasable active substance such as, e.g., caffeine, is used, i.e. the formulation suffers from the drawback of not being general applicable for all kinds of drug substances.

DE 3443586 (Alza Corp) describes an osmotic release system which during a certain period of time releases the drug according to zero-order kinetics and thereafter at a predetermined time period releases a larger amount of drug substance.

EP 338383 (Swarz Pharma AG) describes a controlled release formulation consisting of a core surrounded by several layers such as a layer comprising an active substance, a membrane layer, a layer consisting of a least one physiologically acceptable acid and a further membrane layer.

SUMMARY OF THE INVENTION

We have now developed a novel pharmaceutical formulation comprising a solid ingestible material and a coating (which also is denoted "lag-time controlling outer layer") which is erodable in an aqueous medium.

The present invention relates to a pharmaceutical formulation in the form of a coated solid ingestible material adapted to oral administration, wherein the coating comprises an erodable layer or a combination of erodable layers surrounding and covering the solid material and constituting a barrier delaying the direct exposure of the solid material to gastrointestinal fluids, at least one of the erodable layers containing, as a major constituent, a water soluble cellulose derivative or a mixture of water soluble cellulose derivatives, the viscosity of the cellulose derivative or the mixture of cellulose derivatives in the layer or layers being selected so that a

test composition comprising a combination (C) of 1) a core containing an active substance in an inherently substantially freely releasable form as defined herein and 2) said erodable layer or combination of erodable layers, after a lag-time (A), defined as described herein, of at least 60 minutes during which at the most 30% by weight of the inherently substantially freely releasable active substance contained in the core is released, releases at least 70% by weight of the inherently substantially freely releasable active substance contained in the core within a burst-period (B), defined as described herein, of at the most 45 minutes, the said releases being measured as mean data determined by dissolution testing in purified water at 37°C and in 0.1 N hydrochloric acid at 37°C in accordance with Ph.Eur. V.5.4. (1991 edition), using a dissolution apparatus equipped with baskets rotating at 100 rpm.

The pharmaceutical formulation according to the invention may be produced by relatively simple and inexpensive methods such as double compression or coating-by-compression techniques (see Pharmaceutical Dosage Forms: Tablets. Vol. 1, 2nd edition, edited by Herbert A. Lieberman et al., pages 247-249).

Thus, in an additional aspect the invention relates to a method for preparing a pharmaceutical formulation as defined above comprising placing a solid ingestible material optionally comprising an active substance in an inherently substantially freely releasable form and optionally at least one pharmaceutically acceptable excipient in a die which has been charged with a granulate comprising, as a major constituent, a water soluble cellulose derivative or a mixture of water soluble cellulose derivatives as defined above, adding a further quantity of the granulate so as to completely cover the solid ingestible material, and compressing the granulate around the solid ingestible material to prepare the pharmaceutical formulation.

Upon administration the pharmaceutical formulation is capable of releasing the active substance with a certain predetermined delay, and during the lag-time there is substantially no leakage of the active substance from the core to the body environment, i.e. at the most 30% by weight of the active substance. The lag-time can be

varied by varying the thickness of the erodable lag-time controlling layer and/or the composition thereof, and consequently, the time for onset of the release of the active substance can be controlled. When the release of the active substance from a pharmaceutical formulation according to the present invention starts in the burst-phase, the rate of release of this substance is substantially independent of the lag-time and the composition and thickness of the erodable lag-time controlling outer layer.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a cross-sectional view of a pharmaceutical formulation according to the invention. The formulation comprises an inner core (A) containing the active substance and an erodable lag-time controlling outer layer (B).

Figure 2: For the description of a dissolution or release profile the following key parameters can be determined and these parameters are used in the present context: lag-time (A), burst-period (B), start of burst %, and end of burst %. The inflection tangent (1) can be drawn. The time values at which (1) crosses the abscissa and the 100 % level are the end of the lag-time and the end of the burst- period respectively, i.e. the difference between the two values is the burst-period. By drawing vertical lines through these two time values the start of burst % and the end of burst % are the two ordinates where these lines cross the dissolution or release profile.

Figure 3: Dissolution profile for tablets prepared as described in Example 1 herein based on the stated mean data. The profile illustrates the basic system for a short lag-time tablet, i.e. the outer layer consists of 100% Methocel® E 15.

Figure 4: Dissolution profile for tablets prepared as described in Example 2 herein based on the stated mean data. The profile illustrates the effect of using 15% Macrogol 6000 and 85% Methocel® E 15.

Figure 5: Dissolution profile for tablets prepared as described in Example 3A+B herein based on the stated mean data. The profile illustrates the effect of using 25% Macrogol 6000 and 75% Methocel® E 15.

Figure 6: Dissolution profile for tablets prepared as described in Example 4 herein based on the stated mean data. The profile illustrates the effect of using 25% Avicel® and 75% Methocel® E 15.

Figure 7: Dissolution profile for tablets prepared as described in Example 5 herein based on the stated mean data. The profile illustrates the effect of using 25% lactose and 75% Methocel® E 15.

Figure 8: Dissolution profile for tablets prepared as described in Example 6 herein based on the stated mean data. The profile illustrates the basic system for a long lag-time tablet, i.e. the outer layer consists of 100% Methocel® E 50.

Figure 9: Dissolution profile for tablets prepared as described in Example 7 herein based on the stated mean data. The profile illustrates the effect of using double coating when preparing a long lag-time tablet.

Figure 10: Dissolution profile for tablets prepared as described in Example 8 herein based on the stated mean data. The profile illustrates the effect of using double coating with a combination of 85% Methocel® E 15 and 15% Macrogol 6000 in the first coating when preparing a long lag-time tablet.

Figure 11 shows the levels of lag-time obtained for the tablets prepared in Examples 1-8 and 12 and 13 described herein (95% confidence intervals for factor means). The numbers at the abscissa refer to the Example numbers, whereas the numbers at the ordinate indicate the lag-time measured in minutes.

Figure 12 shows the T_{lag} distribution observed in the *in vivo* study of Example 9 described herein for formulation A (short T_{lag}), B (long T_{lag}) and C (salbutamol).

Figure 13 shows the onset of adverse drug reactions observed in the *in vivo* study of Example 9 herein. Formulation A, B and C are defined as in Figure 12.

Figure 14: Dissolution profile for tablets prepared as described in Example 12 herein based on the stated mean data. The profile illustrates the effect of using double coating with 100% Methocel® E 15 in the first coating and 100% Methocel® K 100 in the second coating.

Figure 15: Dissolution profile for tablets prepared as described in Example 13 herein based on the stated mean data. The profile illustrates the effect of using caffeine as the active substance in the inner core and an outer layer containing 75% Methocel® E 15 and 25% Macrogol 6000.

Figure 16: Dissolution profile for tablets prepared as described in Example 19 herein based on the stated mean data. The profile illustrates the effect of using caffeine as the active substance in the inner core and an outer layer comprising 42.4% Klucel® MF and 12.4% Klucel® LF. The diameter of the tablets is 10 mm.

Figure 17: Dissolution profile for tablets prepared as described in Example 20. The profile illustrates the effect of using caffeine as the active substance in the inner core and an outer layer comprising 42.4% Klucel® MF and 12.4% Klucel® LF, but in amounts which is greater than the amounts used in Example 19. The diameter of the tablets is 10 mm.

Figure 18: Dissolution profile for tablets prepared as described in Example 21. The profile illustrates the effect of using caffeine as the active substance in the inner core and an outer layer comprising 42.4% Klucel® MF and 12.4% Klucel® LF. The diameter of the tablets is 12 mm.

DESCRIPTION OF THE INVENTION

As will be apparent from the above, there is a need for the development of a pharmaceutical formulation which upon oral administration releases the contained active substance after a predetermined lag-time and observing, e.g., the following objectives:

1. during the lag-time, substantially no release of active substance should take place, i.e. there should be substantially no leakage of active substance during the lag-time,

2. the lag-time should be substantially independent of pH,

3. a high extent of reproducibility should characterize the formulation, making the lag-time substantially predictable,

4. at the end of the lag-time, a solid material comprising the active substance should become exposed to an aqueous environment (such as, e.g., gastrointestinal fluids) and in those cases where the active substance is present in a freely releasable form, the active substance should be released substantially instantly, and

5. the formulation principle should be applicable to a vide variety of active substances such as, e.g., freely water soluble active substances, as well as active substances which have a poorer water solubility.

Furthermore, there is a general need for effective drug formulations which are able to effectively release a drug substance within a sufficiently short period (burst-period) after a sufficient predetermined delay (lag-time) during which only a small amount of the drug substance is released.

Pharmaceutical formulations which upon administration releases the contained active substance after a lag-time may also be denoted

"time-controlled" formulations. In the present context the term "time-controlled release" is intended to mean release of the active substance at a predetermined point in time, e.g., the release of the active substance is substantially delayed until this predetermined point in time is reached. The term "controlled release" is used in a broad sense to designate release of the active substance at a desired rate during a predetermined period of time.

The present invention meets the above-mentioned needs by providing a novel pharmaceutical formulation in the form of a coated solid ingestible material adapted to oral administration which provides the desired release profiles by proper selection of the composition of the coating and the solid material, respectively. Furthermore, one of the major drawbacks of the hitherto known formulations has been overcome or at least substantially overcome in that in a formulation according to the present invention it is also possible to incorporate a solid ingestible material comprising a freely water soluble active substance and at the same time substantially avoiding leakage of the active substance during the lag-time period.

The novel pharmaceutical formulation of the invention is useful for medicinal treatment of a number of diseases or conditions for which it is an advantage that the therapeutic effect of the active substance is not exerted immediately after administration of the pharmaceutical formulation, i.e. diseases for which a certain delay in onset of the therapeutic effect is desirable, or in cases where daily variations in the bodily response to the active substance or in the severity of the disease symptoms are to be taken into account.

A pharmaceutical formulation of the invention can be used to achieve three different purposes:

1. to deliver the active substance in such a way that the therapeutic response fits into the daily variations in bodily response and symptoms or severity of the disease. A pharmaceutical formulation directed toward this aspect is formulated in such a way that a predetermined delay in the onset of the therapeutic effect is achieved by delaying the release of the active sub-

stance from the pharmaceutical formulation in a controllable manner;

2. to deliver the active substance to a site in the gastrointestinal tract, e.g. to the site at which the active substance is to exert its effect. A pharmaceutical formulation directed toward this aspect is formulated in such a way that the release of the active substance after, e.g., oral administration is delayed independent of pH until the pharmaceutical dosage unit is delivered to the target site, e.g. to a diseased localized site in the gastrointestinal tract;

3. to deliver the active substance to a site in the gastrointestinal tract from which maximal absorption takes place. A pharmaceutical dosage unit directed toward this aspect is formulated in such a way that the release of the active substance is delayed independent of pH until the pharmaceutical dosage unit is delivered to the site, e.g. in the gastrointestinal tract, where the absorbed fraction is maximal.

The release of the active substance from the pharmaceutical formulation of the invention is in general determined by use of standardized *in vitro* dissolution tests as well as by *in vivo* studies. As it will be apparent from the results and conclusion of the *in vitro* Examples herein, formulations according to the invention have demonstrated a remarkable capability of retaining the active substance completely during the lag-time, furthermore ensuring lag-times which are substantially independent of pH and a high degree of reproducibility of lag-times, and last but not least ensuring a rapid, instant release of the active substance when the lag-time has ended, provided that such a latter release pattern is desirable.

An *in vivo* study described in the Examples herein has moreover successfully confirmed for two pharmaceutical formulations according to the invention (a short lag-time formulation and a long lag-time formulation) that it is possible in a reproducible manner to achieve a delayed dissolution up to 7 hours after which the active substance is released instantly.

Thus, the present invention relates to a pharmaceutical formulation in the form of a coated solid ingestible material adapted to oral administration, wherein the coating comprises an erodable layer or a combination of erodable layers surrounding and covering the solid material and constituting a barrier delaying the direct exposure of the solid material to gastrointestinal fluids, at least one of the erodable layers containing, as a major constituent, a water soluble cellulose derivative or a mixture of water soluble cellulose derivatives, the viscosity of the cellulose derivative or the mixture of cellulose derivatives in the layer or layers being selected so that a test composition comprising a combination (C) of 1) a core containing an active substance in an inherently substantially freely releasable form as defined herein and 2) said erodable layer or combination of erodable layers, after a lag-time (A), defined as described herein, of at least 60 minutes during which at the most 30% by weight of the inherently substantially freely releasable active substance contained in the core is released, releases at least 70% by weight of the inherently substantially freely releasable active substance contained in the core within a burst-period (B), defined as described herein, of at the most 45 minutes, the said releases being measured as mean data determined by dissolution testing in purified water at 37°C and in 0.1 N hydrochloric acid at 37°C in accordance with Ph.Eur. V.5.4. (1991 edition), using a dissolution apparatus equipped with baskets rotating at 100 rpm.

In the present context, the percentages given in connection with the release of active substance are to be calculated on the basis of the contents of active substance prior to exposure to the aqueous body environment.

As it is apparent from the above, the requirements for the coating according to the invention are expressed as specific limits for parameters which can be calculated on the basis of an *in vitro* dissolution test carried out on a test composition, wherein the coating has been deposited on the outermost layer of a core, and wherein the core contains an active substance in an inherently substantially freely releasable form.

It is appreciated than when a coating fulfills these requirements (see above), in principle all types of solid ingestible materials which are adapted for oral administration may be coated with such a coating; solid materials may, e.g., be instant release formulations, controlled-release formulations or another time-controlled release formulation (see below).

In order to determine whether a coating fulfills the requirements, cf. above, the coating which is to be tested is applied on a core which comprises an active substance in an inherently freely releasable form. The thus-obtained coated core, also denoted "test composition", "combination (C)" or "test core", is then tested in accordance with the dissolution test described in Ph. Eur., cf. above. Examples of suitable test cores are given in the Examples 1-13 and 19-21 herein. In general, any pharmaceutical formulation which is capable of being provided with a coating and which contains an active substance in an inherently substantially freely releasable form, as defined below, may be employed as test core in the test for determining whether a specific coating fulfills the requirements and, accordingly, is a coating which is useful in accordance with the present invention.

The term "inherently substantially freely releasable" is used in the present context to designate an active substance in a form which preferably is water-soluble and which - when incorporated in the form of a plain formulation such as a formulation in the form of, e.g., a core - releases at least 70%, preferably at least 80%, more preferably at least 90% by weight of the active substance contained in the plain formulation within a burst-period (B), defined as described herein (see below), of at the most 45 minutes, the release being measured as mean data determined by dissolution testing in purified water at 37°C and in 0.1 N hydrochloric acid at 37°C in accordance with Ph.Eur. V.5.4. (1991 edition), using a dissolution apparatus equipped with baskets rotating at 100 rpm. Examples of inherently substantially freely releasable active substances may be, e.g., active substances having a water-solubility at room temperature of at least 0.1%, preferably at least about 0.5%, most preferably at

least about 1% by weight, such as, e.g., actives substances like caffeine or salbutamol. Such active substances may be incorporated in plain formulations comprising normal excipients such as those described below.

On the basis of an *in vitro* dissolution test carried out in accordance with The European Pharmacopoeia (abbreviated as Ph.Eur.) V.5.4. (1991 edition), using a dissolution apparatus equipped with baskets rotating at 100 rpm, a dissolution profile for a pharmaceutical formulation or composition can be drawn (see Figure 2 herein). In the test, six units (e.g. tablets or capsules) of the pharmaceutical formulation are subjected to the dissolution test. For the description of such a profile the following key parameters can be determined: lag-time (A), burst-period (B), start of burst %, and end of burst %. The inflection tangent (1) can be drawn. The time values at which (1) crosses the abscissa and the 100 % level are the end of the lag-time and the end of the burst-period, respectively, i.e. the difference between the two values is the burst-period (B). By drawing vertical lines through these two time values the start of burst % and the end of burst % are the two ordinates where these lines cross the dissolution or release profile.

The above-mentioned dissolution test and the subsequent calculation of key parameters may of course be employed on any pharmaceutical formulation according to the invention as well as on the test combination (combination (C)) mentioned above.

When testing a coating according to the invention, the requirements for the key parameters can also be expressed as:

1. lag-time (A) is at least 60 minutes,
2. burst-period is at the most 45 minutes,
3. start of burst % is at the most 30% by weight, and
4. the difference between the end of burst% and the start of burst % is at least 70% by weight, i.e. during the burst-period at least 70% by weight of the inherently substantially freely releasable active substance is released.

As it will be explained below, the key parameters may vary dependant on the particular therapeutic application of the pharmaceutical formulation. Thus, the following key parameters and every possible combination thereof are also relevant in connection with a pharmaceutical formulation of the present invention:

1. a lag-time (A) of at least 60 minutes, such as, e.g., at least 90 minutes, at least 2 hours, at least 3 hours or at least 5 hours,
2. a burst-period of at the most 45 minutes, such as, e.g., at the most 30 minutes,
3. a start of burst % of at the most 30%, such as, e.g., at the most 25%, at the most 20%, at the most 15% or at the most 10% by weight, and
4. a difference between the end of burst% and the start of burst % of at least 70% such as, e.g., at least 80% or at least 90% by weight, i.e. during the burst-period at least 70% such as, e.g., at least 80% or at least 90% by weight of the inherently substantially freely releasable active substance is released.

The term "lag-time (A)" is thus, in the present context, used to designate the time elapsing between exposure of a pharmaceutical formulation of the present invention or the combination denoted (C) to an aqueous medium and the time value at which the inflection tangent crosses the abscissa. For any pharmaceutical formulation, this time period can easily be determined by performing *in vitro* studies essentially as described in the Examples herein.

The term "burst" refers to substantially instant release of an active substance, i.e. release of at least 70% by weight of the active substance within a burst-period (B) of the most 45 minutes. A relatively short burst-period like the one of at least 45 minutes as mentioned above is of course only relevant for those pharmaceutical formulations according to the invention in which a delayed but instant release of the active substance is desired in order to rapidly obtain an effective therapeutic concentration in the circulatory system upon administration, i.e. a relatively short burst-period is not a requirement for those pharmaceutical

formulations according to the invention in which a delayed but, e.g., controlled-release of the active substance is desired. The burst-period could also be termed the "burst-phase".

A dissolution or release profile for a pharmaceutical formulation may also be determined based on *in vivo studies*. However, in *in vivo* studies it is not possible to determine the lag-time with the same precision as in *in vitro* studies. The lag-time T_{lag} is therefore defined as the time elapsing between exposure of a pharmaceutical formulation of the invention to an aqueous medium i.e. by means of the patient taking the pharmaceutical formulation of the invention and the time at which a detectable plasma concentration is measured for the first time. For any formulation, *in vivo* studies can be performed essentially as described in Example 9 herein.

Solid ingestible material

In the present context, the term "solid ingestible material" is used to denote any relevant material or substance which is of established safety in connection with therapeutic treatment, which generally do not give rise to undesirable side effects in mammals, especially humans, and which has, or which is provided with, an outermost solid surface upon which the coating may be deposited. Thus, the term embraces not only materials or substances which are substantially solid throughout, but also materials or substances which in themselves are fluids such as, e.g., liquids, but which have been encapsulated in or mixed with a further material so that this material represents the outermost solid surface. An example of a relevant liquid material or substance which may be provided in an encapsulated form before being further provided with a coating according to the invention is, e.g., triglyceryl nitrate and nicotine.

Furthermore, the term "solid ingestible material" is used in the present context to embrace materials which in themselves are pharmaceutical formulations (such as, e.g., instant release formulations, controlled-release formulations or time-controlled release formulations). In such formulation an active substance may be

present in an inherently substantially freely releasable form or in a controlled-release or time-controlled release form (as defined above).

Thus, once the release of the active substance begins from a pharmaceutical formulation according to the invention, the release of the active substance may be, e.g., as an instant release, a controlled release or as a further time-controlled release; in the case of oral pharmaceutical formulations, instant release denotes a release which substantially corresponds to the release of active substances achieved using conventionally formulated plain uncoated tablets (e.g. at least 80% of the drug substance is released within 1 hour, as determined in a standardized *in vitro* test, e.g., as described in United States of America Pharmacopoeia, USP XXII).

In a preferred embodiment of the invention, the solid ingestible material comprises an active substance such as, e.g., an active substance selected from the group consisting of drugs, peptides, proteins, nutrients, vitamins or mixtures thereof.

A pharmaceutical formulation of the invention is preferably intended for oral use and is preferable in form of a unit dosage form, such as,e.g., a tablet. When the pharmaceutical formulation according to the present invention has the form of a tablet, the solid ingestible material preferably also has a shape of a tablet. However, in some cases it may be of advantage to use a solid ingestible material in the form of a capsule or in the form of granules or pellets even in those cases where the resulting pharmaceutical formulation is in the form of a tablet.

Preferably the solid ingestible material comprises the active substance in combination with at least one pharmaceutically acceptable carrier or excipient, although there may be cases where it is advantageous that the solid ingestible material only contains the active substance.

As mentioned above, the solid ingestible material (preferably comprising an active substance) may in itself be in the form of a

pharmaceutical formulation such as, e.g., pellets, granules, unit dosage forms such as, e.g., tablets or capsules, or in the form of cores. In the present context, the term "core" is used in a broad sense to embrace a solid ingestible material comprising an active substance in combination with at least one pharmaceutically excipient.

Examples of suitable carriers and excipients which can be used in the preparation of such a core include:

fillers, such as lactose, saccharose, dextrose, mannitol, sorbitol, maltodextrin, dextrin, calcium phosphate, dicalcium phosphate, tricalcium phosphate, starch and microcrystalline cellulose;

binders such as gelatin, hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, saccharose, acacia, tragacanth, starch, sodium alginate, ammonium calcium alginate, sodium carboxymethylcellulose, ethylcellulose and polyacrylamides;

disintegrants, such as crospovidone, cross-linked sodium carboxymethylcellulose, microcrystalline cellulose, sodium carboxymethyl starch, starch, alginic acid, croscarmellose sodium, guar gum, aluminium magnesium silicate, aluminium silicate and pregelatinized starch;

wetting agents and solubilizing agents such as sodium lauryl sulphate; magnesium lauryl sulphate; dioctyl sodium sulfosuccinate; poloxamers such as Pluronic; polyoxyethylene alkyl ethers such as cetomacrogol; polyoxyethylene esters; polyoxyethylene castor oil derivatives such as Polyoxyl 35 castor oil and Polyoxyl 40 hydrogenated castor oil; polyoxyethylene sorbitan fatty acid esters such as polysorbates 20, 40, 60 and 80; and polyoxyethylene stearates such as polyethyleneglycol 400 monostearate, glycerol monostearate and Polyoxyl 40 stearate;

lubricants or glidants such as calcium stearate, glycerin, hydrogenated vegetable oil, magnesium stearate, zinc stearate, starch, dibasic calcium phosphate, magnesium carbonate, magnesium oxide, calcium

silicate, silica, micronized stearate, light mineral oil, polyethylene glycol, propylene glycol, talc, polyoxyethylene stearates, sodium lauryl sulphate and magnesium lauryl sulphate;

buffering agents such as primary, secondary or tertiary salts of phosphoric acid, salts of phthalic acid, salts of citric acid, salts of tartaric acid, and salts of amino acids such as glycine.

In general, a core is prepared according to methods well known in pharmaceutical practice, and when the core is in the form of a tablet it is prepared by means of compression of the core ingredients into a tablet. Before the compression step, the core ingredients may be admixed and/or granulated such as is well known in the art.

The core may comprise a multiplicity of units, each unit comprising an active substance optionally together with at least one pharmaceutically acceptable excipient and, optionally, being provided with a controlled-release coating. After administration and erosion of the lag-time controlling outer layer the core disintegrates into a multiplicity of units. By using such a core it is possible to obtain a controlled-release of the active substance or it is possible to incorporate different kinds of active substances in the units. Furthermore, it is possible to incorporate in the core, units with different coatings or different thicknesses of the coating to provide the desired release pattern of the active substance. In a specific embodiment, units with coatings as well as uncoated units are incorporated in the core of the dosage unit of the invention.

In a preferred embodiment, the core itself is uncoated (it should, however, be understood that the resulting pharmaceutical formulation of course is coated with a coating of the invention) and the active substance is in an inherently substantially freely releasable form which is released upon contact of the core with the aqueous medium. It should be appreciated that the requirements given above for a coating of the invention when applied on the test core also are fulfilled in those pharmaceutical formulations in which an active

substance in an inherently substantially freely releasable form is comprised in the solid ingestible material such as, e.g., in a core.

One important embodiment of the present invention is a pharmaceutical formulation in which the pattern of release of the active substance from the formulation after a predetermined lag-time corresponds essentially to the pattern of release of the active substance from the core before being provided with the coating. Thus, the coating has the function of limiting the diffusion of active substance but it does not substantially influence the pattern of release of the active substance when the release starts after substantial dissolution or erosion of the coating.

It will be appreciated that if the active substance is released in a controlled manner then the lag-time should not be too long. For formulations adapted to oral administration, the lag-time plus the time for release of the drug substance should obviously not exceed the gastrointestinal transit time of the formulation.

Coating

The term "an erodable layer or a combination of erodable layers" is used in the present context to designate the coating of a solid ingestible material, i.e. an outer layer which surrounds and covers the solid ingestible material of the formulation, and constitutes a barrier delaying the direct exposure of the solid ingestible material to gastrointestinal fluids. At least one of the erodable layers contain, as a major constituent, a water soluble cellulose derivative or a mixture of water soluble cellulose derivatives which have such a viscosity that the above-mentioned requirements for the coating are fulfilled when testing a relevant test combination (C) (see above). By the term "major constituent" is meant that the water soluble cellulose derivative or mixture of water soluble cellulose derivatives constitutes at least 50%, preferably at least 70%, more preferable at least 80% by weight of the coating (which may also be denoted as the lag-time controlling outer layer).

By proper choice of the viscosity of the water soluble cellulose derivative or mixture of water soluble cellulose derivatives and the quantities used thereof in the erodable layer, the lag-time (A) can be varied. Also, as it is apparent from the Examples herein, a shorter lag-time can *inter alia* be obtained by using a smaller amount of water soluble cellulose derivative or mixture of water soluble cellulose derivatives in the erodable layer or by using a water soluble cellulose derivative or mixture of water soluble cellulose derivatives with a lower viscosity, and, correspondingly, at longer lag time can be obtained using a larger amount of water soluble cellulose derivative or mixture of cellulose derivatives, or by using a water soluble cellulose derivative or mixture of water soluble cellulose derivatives of higher viscosity.

It should be mentioned that water soluble cellulose derivatives in general are accepted as coating material, see, e.g., GB 2,245,492 (Zambon Group SPA), DE 3,013,059 (Sandoz Patent GMBH), EP 411,590 (Arnold, J. D.), EP 284,514 (Norwich Easton Pharmaceuticals Inc.), GB 793,818 (Bardani, F. M.), FR 2,276,108 (Shin-Etsu Chemical Co. Ltd.), GB 2,212,396 (The Procter & Gamble Compagny), EP 013,131 (Mundipharma AG), EP 210,540 (Fujisawa Pharmaceutical Co. Ltd.), US 4,775,536 (Patell, M. K.) and EP 299,211 (Bayer AG). Furthermore, in a paper by Salomon, J. L. et al., Pharm. Ind. 41, 1979, pp. 799-802, is described a study performed in order to investigate whether the controlled-release mechanism of a substance (potassium chloride) contained in a core reservoir is influenced by providing the core with a layer of hydroxypropylmethylcellulose. Salomon et al. investigated *inter alia* the controlled-release mechanism of KCl from two compositions, each comprising a core of KCl crystals surrounded by a barrier coating consisting of hydroxypropylmethyl cellulose, the hydroxypropylmethyl cellulose having a viscosity of 100 cP in one composition and a viscosity of 15,000 cP in the other composition, and concluded that the barrier coating did not influence the release mechanisn.

However, in none of these documents is mentioned or indicated that use of an erodable layer or a combination of erodable layers containing, as a major constituent, a water soluble cellulose

derivative or a mixture of water soluble cellulose derivatives could lead to the present invention.

Without being limited to any specific theory, a mechanism of releasing the active substance from a pharmaceutical formulation of the invention is described in the following:

Upon administration of the pharmaceutical formulation according to the present invention and contact of the dosage unit with an aqueous body fluid (e.g. gastric fluid) there are indications that an outermost hydrated layer is formed. This hydrated layer serves an indirect mechanical stabilization function leading to substantial retainment of the shape of the formulation and preventing the formulation from crumbling or disintegrating by preventing the underlying dry, mechanically stable material from hydrating all at once.

The outermost hydrated layer then slowly dissolves or erodes. As new underlying material is exposed to aqueous body fluid it becomes hydrated, thus ensuring the persistence of an outermost hydrated layer. This process occurs continuously until the lag-time controlling outer layer (i.e. the coating itself or an erodable layer comprised in the coating) is substantially eliminated from the formulation.

When the lag-time controlling outer layer is substantially totally dissolved or eroded away, the solid material of the pharmaceutical formulation becomes exposed to the aqueous body fluid. The solid material can then disintegrate so that the active substance will become released, or, in those cases where the solid material is in the form of a non-disintegrating controlled-release matrix, the release of active substance will be initiated by the relevant release mechanisms.

As mentioned above at least one of the erodable lag-time controlling layer or layers of a pharmaceutical formulation according to the invention comprises, as a major constituent, a water soluble cellulose derivative or a mixture of water soluble cellulose

derivatives, which have such a viscosity that a test composition comprising a combination (C) of 1) a core containing an active substance in an inherently substantially freely releasable form as defined herein and 2) said erodable layer or combination of erodable layers, after a lag-time (A), defined as described herein, of at least 60 minutes during which at the most 30% by weight of the inherently substantially freely releasable active substance contained in the core is released, releases at least 70% by weight of the inherently substantially freely releasable active substance contained in the core within a burst-period (B), defined as described herein, of at the most 45 minutes, the said releases being measured as mean data determined by dissolution testing in purified water at 37°C and in 0.1 N hydrochloric acid at 37°C in accordance with Ph.Eur. V.5.4. (1991 edition), using a dissolution apparatus equipped with baskets rotating at 100 rpm.

When measuring the viscosity of a polymer according to the invention, 2.00 grams of the polymer is dissolved in 98 grams of water and when the polymer is completely dissolved, the viscosity is determined as described in Ph. Eur. monograph for measurement of viscosity, section V.6.7 (1986).

By applying a coating on a solid ingestible material, preferably a solid ingestible material in the form of a core, of the formulation, a drug delivery system is obtained from which the release of the active substance can be controlled in such a way that the onset of release first starts after a predetermined period of time.

The coating constitutes a barrier delaying the direct exposure of the solid ingestible material or the active substance contained in the core to gastrointestinal fluids and limits the diffusion of water from the aqueous medium to the solid ingestible material, so that release of an active substance from the solid ingestible material takes place predominantly when the coating has been dissolved or eroded away by the aqueous medium.

The dissolution rate of the water soluble cellulose derivative can be determined as described in Examples 14-16 herein by measuring the

concentration of hydroxypropylmethylcellulose in the dissolution medium when dissolution testing is performed on a formulation as described in Example 14 in purified water at 37°C and in 0.1 N hydrochloric acid at 37°C in accordance with Ph.Eur. V.5.4. (1991 edition), using a dissolution apparatus equipped with baskets rotating at 100 rpm. The standard viscosity of the hydroxypropylmethylcellulose seems to vary inversely proportional to the amount of HPMC dissolved by time as the amounts of HPMC dissolved by time were 0.8 mg/minutes, 0.6 mg/minutes and 0.3 mg/minutes for the standard viscosities of 15 cP, 50 cP and 100 cP, respectively. This finding is consistent with the results of the other Examples herein that when the viscosity of the HPMC is increased (when the same amount of HPMC is used), the lag-time is also increased.

When necessary, the pharmaceutical formulation according to the invention may comprise at least one erodable layer (I), in which the cellulose derivative or the mixture of water soluble cellulose derivatives has a viscosity which contributes to securing that the start of burst % is below 30%, and at least one other erodable layer (II), in which the cellulose derivative or the mixture of water soluble cellulose derivatives has a viscosity which contributes to securing that the lag-time (A) is at least 60 minutes. In a number of therapeutic applications a longer lag-time is desirable, such as, e.g., a lag-time of at least 90 minutes, at least 2 hours, at least 3 hours or at least 5 hours. In the present context such layers are also denoted:

(I) a start of burst %-regulating layer and

(II) a lag-time regulating layer.

In most cases a combination of the above-mentioned mechanisms of regulation (i.e. the start of burst %-regulating and the lag-time regulating effect) is present. Thus, in most cases it is not likely that only one effect is operating, but rather a combination of at least the two effects mentioned above.

Thus, the invention includes pharmaceutical formulations which comprise at least two erodable layers. Such two erodable layers will normally be layers of different composition, and will often be layers both of which are of the types defined herein, but designed so that one layer is particularly designed with respect to obtaining one particular property, such as, e.g., a long lag-time, and another layer is particularly designed with respect to obtaining another property, e.g. a low start of burst %. Thus, one combination according to the invention comprises two layers, the cellulose derivative or mixture of cellulose derivatives of one layer (I) having a viscosity which contributes to securing that the start of burst %, as defined herein, is below 30%, and at least one erodable layer which may either be the same layer (I) or a different layer (II), in which the cellulose derivative has a viscosity which contributes to securing that the lag-time (A) is at least 60 minutes. For a number of pharmaceutical formulations according to the invention, the start of burst %-regulating layer (I) and the lag-time regulating layer (II) are one and the same layer, which means that the cellulose derivative or mixture of cellulose derivatives of such one erodable layer is/are capable of permitting both a satisfactory lag-time, that is, a lag-time within the limitations defined above, and a satisfactory burst. In most cases, it is preferred that the inner layer, that is, the layer which is normally in immediate contact with the solid ingestible material, is the one with the lower viscosity.

A specific embodiment of such pharmaceutical formulations is, accordingly, a formulation comprising two layers, in which the cellulose derivative of the layer (I) has a viscosity of at the most 15 centipoise and the cellulose derivative of the layer (II) has a viscosity of at the most 50 centipoise (see Example 6 herein), and a formulation comprising two layers, in which the cellulose derivative of the layer (I) has a viscosity of at the most 15 centipoise and the cellulose derivative of the layer (II) has a viscosity of at the most 100 centipoise (see Example 12 herein).

Due to variations of pH in the gastrointestinal tract, the lag-time controlling layer of the dosage unit of the present invention may

advantageously hydrate substantially independent of pH in the aqueous body fluid, and the dissolution or erosion of the outer layer should preferably be substantially independent of pH.

As shown in Examples 1-8 and 10-13 herein where one half of the tablets from each Example has been tested in a medium of pH 1.2 and the other half in water, the lag-time has been found to a remarkable extent to be independent of pH. It is therefore to be expected that the release of the active substance *in vivo* is not significantly influenced by pH. Thus, variations in pH of body fluids, e.g. in gastric fluid and intestinal fluid, are without significant influence on the lag-time of the release of the active substance.

The lag-time of release of an active substance can be adjusted in various ways such as those described in the following:

Firstly, the particular choice of the ingredients present in the lag-time controlling layer is of importance, e.g. the choice of the water soluble cellulose derivative or the mixture of water soluble cellulose derivatives can affect the lag-time. Generally, the higher the viscosity of the water soluble cellulose derivative or the mixture of water soluble cellulose derivatives, the longer the lag-time (A). As an example, hydroxypropylmethylcellulose (HPMC) 100 cps hydrates more slowly than hydroxypropylmethyl-cellulose (HPMC) 15 cps.

Another way of regulating the lag-time is to use a polymeric substance of a different nature. Thus, replacing an essentially hydrophilic polymer, e.g. HPMC, with a more hydrophobic polymer, e.g. HPC (hydroxypropylcellulose), provided that the viscosity of a 2% aqueous solution at 20°C is substantially the same for the two types of polymers, it is to be expected that the lag-time increases.

Secondly, the thickness of the coating or lag-time regulating layer may influence the lag-time in such a way that an increase in thickness is assumed to increase the lag-time. In general, the coating has a thickness of at least about 0.1 mm, preferably in a range corresponding to the range of about 0.5-5 mm, and/or the volume

percentage of the coating is at least about 15% of the volume of the total dosage unit.

Thirdly, the use of a combination of erodable layers either of the same polymeric substance but having different viscosities, or of different polymeric substances having the same or different viscosity. In the alternative of using different polymeric substances, an inner layer of, e.g., HPMC may be applied as, e.g., a "start of burst %"-regulating layer, and, e.g., HPC may be applied in an outer layer as, e.g., a "lag-time"-regulating layer.

Preferred cellulose derivatives or constituent of cellulose derivative mixtures are selected from the group consisting of methylcelluloses, such as, e.g., Methocel® A (methylcellulose USP), sodium carboxymethylcelluloses, hydroxyethylcelluloses, hydroxypropylcelluloses (HPC), such as, e.g., Klucel®, and hydroxypropylmethylcelluloses (HPMC), such as, e.g., Methocel® E, F, J and K.

Preferred water soluble cellulose derivatives are HPMC's, HPC's and methylcelluloses.

Especially preferred hydroxypropylmethylcelluloses (HPMC) are HPMC's having a methoxy group content in the range of about 19-30% and/or a hydroxypropyl group content in the range of about 4-12%, such as, e.g., Methocel® E (hydroxypropylmethylcellulose, USP 2910), Methocel® F (hydroxypropylmethylcellulose, USP 2906), Methocel® J and Methocel® K (hydroxypropylmethylcellulose, USP 2208).

Especially preferred hydroxypropylcelluloses (HPC) are, e.g., Klucel® J and L, and especially preferred methylcelluloses are methylcelluloses having a methoxy group content in the range of about 26-33%, such as, e.g., Methocel® A 15.

The cellulose derivative or the mixture of cellulose derivatives of at least one layer of the erodable lag-time controlling layer typically have a viscosity of at the most about 100 centipoise, as measured on a 2% w/w aqueous solution at 20°C, preferably in the

range of about 15-50 cps. Particularly preferred cellulose derivatives are hydroxypropylmethylcelluloses having a viscosity (measured as defined above) in the range of about 1-100 cps. Examples of such HPMC's are Methocel® E 5, Methocel® E 15, Methocel® E 50 and Methocel® K 100. It is believed that any desired viscosity may be obtained by carefully selecting and mixing cellulose derivatives; also cellulose derivatives having a high viscosity such as Methocel® E 4000 can form part of these mixtures.

The erodable coating of the invention may further comprise pharmaceutically acceptable carriers and/or excipients such as those mentioned above in connection with the core, especially preferred further constituents are fillers, lubricants or glidants.

The coating of the invention may additionally contain a non-hydrogel forming water-soluble hydrophilic polymer, such as a glycol. Particularly preferred glycols are polyethylenglycoles, e.g. Macrogol® 6000. As will be apparent from Examples herein, the addition of Macrogol® 6000 have a clear positive effect on the dissolution of the active substance as the "end of burst %" increases.

In cases where the pharmaceutical formulation is targeted for a specific site in the intestines (either because it is desired to treat a disease localized at a specific site or because there is a narrow absorption window for the particular active substance) it may be advantageous to provide the formulation with an outer coating such as an enteric coating. Since the individual gastric transit times vary significantly, in contrast to intestinal transit time, an enteric coating will prevent contact of the dosage unit *per se* with an aqueous medium until the dosage unit has passed into the intestines; the active substance can then be released after a predetermined lag-time corresponding to the transport time to the particular target site.

In one embodiment of the invention, no active substance (e.g. drug) is present in the coating. However, within the concept of the present invention are also pharmaceutical formulations, in which the coating

or the erodable layer or at least one of the erodable layers contains an amount of active substance embedded therein, the active substance being released during and as a consequence of the erosion of the layer. This embodiment of the invention is especially valuable when a combination of time-controlled release and burst-release is a desirable release pattern.

In cases where rapid and immediate action of an active substance is desired, a further layer comprising active substance can be applied on the pharmaceutical formulation according to the invention in order to release the active substance from such an outermost layer substantially immediately after administration of the pharmaceutical formulation.

In those cases where a repeatedly delayed release is desired, a pharmaceutical formulation of the invention comprises a coated solid ingestible material which has further been provided with a coating comprising a layer of a solid ingestible material and at least one erodable layer. In such a formulation the solid ingestible materials contained in the pharmaceutical formulation may be the same or different materials and the same applies for the at least two coatings.

Active substances

As mentioned above, a pharmaceutical formulation of the present invention preferably comprises at least one active substance. The active substance is preferably comprised in the solid ingestible material but may also be in the coating or in an outermost layer of the pharmaceutical formulation.

The term "active substance" is used in the present context to designate any physiologically or pharmacologically active substance which produces a local or systemic effect in animals, which term includes warm-blooded mammals, such as humans. Preferred active substances are drugs, peptides, proteins, vitamins or nutrients.

In general all kinds of active substances may be employed in a pharmaceutical formulation of the invention. The usefulness of a particular active substance is dictated by therapeutic demands and is substantially unaffected of the physico-chemical properties of the active substance itself. Thus, active substances being substantially freely water soluble may successfully be incorporated in a pharmaceutical formulation of the invention as well as active substances being less water soluble. A pharmaceutical formulation of the invention is, however, especially well suited for time-controlled release of active substances which are easily soluble in an aqueous environment.

Variations in the pattern of time-controlled release of an active substance from a pharmaceutical formulation according to the present invention can be achieved by varying the composition of the coating, and, therefore, formulations according to the present invention can advantageously be used for a wide variety of active substances and for a wide variety of medical indications. As an example, a certain lag-time will in some circumstances be of value in order to secure the patient's compliance; therefore slimming agents, tranquilizers and diuretics are examples of embodiments of the pharmaceutical formulations according to the invention wherein pharmaceutical formulations having a lag-time (A) of at least 90 minutes are considered to be useful.

As it is explained in greater detail below, many patients with cardiovascular disease or asthma experience nocturnal aggravation. Therefore, for medicaments against asthma bronchiale or congestive heart failure, suitable dosage units according to the invention will be pharmaceutical formulations wherein a lag-time (A) of at least 2 hours e.g. at least 3 hours is obtained. For the above and a number of medicinal indications as will be described in more detail in the following dosage units according to the invention wherein the lag-time (A) is at least 5 hours will in some circumstances be preferred.

In diseases with circadian variation in severity of symptoms, use of a pharmaceutical formulation of the invention will be advantageous since the dosage unit can be ingested at a time convenient for the

patient and the therapeutic effect will be exerted at a time when the severity of disease symptoms is maximal or the sensitivity toward side-effects is minimal.

A drug substance which is especially suitable for use in a pharmaceutical formulation of the present invention is a drug substance having a short to medium biological half-life and exhibiting a therapeutic effect which is well correlated with the concentration in the biophase (e.g. the concentration of the drug substance in the blood after administration), and which becomes relatively rapidly distributed in the biophase.

It will be appreciated that circadian variations in the kinetic parameters for the particular drug substance must be taken into account when designing a particular pharmaceutical formulation. In general, daily variations have been reported for absorption rate, renal clearance, volume of distribution, protein binding and hepatic recirculation of drug substances.

Relevant to the time-controlled release is the diurnal variation of various processes within the body, i.e. the variations taking place over a 24-hour period. Schematically, the variations can be split up in pharmacodynamic variations, i.e. variations in drug sensitivity, and in pharmacokinetic variations, i.e. variations in absorption, distribution, metabolism and excretion processes. The common background is physiological variations in the autonomic nerve system, in the hormonal system and in CNS functions. As a consequence of these physiological variations many diseases may be presumed to show diurnal variations in symptoms or severity.

At present, 24-hour rhythmic activity in exacerbation of symptoms or occurrence of disease has been identified for the following conditions:

1. Cardiovascular diseases

   Cardiovascular parameters, e.g. blood pressure, heart rate, blood flow, blood volume and ECG, exhibit pronounced diurnal

variations, and so do cardiovascular diseases, e.g. ischemic heart diseases, acute myocardial infarction, stroke, hypertension and angina pectoris. Preferred drug substances for use in a pharmaceutical formulation of the invention for the treatment of cardiovascular diseases are e.g. adrenergic beta-receptor blocking agents, such as, e.g., metoprolol; calcium antagonists, such as, e.g., nifedipine; organic nitrates, such as, e.g., sorbid nitrate, isosorbid nitrate including isosorbid mono- and dinitrate; or diuretics, such as, e.g., furosemide or combinations thereof.

2. Rheumatoid arthritis and pain

A classical symptom in rheumatoid arthritis is morning stiffness. Long-acting NSAID (non-steroid anti-inflammatory drugs) or controlled-release formulations of short-acting drug substances have previously been developed in order to maintain a constant therapeutically active concentration during the morning hours. For some of the long-acting drug substances, however, the maintenance of the concentration is believed to be at the expense of an observed increase in frequency of side effects. Clinical studies have demonstrated a better therapeutic effect and a decrease in side-effects by use of a high evening dose. A pharmaceutical formulation of the present invention which is formulated to obtain a time-controlled release with a high release in the late evening and a low release in the morning is believed to combine convenient dosing for the patients with an optimal plasma profile. Peripherally acting analgesics with short to medium duration of therapeutic effects, such as indomethacin and ibuprofen, are therefore preferred drug substances for use in a pharmaceutical formulation of the invention.

3. Respiratory diseases

In asthma, the normally observed nocturnal aggravation is known as the "nocturnal dip". 40% of the respiratory distress in asthmatic patients and 50% of attacks in patients with bronchitis occurred at early morning hours. In lung function tests, identical daily variations in vital capacity and in peak expiratory flow are found, independent of environmental changes, i.e. at the same time of day for persons working during the day and working at night. The underlying mechanism is not known. Variations in beta-receptor function (caused either by changes in sensitivity or in concentration of circulating epinephrine being lower during night hours) have been invoked, and so has the documented rise in plasma histamine in the early hours of the morning. A pharmaceutical formulation of the invention may be formulated to release the active substance in the morning, and preferred drug substances for use in such a pharmaceutical formulation for the treatment of respiratory diseases, e.g. asthma and bronchitis, are xanthine derivatives, such as, e.g., theophylline; and adrenergic beta-receptor stimulating drugs, such as, e.g., salbutamol.

4. Gastrointestinal diseases

Circadian variations in connection with peptic ulcer are based on the clinical finding that a single evening dose of cimetidine is just as effective as dosage twice daily with respect to both the healing time for ulcers and the prevention of recurrence of peptic ulcers. A treatment with a pharmaceutical formulation of the invention that secures a neutral stomach during the night hours and the early morning hours is therefore believed to give an effective treatment. Preferred drug substances for use in a pharmaceutical formulation of the present invention for the treatment of gastrointestinal ulcers are antacids, or H_2 histamine receptor blocking agents, such as, e.g., cimetidine.

5. Mental disorders

In general, it is known that patients suffering from depression have significant symptoms in the morning, especially in connection with waking. Cyclic antidepressant drugs such as, e.g., trimipramin are preferred for use in a pharmaceutical formulation of the present invention for the treatment of depression.

6. Hormonal insufficiencies

It is known that daily variations in the blood concentration of endogenous hormones occur, and a hormone substitution therapy that mimics the normal variation is preferable. Preferred drug substances for use in a pharmaceutical formulation of the invention are, e.g., corticosteroids.

7. Cancer

Minimization of the side effects of cancer treatment is mandatory, and the sensitivity towards side effects has been shown to vary throughout the day. Preferred drug substances for use in a pharmaceutical formulation of the present invention for the treatment of cancer are, e.g., antibiotics such as, e.g., doxorubicin; alkylating agents as well as other cytostatic agent such as, e.g., cisplatin.

As a number of the above mentioned diseases and conditions are influenced by feedback systems (e.g. the feedback relationship between the anterior pituitary and its three target glands - the gonads, the adrenal cortex, and the thyroid) it is contemplated that for a number of diseases and conditions it will be advantageous to use dosage units according to the invention wherein at the most 25%, such as at the most 10%, 15% or 20 % of the active substance is released during the lag-time (A) in order to ensure that the feedback system is not triggered and the medicament thus can exert maximal effect when it is released.

A dosage unit according to the invention can also be used with the purpose of achieving local effect in the gastrointestinal tract. A preferred drug substance for this use is, e.g., 5-aminosalicylic acid.

Furthermore, a dosage unit according to the invention can be used to deliver the drug at a specific site from which the fraction absorbed into the systemic system is maximal. It is contemplated that especially under such circumstances but not limited to these it will be advantageous to use a pharmaceutical dosage unit according to the invention in which at least 70% by weight of the active substance is released within a burst-period (B) of the most 30 minutes. For some clinical conditions it might even be advantageous to use a pharmaceutical dosage unit according to the invention in which at least 80% of the active substance is released during the burst-period (B). Preferred drug substances for this use are, e.g., peptides and proteins, such as, e.g., antidiuretic hormone or calcitonin.

In a number of situations, especially in those situations where a delayed but rapid release of an active substance is desirable, a pharmaceutical formulation of the invention may preferably be a pharmaceutical formulation unit for oral administration, comprising a combination (C) of 1) a core containing an active substance in an inherently substantially freely releasable form and 2) an erodable layer or a combination of erodable layers surrounding and covering the core and constituting a barrier delaying the direct exposure of the inherently substantially freely releasable active substance contained in the core to gastrointestinal fluids, at least one of the erodable layers containing, as a major constituent, a water soluble cellulose derivative or a mixture of water soluble cellulose derivatives, the cellulose derivative or the mixture of cellulose derivatives having a viscosity which permits that the unit, after a lag-time (A), defined as described herein, of at least 60 minutes during which at the most 30% by weight of the inherently substantially freely releasable active substance contained in the core is released, releases at least 70% by weight of the inherently substantially freely releasable active substance contained in the core within a burst-period (B), defined as described herein, of the

most 45 minutes, the said releases being measured as mean data determined by dissolution testing in purified water at 37°C and in 0.1 N hydrochloric acid at 37°C in accordance with Ph.Eur. V.5.4. (1991 edition), using a dissolution apparatus equipped with baskets rotating at 100 rpm.

As will be understood from the description which follows, this combination (C) may be combined with further barrier layers of the same or different release principle and/or further or more elaborate cores containing the same or different active substances.

Thus, in one special aspect, the invention relates to a pharmaceutical formulation comprising a combination (C) as defined above combined with a further combination (C) as defined above (termed C'), the erodable barrier layer 2 (termed 2') of which is arranged so that it becomes exposed when the inherently substantially freely releasable active substance (1) of the first combination (C) is released, so that the pharmaceutical formulation, after a lag-time (A') of at least 60 minutes during which at the most 30% by weight of the inherently substantially freely releasable active substance is released, releases at least 70% by weight of the inherently substantially freely releasable active substance (1') contained in the further combination (C') within a burst-period (B'), defined as described herein, of at the most 45 minutes, the said releases being measured as mean data determined by dissolution testing in purified water at 37°C and in 0.1 N hydrochloric acid at 37°C in accordance with Ph.Eur. V.5.4. (1991 edition), using a dissolution apparatus equipped with baskets rotating at 100 rpm. This special aspect, thus, permits either a double burst release of the same active substance, with the same or different lag-times, or one burst release of a first active substance, and a later burst release of a second, different active substance. It is evident that the lag-time (A) and the lag-time (A') can be the same or different. Accordingly, the burst-period (B) and the burst-period (B') may also be the same or different.

Within the concept of the present invention are also dosage units, in

which the combination (C) is combined with an additional amount of active substance contained in the core, the additional amount of active substance being in a controlled release formulation. It is, however, obvious that substantially all of the active substance present in the core of a pharmaceutical formulation according to the invention should be released after a certain period of time after administration, which period together should not exceed the total time of transit of the dosage unit through the gastrointestinal tract.

Other embodiments of the invention comprising an active substance in an inherently substantially freely releasable form are pharmaceutical formulations in which the erodable layer 2) or at least one of the erodable layers 2) (see above) of the combination (C) contains an amount of active substance embedded therein so that the active substance is released during and as a consequence of the erosion of the layer. Furthermore, an additional amount of active substance may be applied on a pharmaceutical formulation of the invention in order to substantially immediately releasing the active substance after administration.

The pharmaceutical formulation of the invention is preferably intended for oral use in the form of a dosage unit. Formulations for oral use comprise tablets and capsules. A preferred dosage unit for oral use is in the form of a tablet.

A pharmaceutical formulation according to the present invention can be in the form of a single-unit formulation or a multiple-unit formulation.

Preparation of a pharmaceutical formulation according to the invention

The coating may, e.g., be applied on the solid ingestible material by means of a coating-by-compression technique, i.e. a solid ingestible material optionally comprising an active substance and optionally at least one pharmaceutically acceptable excipient is placed in a die which has been charged with a granulate comprising, as a major

constituent, a water soluble cellulose derivative or a mixture of water soluble cellulose derivatives, thereafter a further quantity of the granulate so as to completely cover the solid ingestible material is added, and the granulate is compressed around the solid ingestible material to prepare the pharmaceutical formulation. It is contemplated that it is of importance that the solid ingestible material is placed centrally with accuracy in order to ensure that a reproducible lag-time is obtained.

When described in detail, the method for the preparation of a pharmaceutical formulation according to the present invention may comprise the following steps (in the following the method is described for a pharmaceutical formulation in which the solid ingestible material is in the form of a core comprising an active substance):

1) Preparation of the core by sieving the active substance and optionally mixing and sieving with at least one pharmaceutically acceptable excipient, followed by compression of the mixture into a tablet, i.e. the core.

2) Preparation of the material for the lag-time controlled outer layer by sieving and mixing the ingredients and optionally granulating and drying the mixture.

3) Preparation of a tablet having a core and a coating (lag-time controlling outer layer) by placing the core, prepared as described in 1) centrally in a die which has been charged with a sufficient and well-defined quantity of material as described in 2) as the bottom layer. In order to ensure that the core is placed centrally, a metal tube may be used having an internal diameter of the same dimension as the core and an external diameter as the die. Subsequently, an additional, well-defined quantity of material as described in 2) is added as a top layer, and a tablet is compressed.

4) Optional the above-mentioned process can be repeated using the tablet produced under 3) as core.

5) Optionally the tablet produced as described in 3) or 4) can be provided with a coating, preferably an enteric coating, by means of methods well known in the art.

The invention is disclosed in further detail in the following examples which should not be construed as limiting the invention in any way.

EXAMPLES

MATERIALS

Core composition

A Salbuvent® 4 mg tablet prepared by Nycomed consisting of the ingredients given below, was used as core in the Examples 1-9. The dissolution profile of the core was determined by dissolution testing in purified water at 37°C and in 0.1 N hydrochloric acid at 37°C in accordance with Ph. Eur. V.5.4. (1991 edition), using a dissolution apparatus equipped with baskets rotating at 100 rpm. Determined as mean data, the core releases at least 90% by weight of the total content of salbutamol sulfate during a period of at the most 45 minutes.

	% w/w
Salbutamoli sulfas	2.0
Amylum maydis	40.0
Lactosum 150 mesh	40.0
Povidone	2.5
Talcum	2.5
Cellulosum microcrist.	12.5
Magnesii stearas	0.5
	100.0
Spiritus fortis	q.s.
Aqua purificata	q.s.

Further materials were as follows:

Ac-Di-Sol®	Croscarmellose sodium manufactured by FMC
Avicel® PH 101	Microcrystalline cellulose manufactured by FMC
Caffeine	Caffeine manufactured by Boehringer Ingelheim (Germany)
Macrogol 6000	Macrogol manufactured by Hoechst AG
Magnesium stearate	Magnesium stearate manufactured by Breyer Chemie B.V.
Methocel® E 15	Methocel® E 15 LV Premium manufactured by Dow Chemical Corp.
Methocel® E 50	Methocel® E 50 Premium manufactured by Dow Chemical Corp.
Methocel® K 100	Methocel® K 100 LV Premium manufactured by Dow Chemical Corp.
Methocel® E 4M	Methocel® E 4M Premium manufactured by Dow Chemical Corp.
Klucel® MF	Klucel® MF manufactured by Aqualon
Klucel® LF	Klucel LF manufactured by Aqualon
Lactose	A fine particular lactose manufactured by Cooperative Çondensfabrik-Friesland Co.

Tabletose®	A direct compressible lactose manufactured by Meggle
Talc	Talco Val Chisone

METHOD OF ANALYSIS

Dissolution testing

The dissolution testing is performed in accordance with Ph.Eur. V.5.4. (1991 edition).

Apparatus

The apparatus used is a USP/Ph.Eur. dissolution apparatus (Sotax AT6 or AT7) equipped with baskets.

Testing conditions

The dissolution medium is thermostatically controlled at 37°C, and the rotation speed for the baskets is set at 100 rpm.

Dissolution media

The test is performed in purified water as well as in 0.1 N-hydrochloric acid.

Results

Sampling is performed every 15 minutes.

On the basis of the results obtained in each of the following Examples 1-8, 12 and 13, a dissolution profile is drawn for each of the Examples. For the description of the profile, the following key parameters are determined: Lag-time (A), burst-period (B), start of burst %, and end of burst %. Figure 2 and legend to figure 2 can be used as a guide.

The following Examples describe the results of studies carried out *in vitro* as well as *in vivo*. The influence of different parameters relating to the formulation is described.

EXAMPLE 1

Preparation of a pharmaceutical formulation according to the invention

A Salbuvent® 4 mg tablet, manufactured by Nycomed, was used as tablet core. The composition of the core is described above, and the diameter of the core was 8.0 mm. An outer layer was applied on the core by means of a coating-by-compression technique. Different compositions of the coating, i.e. of the outer layer or outer layers, are used in the examples 1-9.

Outer layer composition 1

The following ingredient was used:

	% w/w
Methocel® E 15 Premium =	100

Coating-by-compression

97.5 mg (39.4%) outer layer material was pre-charged in a die with a punch diameter of 11.0 mm. The core was placed centrally in the die by means of a centering tube. Having centered the core in the die, the die was filled with the remaining amount of the outer layer granulate (150.0 mg) and a circular, plane tablet was produced by compression in special compression equipment (Fette Exacta 1/F, instrumentated tabletting machine) applying a pressure of about 9-11 kN. The tablets produced according to the above description had an average height of approx. 4.2 mm.

Results

The tablets prepared in Example 1 were tested and analyzed as described under "Method of Analysis", i.e. for all tablets dissolution testing was carried out in acidic as well as neutral dissolution media. The results are given below in the form of a table and in Figure 3 as dissolution profile. In Figure 11 is shown the lag-times obtained for tablets prepared according to Examples 1-8.

6 tablets were produced as described in Example 1 in a first experiment A, and 12 tablets were produced as described in Example 1 in a second experiment B. The results of the dissolution testing of the tablets prepared appear below as Table 1 including results for experiment A (6 tablets), B (12 tablets) and cummulated results for experiment A+B (18 tablets). The dissolution profile based on the stated mean data for experiment A+B appears from Figure 3.

TABLE 1

	Mean			Standard deviation S.D		
	A+B	A	B	A+B	A	B
Lag-time (min)	117.1	111.7	119.8	15.3	18.6	13.5
Burst-period (min)	23.8	30.0	20.8	7.6	8.6	5.1
Start of burst %	8.8	7.6	9.5*	3.8	4.3	3.6*
End of burst %	81.4	81.1	81.6	6.8	6.6	7.1

*) n=11

EXAMPLE 2

Preparation of a pharmaceutical formulation according to the invention

Tablets were prepared as in Example 1 using an outer layer composition as follows:

Outer layer composition 2

The following ingredients were used:

	% w/w
Methocel® E 15 Premium	85
Macrogol 6000	15
	100

Macrogol 6000 was sieved (300 µm mesh screen) and then premixed with Methocel® E 15 Premium (300 µm mesh screen). The mixture was then sieved (300 µm mesh screen) and finally mixed.

Coating-by-compression

150 mg (45.5%) outer layer granulate was pre-charged in a die with a punch diameter of 11.0 mm. The core was placed centrally in the die by means of a centering tube. Having centered the core in the die, the die was filled with the remaining amount of the outer layer granulate (180 mg) and a round, plane tablet was produced by applying a compression pressure of approximately 10-12 kN. The tablet height was approximately 4.8 mm.

Results

The tablets prepared in Example 2 were tested and analyzed as described under "Method of Analysis", i.e. for all tablets dissolution testing was carried out in acidic as well as neutral dissolution media. The results are given below in the form of a table and in Figure 4 as dissolution profile. In Figure 11 is shown

the lag-times obtained for tablets prepared according to Examples 1-8.

6 tablets were produced as described in Example 2. The results of the dissolution testing of the 6 tablets prepared appear below as Table 2, and the dissolution profile based on the stated mean data appears from Figure 4.

TABLE 2

	Mean	Standard deviation S.D.
Lag-time (min)	182.7	29.4
Burst-period (min)	29.0	2.0
Start of burst %	14.7	5.8
End of burst %	94.4	1.6

EXAMPLE 3A

Preparation of a pharmaceutical formulation according to the invention

Tablets were prepared as described in Example 1 using an outer layer composition as the following:

Outer layer composition 3

The following ingredients were used:

	% w/w
Methocel® E 15 Premium	75
Macrogol 6000	25

Macrogol 6000 was sieved (mesh screen 300 μm) and was then premixed with Methocel® E 15 Premium (mesh screen 300 μm). The mixture was then sieved (mesh screen 300 μm) followed by final mixing.

Coating-by-compression

Tablets were produced as described in Example 2.

Tablets were produced applying a compression pressure of approximately 15-20 kN. Tablets produced as described had an average height of approx. 4.7 mm.

EXAMPLE 3B

Preparation of a pharmaceutical formulation according to the invention

Tablets were prepared as described in Example 3A, i.e. using outer layer composition 3.

Coating-by-compression

Tablets were produced as described in Example 3A. Tablets were produced by applying a pressure of approximately 11-13 kN. Tablets manufactured as described had a height of 4.8 mm.

Results

The tablets prepared in Examples 3A and 3B were tested and analyzed as described under "Method of Analysis", i.e. for all tablets dissolution testing was carried out in acidic as well as neutral dissolution media. The results are given below in the form of a table and in Figure 5 as dissolution profile. In Figure 11 is shown the lag-times obtained for tablets prepared according to Examples 1-8.

80 tablets were produced as described in Example 3A, and 12 tablets were produced as described in Example 3B. The results of the dissolution testing of the tablets prepared appear below as Table 3 including results for Example 3A (5 tablets), Example 3B (12 tablets), and cummulated results for Example 3A+B (17 tablets). The dissolution profile based on the stated mean data for Example 3A+B appears from Figure 5.

TABLE 3

	Mean			Standard Deviation S.D.		
	A+B	A	B	A+B	A	B
Lag-time (min)	124.3	133.4	120.5	31.3	24.7	33.9
Burst-period (min)	26.9	28.6	26.2	10.3	2.9	12.2
Start of burst %	8.3	8.7*	8.2	3.0	2.5*	3.3
End of burst %	93.9	96.2	92.9	3.2	2.7	3.0

*) n=4

EXAMPLE 4

Preparation of a pharmaceutical formulation according to the invention

Tablets were prepared as in Example 1 using an outer layer composition as follows:

Outer layer composition 4

The following ingredients were used:

	% w/w
Methocel® E 15 Premium	75
Avicel® PH 101	25
	100

Avicel® PH 101 was sieved (300 µm mesh screen) and then premixed with Methocel® E 15 Premium (300 µm mesh screen). The mixture was then sieved (300 µm mesh screen) and finally mixed.

Coating-by-compression

Tablets was manufactured as described in Example 2. Tablets were produced by applying a compression pressure of approx. 20-23 kN. The tablets manufactured as described had an average height of approximately 4.5 mm.

Results

The tablets prepared in Example 4 were tested and analyzed as described under "Method of Analysis", i.e. for all tablets dissolution testing was carried out in acidic as well as neutral dissolution media. The results are given below in the form of a table and in Figure 6 as dissolution profile. In Figure 11 is shown the lag-times obtained for tablets prepared according to Examples 1-8.

6 tablets were produced as described in Example 4. The results of the dissolution testing of the tablets prepared appear below as Table 4, and the dissolution profile based on the stated mean data appears from Figure 6.

TABLE 4

	Mean	Standard Deviation S.D.
Lag-time (min)	150.0	20.1
Burst-period (min)	29.7	8.2
Start of burst %	4.2	2.0
End of burst %	83.2	4.5

EXAMPLE 5

Preparation of a pharmaceutical formulation according to the invention

Tablets were prepared as in Example 1 using an outer layer composition as follows:

Outer layer composition 5

The following ingredients were used:

	% w/w
Methocel® E 15 Premium	75
Lactose	25
	100

Lactose was sieved (300 µm mesh screen) and then premixed with Methocel® E 15 Premium. The mixture was then sieved (300 µm mesh screen) and finally mixed.

Coating-by-compression

Tablets were manufactured as described in Example 2 by applying a compression pressure of approximately 12-14 kN. The tablets manufactured as described had an average height of approximately 4.7 mm.

Results

The tablets prepared in Example 5 were tested and analyzed as described under "Method of Analysis", i.e. for all tablets dissolution testing was carried out in acidic as well as neutral dissolution media. The results are given below in the form of a table and in Figure 7 as dissolution profile. In Figure 11 is shown the lag-times obtained for tablets prepared according to Examples 1-8.

6 tablets were produced as described in Example 5. The results of the dissolution testing of the tablets prepared appear below as Table 5 and the dissolution profile based on the stated mean data appears from Figure 7.

TABLE 5

	Mean	Standard Deviation S.D.
Lag-time (min)	133.5	13.8
Burst-period (min)	16.8	4.5
Start of burst %	10.2	2.0
End of burst %	84.8	6.4

EXAMPLE 6

Preparation of a pharmaceutical formulation according to the invention

Tablets were prepared as described in Example 1 using an outer layer composition as follows:

Outer layer composition 6

The following ingredient was used:

	% w/w
Methocel® E 50 premium	100

Coating-by-compression

Tablets were manufactured as described below.

132 mg (44.4%) outer layer material was pre-charged in a die with a punch diameter of 11.0 mm. The core was placed centrally in the die by means of a centering tube. Having centered the core in the die, the die was filled with the remaining amount of the outer layer granulate (165 mg) and a circular, plane tablet was produced by compression in special compression equipment (Fette Exacta 1/F, instrumentated tabletting machine) applying a pressure of about 15-19 kN. The tablets produced according to the above description had an average height of approx. 4.4 mm.

Results

The tablets prepared in Example 6 were tested and analyzed as described under "Method of Analysis", i.e. for all tablets dissolution testing was carried out in acidic as well as neutral dissolution media. The results are given below in the form of a table and in Figure 8 as dissolution profile. In Figure 11 is shown the lag-times obtained for tablets prepared according to Examples 1-8.

80 tablets were produced as described in Example 6. The results of the dissolution testing of 6 of the tablets prepared appear below as Table 6 and the dissolution profile based on the stated mean data appears from Figure 8.

TABLE 6

	Mean	Standard Deviation S.D.
Lag-time (min)	317.2	50.9
Burst-period (min)	21.2	3.1
Start of burst %	22.1	8.2
End of burst %	93.1	2.2

EXAMPLE 7

Preparation of a pharmceutical formulation according to the invention

Tablets were prepared as described in Example 1 using a first and a second outer layer composition as follows:

Outer layer composition 7A

The following ingredient was used:

	% w/w
Methocel® E 15 Premium	100.0

Methocel® E 15 Premium was sieved (300 µm mesh screen).

Outer layer composition 7B

The following ingredient was used:

	% w/w
Methocel® E 50	100.0

Methocel® E 50 was sieved (300 µm mesh screen).

Coating-by-compression

Tablets were manufactured in a double compression as described below.

First coating-by-compression (7A)

50 mg Methocel® E 15 Premium outer layer material was pre-charged in a die with a punch diameter of 10.0 mm. The core was placed centrally in the die by means of a centering tube. Having centered the core in the die, the die was filled with the remaining amount of the outer layer granulate, 85 mg, and a circular, plane tablet was produced by compression in a single punch tabletting machine (Diaf TM-20)

applying medium pressure. The tablets produced according to the above description had a height of approximately 4.5 mm.

Second coating-by-compression (7B)

100 mg Methocel® E 50 was pre-charged in a die with a punch diameter of 12.0 mm. Having placed the double-compressed unit, consisting of core and first layer (7A), centrally in the die, the die was filled with the remaining amount of the outer layer granulate, 150 mg, and a circular, plane tablet was produced by compression in a single punch tabletting machine (Diaf TM-20). The tablets produced according to the above description had a height of approximately 4.8 mm.

Results

The tablets prepared in Example 7 were tested and analyzed as described under "Method of Analysis", i.e. for all tablets dissolution testing was carried out in acidic as well as neutral dissolution media. The results are given below in the form of a table and in Figure 9 as dissolution profile. In Figure 11 is shown the lag-times obtained for tablets prepared according to Examples 1-8.

6 tablets were produced as described in Example 7. The results of the dissolution testing of the tablets prepared appear below as Table 7 and the dissolution profile based on the stated mean data appears from Figure 9.

TABLE 7

	Mean	Standard Deviation S.D.
Lag-time (min)	335.8	39.2
Burst-period (min)	23.3	2.6
Start of burst %	11.8	6.3
End of burst %	92.2	2.8

EXAMPLE 8

Preparation of a pharmaceutical formulation according to the invention

Tablets were prepared as described in Example 7 using a first and a second outer layer composition as follows:

Outer layer composition 8A

The following ingredients were used:

	% w/w
Methocel® E 15 Premium	85.0
Macrogol 6000	15.0

Macrogol 6000 and Methocel® E 15 Premium were sieved (300 µm mesh screen), premixed and sieved (300 µm mesh screen) followed by final mixing.

Outer layer composition 8B

The following ingredient was used:

	% w/w
Methocel® E 50	100.0

Methocel® E 50 was sieved (300 μm mesh screen).

Coating-by-compression

First coating-by-compression (8A)

59 mg outer layer material was pre-charged in a die with a punch diameter of 10.0 mm. The core was placed centrally in the die by means of a centering tube. Having centered the core in the die, the die was filled with the remaining amount of the outer layer granulate, 100 mg, and a circular, plane tablet was produced applying medium pressure. The tablets produced according to the above description had a height of approximately 4.6 mm.

Second coating-by-compression (8B)

Tablets were compressed as described in Example 7B.

The tablets produced according to the above description had a height of approximately 4.8 mm.

Results

The tablets prepared in Example 8 were tested and analyzed as described under "Method of Analysis", i.e. for all tablets dissolution testing was carried out in acidic as well as neutral dissolution media. The results are given below in the form of a table and in Figure 10 as dissolution profile. In Figure 11 is shown the lag-times obtained for tablets prepared according to Examples 1-8.

Outer layer: First coating: 85% Methocel® E 15 + 15% Macrogol 6000
Second coating: 100% Methocel® E 50

6 tablets were produced as described in Example 8. The results of the dissolution testing of the tablets prepared appear below as Table 8 and the dissolution profile based on the stated mean data appears from Figure 10.

TABLE 8

	Mean	Standard Deviation S.D.
Lag-time (min)	365.0	39.7
Burst-period (min)	45.0	26.1
Start of burst %	11.2	3.8
End of burst %	96.0	2.0

CONCLUSION OF EXAMPLES 1-8

An aim of the present invention has been to develop a pharmaceutical formulation in the form of a coated solid ingestible material, preferably in the form of a unit dosage form. The formulation should be substantially capable of retaining an active substance, observing four major objectives:

1) during the lag-time, no release of active substance should take place,

2) the lag-time should be substantially independent of pH,

3) a high extent of reproducibility should characterize the system, making the lag time predictable, and

4) at the end of the lag-time, the active substance should be released instantly.

Conclusion of Examples 1-5

Examples 1-5, using the hydroxypropylmethylcellulose derivative Methocel® E 15 as the basis polymer (Example 1: 100% Methocel® E 15; Examples 2 and 3A+B containing 15% and 25% Macrogol 6000, respectively; and Examples 4 and 5 containing 25% Avicel® and lactose, respectively), convincingly show that tablets according to the invention with a comparatively short lag-time have been successfully manufactured. Lag-times are from 117.1 to 182.7 min. All of the tablets are capable of retaining the active substance for the greater part of the lag phase. Not until the end of the lag phase, immediately before the beginning of the burst-period, can incipient release be observed as the beginning of the subsequent burst-period.

The lag-time is to a remarkable extent independent of pH as shown when testing one half of the tablets from each Example in a medium of pH 1.2 and the other half in water.

On the basis of the composition selected, in combination with a careful and accurate manufacturing method, unique reproducibility of the lag-time has been achieved. This can be seen from the results of Example 1 in which the same composition containing 100% Methocel® E 15 was manufactured and tested in two consecutive series of trials. 6 tablets were produced as described in Example 1 in a first experiment A, and 12 tablets were produced as described in Example 1 in a second experiment B. The data show mean lag-time of 111.7 min. (standard deviation 18.6 minutes) for experiment A, and 119.8 minutes (standard deviation 13.5 minutes) for experiment B.

This can furthermore be seen in Examples 3A and 3B in which the same composition containing 75% Methocel® E 15 and 25% Macrogol 6000 was manufactured and tested in two consecutive series of trials. In Example 3A a total of 80 tablets was manufactured for *in vivo*-study purposes (Example 9). 5 of these tablets were tested, and subsequently another batch of 12 tablets was prepared and tested in

Example 3B. The data show mean lag-time of 133.4 min. (standard deviation 24.7 minutes) in Example 3A, and 120.5 minutes (standard deviation 33.9 minutes) in Example 3B.

Moreover, it has been shown that after the end of the lag phase, rapid and controlled release of the active substance is ensured. Up to 94.4% had been released at the defined "end of burst%".

Consequently, the dissolution of the active substance has not been negatively effected by the outer layer providing the lag-time.

The addition of a polyethyleneglycol, Macrogol 6000, has been observed to have a clear positive effect on the dissolution of the active substance as the "end of burst %" has increased from 81.4% (standard deviation 6.8%) in Example 1 to 93.9% (standard deviation 3.2%) in Example 3A+B, and to 94.4% (standard deviation 1.6%) in Example 2.

Examples 4 and 5, in which 25% Avicel® and lactose, respectively, have been added to 75% Methocel® E 15, show that the presence of these tablet excipients does not impair or compromise the performance of the system as neither the lag phase nor the burst phase is affected.

Conclusion of Examples 6-8

In Examples 6-8, the hydroxypropylmethylcellulose derivative Methocel® E 50 has been used as the basis polymer. The tablets prepared in Example 6 contain 100% Methocel® E 50, whereas the tablets prepared in Example 7 contain a double-coating system in which 100% Methocel® E 15 was compression coated in the first coating and 100% Methocel® E 50 in the second coating. The tablets prepared in Example 8 contain a double-coating system in which 85% Methocel® E 15 and 15% Macrogol 6000 added was compression coated in the first coating and 100% Methocel® E 50 was used for the second coating.

Examples 6-8 convincingly show that tablets according to the invention having a significantly longer lag-time than the short lag-

time achieved with Methocel® E 15 as the basis polymer have been successfully manufactured. The lag-times obtained are very long, from 317.2 minutes to 365.0 minutes. All the tablets are capable of retaining the active substance for the greater part of the lag phase as almost no active substance is dissolved. Not until the end of the lag phase, immediately before the beginning of the burst-period, can incipient release be observed as the beginning of the subsequent burst-period. It is worth noting that positive effect on the dissolution has been achieved from the double-coating system using Methocel® E 15 in the first layer, especially the combination of Methocel® E 15 with Macrogol 6000 which has the effect of less release during the lag phase, and Methocel® E 50 in the outer layer. As a result, a higher dissolution rate is observed after the end of the lag-time. This is a result of the combined effect of Methocel® E 50 providing the remarkably long lag-time and Methocel® E 15 (combined with Macrogol 6000 if desired) ensuring a more complete retention of the active substance before the start of the burst-period. A marked reduction has been observed in the dissolved start of burst % from 22.1% (standard deviation 8.2%) in Example 6 to 11.8% (standard deviation 6.3%) in Example 7, and 11.2% (standard deviation 3.8%) in Example 8.

Furthermore, the lag-time is to a remarkable extent independent of pH as shown when testing one half of the tablets from each Example in a medium of pH 1.2 and the other half in water.

On the basis of the coating composition selected, in combination with a careful and accurate manufacturing method, unique reproducibility of the lag-time has been achieved as discussed above. The assessment of reproducibility should also take into account the remarkably long lag-times during which the active substance was retained for up to approximately 6 hours. Observed lag-times were from 317.2 minutes (standard deviation 50.9 min.) in Example 6 to 365.0 minutes (standard deviation 39.7 min.) in Example 8. The use of the double-coating technique in Examples 7 and 8 may improve reproducibility.

Furthermore, it has been shown that after the lag phase has ended,

rapid of the active substance is ensured. The defined end of burst % has been up to 96.0% (Example 8).

Consequently, the dissolution of the active substance has not been negatively effected by the outer layer providing the lag-time. On the basis of the compositions selected together with careful manufacturing and analytical methods, the tablets prepared and analyzed in the *in vitro* Examples 1-8 demonstrate that it is possible to achieve short lag-times from approximately 2 hours up to approximately 6 hours. Lag-times between 2 and 6 hours are expected to be obtained by qualitative adjustments of the composition (e.g. mixing of the basis polymers Methocel® E 15 and Methocel® E 50) as well as quantitative adjustments.

In conclusion, a pharmaceutical formulation according to the invention has a remarkable capability of retaining the active substance completely during the lag-time, ensuring that the lag-time is substantially independent of pH, ensuring a high degree of reproducibility of the lag-time, and in those cases where a core containing an inherently substantially freely releasable active substance is used a rapid, instant release of the active substance takes place when the the lag-time has ended.

A pharmceutical formulation according to the invention has successfully fulfilled the objectives defined.

EXAMPLE 9

In vivo study

The aim of this study was to investigate the bioavailability of the two pharmaceutical formulations of the invention compared to conventional Salbutamol® 4 mg tablets using the area under the plasma concentration-time curves (AUC), the maximum plasma concentration (C_{max}) and the lag-time T_{lag} as test variables. The lag-time T_{lag} is defined as the time period between the ingestion of the drug and the time, at which a detectable plasma concentration was measured for the first time.

Materials and methods

The study was an open, controlled, randomized, balanced cross-over study with three study periods.

Nine volunteers participated in the study. Each volunteer received one tablet (4 mg) of each formulation with a one week interval together with 150 ml water.

The study drugs were:

A: The tablet prepared as described in Example 3A

B: The tablet prepared as described in Example 6

C: Salbuvent® tablet 4 mg

The volunteers had a light breakfast 1 1/2 hour before tablet ingestion, lunch 4 hours, and dinner 10 hous after ingestion. Liquid consumption was controlled in the first 4 hours.

Blood was sampled with 1 hour interval for 12 hours on each study day.

Any adverse drug reactions were registered.

Results

The mean and standard deviations (S.D.) are listed in the following tables:

TABLE 9A

Plasma concentrations of salbutamol ng/ml		
Formulation A		
Hours	Mean	S.D
0	nd	nd
1	0.3	0.9
2	1.8	3.3
3	6.6	2.7
4	9.7	5.0
5	8.1	2.6
6	6.1	1.8
7	4.9	1.2
8	4.0	1.1
9	3.8	1.0
10	3.4	1.1
11	3.0	0.8
12	2.8	0.8

TABLE 9B

Plasma concentrations of salbutamol (ng/ml)		
Formulation B		
Hours	Mean	S.D.
0	nd	nd
1	nd	nd
2	nd	nd
3	0.2	0.5
4	0.3	0.8
5	0.3	0.8
6	0.3	0.8
7	1.6	2.6
8	2.2	4.0
9	2.6	3.3
10	2.2	3.0
11	2.1	2.3
12	1.4	2.2

TABLE 9C

Plasma concentrations of salbutamol (ng/ml)		
Formulation C		
Hours	Mean	S.D.
0	nd	nd
1	10.7	5.2
2	10.7	3.3
3	9.2	2.3
4	8.1	2.0
5	7.1	1.2
6	6.0	0.9
7	4.8	0.8
8	4.3	0.6
9	3.9	1.0
10	3.4	0.6
11	3.1	0.8
12	2.7	0.8

The statistical results are given as the ratio of the medians for AUC and C_{max} and as the difference of the medians for the lag-time T_{lag} together with the 90% confidence limits as shown in the next tables 9D-9G.

TABLE 9D

Parameter	Ratio	
	A/C	B/C
AUC	0.87	0.14
C_{max}	0.80	0.24

TABLE 9E

Parameter	90% confidence limits			
	lower		upper	
	A/C	B/C	A/C	B/C
AUC	0.67	0.08	1.13	0.27
C_{max}	0.63	0.17	1.03	0.35

TABLE 9F

Parameter	Difference		
		A-C	B-C
T_{lag}		1.56	6.66

TABLE 9G

Parameter	90% confidence limits					
	lower			upper		
		A-C	B-C		A-C	B-C
T_{lag}		1.12	5.39		1.99	7.92

Most of the volunteers experienced tremor and agitation with some of the formulations. The onset of these adverse drug reactions is shown in Figure 13.

CONCLUSION

The purpose of the study was to investigate the bioavailability of two tablets according to the invention, one tablet having a short lag-time and the other tablet having a lag-time which is long compared with the gastrointestinal transit time of a pharmaceutical formulation according to the invention. The *in vivo* study has confirmed the capability of the pharmaceutical formulation according to the invention to give the desired unique release. Formulation A (the tablet prepared as described in Example 3A) showed a significant lag-time when compared to the uncoated core which was used as a reference formulation C in the study (see Tables 9F and 9G as well as Figure 12).

As can be seen from Tables 9D and 9E, the bioavailability of the tablets of formulations A and C are not significantly different, as the 90% confidende limits include 1.00 for the ratios A/C for C_{max} and AUC. The rapid burst from the composition is proven by the fact that the maximum plasma concentration after intake of formulation A did not deviate significantly from the peak concentration seen after intake of formulation C, the uncoated core. An extent of availability similar to the availability obtained by use of the reference formulation C proved a complete release of active substance from formulation A: A remarkable one-to-one *in vitro/in vivo* correlation in terms of duration of lag-time was observed.

Formulation B showed a longer lag-time than formulation A in all subjects, and the lag-time T_{lag} appeared to be considerably longer than the lag-time determined *in vitro*, so the prototype formulation chosen for the *in vivo* study bursted at a time (median 7.5 hours) when the formulation, according to general knowledge about transit times, is expected to be in the colon, i.e. at a site where the absorption capacity for salbutamol and not the release from the formulations is the limiting factor for absorption.

The findings from the kinetic study are supported by observations made in connection with adverse drug reactions, tremor and agitation,

(see Figure 13), the onset of which also showed rank order related to the short and long lag-times, respectively.

The *in vivo* study has thus clearly demonstrated for the short lag-time pharmaceutical formulation according to the invention that it is possible in a reproducible manner to achieve delayed dissolution of up to 3 hours after which the active substance is released instantly. For the long lag-time pharmaceutical formulation it is successfully demonstrated that it is possible to achieve delayed dissolution of up to 7 hours.

EXAMPLE 10

Preparation of a pharmaceutical formulation having a coating of Methocel® K 100

A Salbuvent® 4 mg tablet, manufactured by Nycomed, was used as tablet core, and tablets were prepared as described in Example 1 using an outer layer composition as follows:

Outer layer composition 10

The following ingredient was used:

	% w/w
Methocel® K 100	100

Methocel® K 100 was sieved (300 µm mesh screen).

Coating by compression

122 mg outer layer material was charged in a die with a punch diameter of 11.0 mm. The core was placed centrally in the die by means of a centering tube. Having centered the core in the die, the die was filled with the remaining amount of the outer layer granulate (175 mg) and a circular, plane tablet was produced by compression in special compression equipment (Fette Exacta 1/F, instrumentated tabletting machine) applying a pressure of about 17 kN. The tablets

produced according to the above description had an average height of approximately 3.2 mm.

Results

The tablets prepared in Example 10 were tested and analyzed as described under "Method of Analysis", i.e. for all tablets dissolution testing was carried out in acidic as well as neutral dissolution media. The results are given below in the form of a table.

6 tablets were produced as described in Example 10. The results of the dissolution testing of the tablets prepared appear below as Table 10.

TABLE 10

	Mean	Standard deviation S.D.
Lag-time (min)	485.2	35.2
Burst-period (min)	70.4	47.4
Start of burst %	35.1	6.5
End of burst %	92.2	4.1

EXAMPLE 11

Preparation of a pharmaceutical formulation having a coating of Methocel® K 100

Tablets were prepared as described in Example 1 using an outer layer composition as follows:

Outer layer composition 11

The following ingredient was used:

	% w/w
Methocel® K 100	100

Methocel® K 100 was sieved (300 μm mesh screen).

Coating by compression

96 mg outer layer material was charged in a die with a punch diameter of 11.0 mm. The core was placed centrally in the die by means of a centering tube. Having centered the core in the die, the die was filled with the remaining amount of the outer layer granulate (142 mg) and a circular, plane tablet was produced by compression in special compression equipment (Fette Exacta 1/F, instrumentated tabletting machine) applying a pressure of approximately 9 kN. The tablets produced according to the above descriptions had an average height of approximately 4.1 mm.

Results

The tablets prepared in Example 11 were tested and analyzed as described under "Method of Analysis", i.e. for all tablets dissolution testing was carried out in acidic as well as neutral dissolution media. The results are given below in the form of a table.

6 tablets were produced as described in Example 11. The results of the dissolution testing of the tablets prepared appear below as Table 11.

TABLE 11

	Mean	Standard Deviation S.D.
Lag-time (min)	381.8	16.2
Burst-period (min)	31.1	11.3
Start of burst %	28.9	5.7
End of burst %	92.4	5.9

EXAMPLE 12

Preparation of a pharmaceutical formulation according to the invention

Tablets were prepared as described in Example 7 using a first and a second outer layer composition as follows:

Outer layer composition 12a

The following ingredient was used:

	% w/w
Methocel® E 15	100

Methocel® E 15 was sieved (300 µm mesh screen).

Outer layer composition 12b

The following ingredient was used:

	% w/w
Methocel® K 100	100

Methocel® K 100 was sieved (300 µm mesh screen).

Coating by compression

Tablets were manufactured in double compression as described below.

First coating by compression (12a)

50 mg outer layer material was charged in a die with a punch diameter of 10.0 mm. The core was placed centrally in the die by means of a centering tube. Having centered the core in the die, the die was filled with the remaining amount of the outer layer granulate (85 mg) and a circular, plane tablet was produced by compression in a single-punch tabletting machine (Diaf TM 20). The tablets produced according to the above description had a height of approximately 4.5 mm.

Second coating by compression (12b)

100 mg outer layer material was charged in a die with a punch diameter of 12.0 mm. Having placed the double-compressed unit consisting of core and first coating-by-compression layer (14a) centrally in the die, the die was filled with the remaining amount of the outer layer granulate (150 mg) and a circular, plane tablet was produced by compression in a single-punch tabletting machine (Diaf TM 20). The tablets produced according to the above description had a height of approximately 5.7 mm.

Results

The tablets prepared in Example 12 were tested and analyzed as described under "Method of Analysis", i.e. for all tablets dissolution testing was carried out in acidic as well as neutral dissolution media. The results are given below in the form of a table and in Figures 14 as dissolution profile. In Figure 11 is also shown the lag-times obtained for tablets prepared according to Example 12.

Outer layer: First coating: 100% Methocel® E 15
Second coating: 100% Methocel® K 100

6 tablets were produced as described in Example 12. The results of the dissolution testing of the tablets prepared appear below as Table 12 and the dissolution profile based on the stated mean data appears from Figure 14.

TABLE 12

	Mean	Standard Deviation S.D.
Lag-time (min)	363.9	47.5
Burst-period (min)	13.9	3.1
Start of burst %	7.1	5.4
End of burst %	93.2	3.0

EXAMPLE 13

Preparation of a pharmaceutical formulation according to the invention

A tablet consisting of the following ingredients was used as core in this example:

Core composition 13

	%
Tablettose	74
Ac-Di-Sol	1
Avicel® PH 101	15
Caffeine	5
Magnesium stearate + talc (1:9)	5

The dissolution profile of the core was determined by dissolution testing in purified water at 37°C and in 0.1 N hydrochloric acid at 37°C in accordance with Ph. Eur. V.5.4. (1991 edition), using a

dissolution apparatus equipped with baskets rotating at 100 rpm. Determined as mean data, the core releases at least 90% by weight of the total content of caffeine during a period of at the most 45 minutes.

Tablettose, Ac-Di-Sol, Avicel® PH 101, and caffeine were sieved (300 μm mesh screen) and mixed. Magnesium stearate + talc (1:9) were sieved (300 μm mesh screen) and mixed with the rest of core composition 13.

Circular, plane tablets were produced by compression in a single punch tabletting machine (Diaf TM 20). The tablets produced according to the above description had an average height of approximately 4.0 mm and an average weight of approximately 246 mg.

An outer layer was applied on the cores described above by means of a coating-by-compression technique.

Outer layer composition 13

The following ingredients were used:

	% (w/w)
Methocel® E 15	75
Macrogol 6000	25

Coating by compression

150 mg outer layer granulate was pre-charged in a die with a punch diameter of 11.0 mm. The core was placed centrally in the die by means of a centering tube. Having centered the core in the die, the die was filled with the remaining amount of the outer layer granulate (180 mg) and a circular, plane tablet was produced by compression in special compression equipment (Fette Exacta 1/F, instrumentated tabletting machine) applying a pressure of about 13 kN. The tablets produced according to the above description had an average height of approximately 4.7 mm.

Results

The tablets prepared in Example 13 were tested and analyzed as described under "Method of Analysis", i.e. for all tablets dissolution testing was carried out in acidic as well as neutral dissolution media. The results are given below in the form of a table and in Figure 15 as dissolution profile. In Figure 11 is also shown the lag-times obtained for tablets prepared according to Example 13.

6 tablets were produced as described in Example 13. The results of the dissolution testing of the tablets prepared appear below as Table 13 and the dissolution profile based on the stated mean data appears from Figure 15.

TABLE 13

	Mean	Standard Deviation S.D.
Lag-time (min)	118.0	19.1
Burst-period (min)	35.7	12.4
Start of burst %	8.0	4.6
End of burst %	96.0	1.1

CONCLUSION EXAMPLES 10-13

Conclusion of Examples 10 and 11

In Examples 10 and 11, the hydroxypropylmethylcellulose derivative Methocel® K 100 has been used as the basis polymer. The tablets prepared in Example 10 contain 297 mg Methocel® K 100, whereas the tablets prepared in Example 11 contain 238 mg Methocel® K 100. When comparing the tablets prepared according to Example 10 with the tablets prepared according to Example 6 (in which 297 mg Methocel® E

50 was used), a considerably longer lag-time was found (mean lag-time 485.2 minutes versus 317.2 minutes), and the burst-period was also considerably prolonged (mean burst-period 70.4 minutes versus 21.2 minutes). If only 238 mg Methocel® K 100 is used in the outer layer (Example 11), the lag-time was less prolonged (mean lag-time 381.8 minutes versus 317.2 minutes), and moreover, the burst-period was less prolonged (mean burst-period 31.1 minutes versus 21.2 minutes). It can thus be concluded that a shorter lag-time can be obtained by using a smaller amount of erodable layer material thus obtaining a thinner outer layer or by using a cellulose derivative with a lower viscosity.

Conclusion of Example 12

In this Example, 100% Methocel® E 15 was used in a first coating and 100% Methocel® K 100 in a second coating. The lag-time obtained was not considerably prolonged when compared to the lag-time obtained in Example 11 (mean lag-time 363.9 minutes versus 381.8 minutes). The burst-period obtained in Example 12 was, however, considerably shorter than the burst-period obtained in Example 11 (mean burst-period 13.9 minutes versus 31.1 minutes). The effect of the double-coating when compared with the results obtained in Example 11 was thus, that a lag-time of about the same length could be obtained and at the same time a considerably shorter burst-period.

Conclusion of Example 13

In this Example, caffeine was the active substance used in the inner core, and the outer layer consisted of 75% Methocel® E 15 and 25% Macrogol 6000. When comparing the results of Example 13 with the results of Example 3, the lag-times are almost identical (mean lag-time 118.0 minutes versus 124.3 minutes) and the moreover, the burst-periods were almost identical (35.7 minutes versus 31.3). It can thus be concluded that the performance of the outer layer was independent of which active substance was contained in the inner core. As will be apparant when studying tables 3 and 15, lag-times, burst-periods, start of burst % and end of burst % were not affected by the change of active substance in the inner core.

EXAMPLE 14

Preparation of a formulation without any core

Tablets were prepared consisting exclusively of the outer layer, i.e. no core was used. The outer layer composition was as follows:

Outer layer composition 14

The following ingredient was used:

	% w/w
Methocel® E 15	100

Methocel E® 15 was sieved (300 µm mesh screen).

Coating by compression

330 mg outer layer material was charged in a die with a punch diameter of 11.0 mm. A circular, plane tablet was produced by compression in special compression equipment (Fette Exacta 1/F, instrumentated tabletting machine) applying a compression pressure of approximately 5 kN. The tablet produced according to the above description had an average height of approximately 3.5 mm.

EXAMPLE 15

Preparation of a formulation without any core

Tablets were prepared consisting exclusively of the outer layer, i.e. no core was used. The outer layer composition was as follows:

Outer layer composition 15

The following ingredient was used:

	% w/w
Methocel® E 50	100

Methocel® E 50 was sieved (300 μm mesh screen).

Coating by compression

297 mg outer layer material was charged in a die with a punch diameter of 11.0 mm. A circular, plane tablet was produced by compression in special compression equipment (Fette Exacta 1/F, instrumentated tabletting machine) applying a compression pressure of approximately 6 kN. The tablet produced according to the above description had an average height of approximately 3.1 mm.

EXAMPLE 16

Preparation of a formulation without any core

Tablets were prepared consisting exclusively of the outer layer, i.e. no core was used. The outer layer composition was as follows:

Outer layer composition 16

The following ingredient was used:

	% w/w
Methocel® K 100	100

Methocel® K 100 was sieved (300 μm mesh screen).

Coating by compression

238 mg outer layer material was charged in a die with a punch diameter of 11.0 mm. A circular, plane tablet was produced by compression

in special compression equipment (Fette Exacta 1/F, instrumentated tabletting machine) applying a compression pressure of approximately 2-5 kN. The tablet produced according to the above description had an average height of approximately 3.2 mm.

RESULTS OF EXAMPLES 14-16

Results

The tablets prepared in Examples 14-16 were tested and analyzed as described under "Method of Analysis", i.e. for all tablets dissolution testing was carried out in acidic as well as neutral dissolution media. The concentration of the hydroxypropylmethylcellulose in question in the dissolution medium was measured until no further increase of the concentration was observed. The concentration of the hydroxypropylmethylcellulose was found to increase liniarly by time. The results are given below in the form of Table 14.

TABLE 14

Amount of HPMC dissolved by time (mg/min)

Methocel® E 15	Approximately 0.8
Methocel® E 50	Approximately 0.6
Methocel® K 100	Approximately 0.3

CONCLUSION EXAMPLES 14-16

As can be seen from Table 14, the standard viscosity of the hydroxypropylmethylcellulose varied inversely proportional to the amount of HPMC dissolved by time as the amounts of HPMC dissolved by time were 0.8 mg/minutes, 0.6 mg/minutes and 0.3 mg/minutes for the standard viscosities of 15 cP, 50 cP and 100 cP. This finding was consistent with the results of the former Examples that when increasing the viscosity of the HPMC (when the same amount of HPMC is used), the lag-time was also increased.

EXAMPLE 17

Preparation of a pharmaceutical formulation having a coating of Methocel® E 4M

Tablets were prepared as described in Example 1 using an outer layer composition as follows:

Outer layer composition 17

The following ingredient was used:

	% w/w
Methocel® E 4M Premium	100

Coating-by-compression

Tablets were manufactured as described below:

96 mg (40.3%) outer layer material was pre-charged in a die with a punch diameter of 11.0 mm. The core was placed centrally in the die by means of a centering tube. Having centered the core in the die, the die was filled with the remaining amount of the outer layer granulate (142 mg), and a circular, plane tablet was produced by compression in special compression equipment (Fette Exacta 1/F, instrumentated tabletting machine) applying a pressure of about 12 kN. The tablets produced according to the above description had an average height of approx. 4.0 mm.

Results

The tablets prepared in Example 1were tested and analyzed as described under "Method of Analysis", i.e. for all tablets dissolution testing was carried out in acidic as well as neutral dissolution media. The results are given below in the form of a table.

6 tablets were produced as described in Example 17. The results of the dissolution testing of the 6 tablets prepared appear below as Table 15.

TABLE 15

	Mean	Standard Deviation S.D.
Lag-time (min)	267.0	14.8
Burst-period (min)	673.1	58.8
Start of burst %	8.7	2.2
End of burst %	76.6	1.3

EXAMPLE 18

Preparation of a pharmaceutical formulation having a coating of Methocel® E 4M

Tablets were prepared as described in Example 1 using an outer layer composition as follows:

Outer layer composition 18

The following ingredient was used:

	% w/w
Methocel E 4M Premium	100

Coating-by-compression

Tablets were manufactured as described below:

122 mg (41.1%) outer layer material was pre-charged in a die with a punch diameter of 11.0 mm. The core was placed centrally in the die by means of a centering tube. Having centered the core in the die, the die was filled with the remaining amount of the outer layer granulate (175 mg), and a circular, plane tablet was produced by compression in special compression equipment (Fette Exacta 1/F,

nstrumentated tabletting machine) applying a pressure of about 17 kN. The tablets produced according to the above description had an average height of approx. 4.4 mm.

Results

The tablets prepared in Example 13 were tested and analyzed as described under "Method of Analysis", i.e. for all tablets dissolution testing was carried out in acidic as well as neutral dissolution media. The results are given below in the form of a table.

6 tablets were produced as described in Example 18. The results of the dissolution testing of the 6 tablets prepared appear below as Table 16.

TABLE 16

	Mean	Standard Deviation S.D.
Lag-time (min)	425.0	25.0
Burst-period (min)	750.0	25.0
Start of burst %	7.2	1.3
End of burst %	74.2	2.9

CONCLUSION EXAMPLES 17-18

Examples 17-18 using the hydroxypropylmethylcellulose derivative Methocel® E 4M as the polymer in the outer layer convincingly show that on this basis tablets do not have a satisfactorily short burst-period after the end of the lag-time. Variation in the amount of Methocel® E 4M used in the outer layer does not remedy this problem. Thus a lag-time of 267.0 minutes resulted in a burst-period of 673.1

minutes, and a lag-time of 425.0 minutes resulted in a burst-period of 750 minutes.

The amount of active substance released during the burst-period is not quite satisfactory either. Values of 67.9% and 67.0% were achieved.

Thus it can be concluded that the use of Methocel® E 4M alone in a coating does not seem to be a preferred material in this invention.

EXAMPLE 19

Preparation of a pharmaceutical formulation having a coating of a mixture of Klucel® MF and LF

A tablet consisting of the following ingredients was used as core in this example.

Core composition 19

	% w/w
Tabletose®	71.5
Avicel® PH 101	14.9
Caffeine	8.6
Magnesium stearate + talc (1:9)	5.0

The dissolution profile of the core was determined by dissolution testing in purified water at 37°C and in 0.1 N hydrochloric acid at 37°C in accordance with Ph. Eur. V.5.4. (1991 edition), using a dissolution apparatus equipped with baskets rotating at 100 rpm. Determined as mean data, the core releases at least 90% by weight of the total content of caffeine during a period of at the most 45 minutes.

Tabletose®, Avicel® PH 101 and caffeine were sieved (300 µm mesh screen) and mixed. Magnesium stearate + talc (1:9) were sieved (300 µm mesh screen) and mixed with the rest of core composition 19.

Circular, plane tablets were produced by compression in a single punch tabletting machine (Diaf TM 20). The tablets produced according to the above description had an average weight of approximately 103 mg and a diameter of 6 mm.

An outer layer was applied on the cores described above by means of a coating-by-compression technique.

Outer layer composition 19

The following ingredients were used:

	% (w/w)
Klucel® MF	42.4
Klucel® LF	12.4
Lactose	44.6
Magnesium stearate	0.6

Klucel® MF, Klucel® LF and lactose were mixed and subsequently granulated with water. After drying and sieving (300 µm mesh screen) magnesium stearate was admixed.

Coating-by-compression

100 mg outer layer granulate was pre-charged in a die with a punch diameter of 10.0 mm. The core was placed centrally in the die. Having centered the core in the die, the die was filled with the remaining amount of the outer layer granulate (100 mg), and a circular, plane tablet was produced by compression in a single punch tabletting machine (Diaf TM 20).

Results

The tablets prepared in Example 19 were tested and analyzed as described under "Method of Analysis", i.e. for all tablets dissolution testing was carried out in acidic as well as neutral

dissolution media. The results are given below in the form of a table and in Figure 16 as dissolution profile.

2 tablets were produced as described in Example 19. The dissolution testing was only performed under acidic conditions and the results are given below in Table 17. The dissolution profile based on the stated mean data appears from Figure 16.

TABLE 17

	Mean	Standard Deviation S.D.
Lag-time (min)	125.0	70.7
Burst-period (min)	321.0	29.7
Start of burst %	7.1	1.8
End of burst %	89.8	2.1

EXAMPLE 20

Preparation of a pharmaceutical formulation having a coating of a mixture of Klucel® MF and LF

A core as described in Example 19, i.e. core composition 19, was used, and tablets were prepared as described in Example 19, using the outer layer composition 19.

Coating-by-compression

150 mg outer layer granulate was pre-charged in a die with a punch diameter of 10.0 mm. The core was placed centrally in the die. Having centered the core in the die, the die was filled with the remaining amount of the outer layer granulate (150 mg), and a circular, plane

tablet was produced by compression in a single punch tabletting machine (Diaf TM 20).

Results

The tablets prepared in Example 20 were tested and analyzed as described under "Method of Analysis", i.e. for all tablets dissolution testing was carried out in acidic as well as neutral dissolution media. The results are given below in the form of a table and in Figure 17 as dissolution profile.

2 tablets were produced as described in Example 20. The dissolution testing was only performed under acidic conditions and the results are given below in Table 18. The dissolution profile based on the stated mean data appears from Figure 17.

TABLE 18

	Mean	Standard Deviation S.D.
Lag-time (min)	291.5	12.0
Burst-period (min)	525.5	23.3
Start of burst %	5.0	1.1
End of burst %	90.0	0

EXAMPLE 21

Preparation of a pharmaceutical formulation having a coating of a mixture of Klucel® MF and LF

A tablet consisting of the following ingredients was used as core in this example.

Core composition 21

	% w/w
Tabletose®	71.5
Avicel® PH 101	14.9
Caffeine	8.6
Magnesium stearate + talc (1:9)	5.0

The dissolution profile of the core was determined by dissolution testing in purified water at 37°C and in 0.1 N hydrochloric acid at 37°C in accordance with Ph. Eur. V.5.4. (1991 edition), using a dissolution apparatus equipped with baskets rotating at 100 rpm. Determined as mean data, the core releases at least 90% by weight of the total content of caffeine during a period of at the most 45 minutes.

Tabletose®, Avicel® PH 101 and caffeine were sieved (300 µm mesh screen) and mixed. Magnesium stearate + talc (1:9) were sieved (300 µm mesh screen) and mixed with the rest of core composition 21.

Circular, plane tablets were produced by compression in a single punch tabletting machine (Diaf TM 20). The tablets produced according to the above description had an average weight of approximately 370 mg and a diameter of 10 mm.

An outer layer was applied on the cores described above by means of a coating-by-compression technique.

Outer layer composition 21

The following ingredients were used:

	% (w/w)
Klucel® MF	42.4
Klucel® LF	12.4
Lactose	44.6
Magnesium stearate	0.6

Klucel® MF, Klucel® LF and lactose were mixed and subsequently granulated with water. After drying and sieving (300 μm mesh screen) magnesium stearate was admixed.

Coating-by-compression

200 mg outer layer granulate was pre-charged in a die with a punch diameter of 12.0 mm. The core was placed centrally in the die. Having centered the core in the die, the die was filled with the remaining amount of the outer layer granulate (200 mg), and a circular, plane tablet was produced by compression in a single punch tabletting machine (Diaf TM 20).

Results

The tablets prepared in Example 21 were tested and analyzed as described under "Method of Analysis", i.e. for all tablets dissolution testing was carried out in acidic as well as neutral dissolution media. The results are given below in the form of a table and in Figure 18 as dissolution profile.

2 tablets were produced as described in Example 21. The dissolution testing was only performed under acidic conditions and the results are given below in Table 19. The dissolution profile based on the stated mean data appears from Figure 18.

TABLE 19

	Mean	Standard Deviation S.D.
Lag-time (min)	451.5	54.4
Burst-period (min)	219.5	46.0
Start of burst %	31.9	4.4
End of burst %	91.3	1.8

CONCLUSION EXAMPLES 19-21

Examples 19-21 using the hydroxypropylcellulose derivatives Klucel® MF and Klucel® LF as the basic polymers in the outer layer convincingly show that on this basis tablets do not have a satisfactorily short burst-period after the end of the lag-time. Variation in the amount of material used in the outer layer does not remedy this problem. Thus a lag-time of 125 minutes resulted in a burst-period of 321 minutes, and a lag-time of 291 minutes resulted in a burst-period of 525 minutes (Examples 19 and 20). A change of the diameter of the core and the finished tablet did not result in satisfactory time intervals for the burst-period either. Thus a lag-time of 451 minutes resulted in a burst-period of 219 minutes (Example 21).

The amount of active substance released during the burst-period is not satisfactory when a core diameter of 10 mm and a diameter of the finished tablet of 12 mm are used. A value of 59.4% was achieved.

Thus, it can be concluded that the tested mixture of Klucel® MF and LF (1:0.3) is not a preferred material for use in accordance with the present invention.

CLAIMS

1. A coated solid ingestible material adapted to oral administration, wherein the coating comprises an erodable layer or a combination of erodable layers surrounding and covering the solid material and constituting a barrier delaying the direct exposure of the solid material to gastrointestinal fluids, at least one of the erodable layers containing, as a major constituent, a water soluble cellulose derivative or a mixture of water soluble cellulose derivatives, the viscosity of the cellulose derivative or the mixture of cellulose derivatives in the layer or layers being selected so that a test composition comprising a combination (C) of 1) a core containing an active substance in an inherently substantially freely releasable form as defined herein and 2) said erodable layer or combination of erodable layers, after a lag-time (A), defined as described herein, of at least 60 minutes during which at the most 30% by weight of the inherently substantially freely releasable active substance contained in the core is released, releases at least 70% by weight of the inherently substantially freely releasable active substance contained in the core within a burst-period (B), defined as described herein, of at the most 45 minutes, the said releases being measured as mean data determined by dissolution testing in purified water at 37°C and in 0.1 N hydrochloric acid at 37°C in accordance with Ph.Eur. V.5.4. (1991 edition), using a dissolution apparatus equipped with baskets rotating at 100 rpm.

2. A coated solid ingestible material according to claim 1, wherein the coating comprises at least two erodable layers:

(I) a start of burst %-regulating layer and

(II) a lag-time regulating layer,

each of which comprises, as a major constituent, a water soluble cellulose derivative or a mixture of water soluble cellulose derivatives, the cellulose derivative or the mixture of water soluble cellulose derivatives in said layer (I) having a viscosity which contributes to securing that at the most 30% by weight of said

inherently substantially freely releasable active substance contained in said core is released during said lag-time (A), and the cellulose derivative or the mixture of cellulose derivatives in the layer (II) having a viscosity which contributes to securing that the lag-time (A) is at least 60 minutes.

3. A coated solid ingestible material according to any one of claims 1 and 2, wherein said lag-time (A) is at least 90 minutes.

4. A coated solid ingestible material according to any one of claims 1 and 2, wherein said lag-time (A) is at least 3 hours.

5. A coated solid ingestible material according to any one of the preceding claims, wherein at the most 25% of said inherently substantially freely releasable active substance is released during said lag-time (A).

6. A coated solid ingestible material according to any one of the preceding claims, wherein said burst-period (B) is at the most 30 minutes.

7. A coated solid ingestible material according to any one of the preceding claims, wherein at least 90% of said inherently substantially freely releasable active substance is released during said burst-period (B).

8. A coated solid ingestible material according to any one of the preceding claims, wherein the cellulose derivative or mixtures of cellulose derivatives of at least one erodable layer is selected from the group consisting of methylcelluloses, sodium carboxymethyl-celluloses, hydroxyethylcelluloses, hydroxypropylcelluloses, hydroxy-propylmethylcelluloses and mixtures thereof.

9. A coated solid ingestible material according to claim 8, wherein the cellulose derivative or mixture of cellulose derivatives has a viscosity of at the most 100 centipoise, as measured on a 2% w/w aqueous solution at 20°C.

10. A coated solid ingestible material according to claim 8, wherein the viscosity of the cellulose derivative or mixture of cellulose derivatives is at the most 50 centipoise, as measured on a 2% w/w aqueous solution at 20°C.

11. A coated solid ingestible material according to claim 8, wherein the cellulose derivative is a hydroxypropylmethylcellulose.

12. A coated solid ingestible material according to any one of the preceding claims, wherein the concentration of the cellulose derivative or the mixture of cellulose derivatives in the erodable layer is at least 70% by weight.

13. A coated solid ingestible material according to any one of the preceding claims, wherein the erodable layer or the combination of erodable layers comprising the water soluble cellulose derivative or the mixture of water soluble cellulose derivatives further comprises at least one pharmaceutically acceptable excipient.

14. A coated solid ingestible material according to any one of the preceding claims, wherein the erodable layer further comprises a non-hydrogel forming water soluble hydrophilic polymer.

15. A coated solid ingestible material according to claim 14, wherein the non-hydrogel forming water-soluble hydrophilic polymer is a glycol.

16. A coated solid ingestible material according to claim 14, wherein the non-hydrogel forming water-soluble hydrophilic polymer is a polyethyleneglycol.

17. A coated solid ingestible material according to claim 2, wherein the coating comprises at least two erodable layers (I) and (II) each of which comprises, as a major constituent, a water soluble cellulose derivative or a mixture of water soluble cellulose derivatives as defined in claim 1, the cellulose derivative or the mixture of cellulose derivatives in one layer having a viscosity which is

different from the viscosity of the cellulose derivative or the mixture of cellulose derivatives in the other layer.

18. A coated solid ingestible material according to claim 17, wherein the cellulose derivative of the layer (I) has a viscosity of at the most 15 centipoise and the cellulose derivative of the layer (II) has a viscosity of at the most 50 centipoise.

19. A coated solid ingestible material according to claim 17, wherein the cellulose derivative of the layer (I) has a viscosity of at the most 15 centipoise and the cellulose derivative of the layer (II) has a viscosity of at the most 100 centipoise.

20. A coated solid ingestible material according to any one of the preceding claims, wherein the solid ingestible material comprises an active substance selected from the group consisting of drugs, peptides, proteins, nutrients and vitamins.

21. A coated solid ingestible material according to any one of the preceding claims, wherein the solid ingestible material is in the form of granules or pellets.

22. A coated solid ingestible material according to any one of claims 1-20, wherein the solid ingestible material is in the form of a unit dosage form.

23. A coated solid ingestible material according to claim 22, wherein the solid ingestible material is in the form of a tablet or a capsule.

24. A coated solid ingestible material according to any one of the preceding claims, wherein the solid ingestible material is in the form of a core.

25. A coated solid ingestible material according to claim 24, wherein the core comprises an active substance in an inherently substantially freely releasable form as defined herein.

26. A coated solid ingestible material according to claim 24, wherein the core comprises a multiplicity of units each comprising an active substance together with at least one pharmaceutically acceptable excipient.

27. A coated solid ingestible material according to any one of the preceding claims, wherein the solid material comprises an active substance in admixture with at least one pharmaceutically acceptable excipient.

28. A coated solid ingestible material according to any one of the preceding claims, wherein at least a part of the active substance comprised in the solid ingestible material is in the form of a controlled release formulation.

29. A coated solid ingestible material according to any one of the preceding claims, wherein the erodable layer or at least one of the erodable layers further comprises an amount of active substance embedded therein, the active substance being released during and as a consequence of the erosion of the layer.

30. A coated solid ingestible material according to any one of the preceding claims, wherein an additional amount of active substance is applied on the coating, the additional amount of the active substance being released substantially immediately after the administration of the coated solid ingestible material.

31. A coated solid ingestible material according to any one of the preceding claims, wherein the coated solid ingestible material is further provided with a coating comprising a layer of a solid ingestible material and at least one erodable layer as defined in claim 1.

32. A coated solid ingestible material according to any one of the preceding claims in the form of a single-unit pharmaceutical formulation.

33. A coated solid ingestible material according to any one of claims 1-31 in the form of a multiple-unit pharmaceutical formulation.

34. A coated solid ingestible material according to any one of the preceding claims, wherein the erodable layer has been applied on the solid ingestible material by means of a coating-by-compression technique.

35. A coated solid ingestible material according to any one of the preceding claims, wherein the coated material is further provided with an enteric coating.

36. A method for preparing a coated solid ingestible material according to claim 1, comprising placing a solid ingestible material and optionally at least one pharmaceutically acceptable excipient in a die which has been charged with a granulate comprising, as a major constituent, a water soluble cellulose derivative or a mixture of water soluble cellulose derivatives, adding a further quantity of the granulate so as to completely cover the solid material, and compressing the granulate around the solid material to prepare the coated solid material, the viscosity of the cellulose derivative or the mixture of cellulose derivatives being selected so that a test composition comprising a combination (C) of 1) a core containing an active substance in an inherently substantially freely releasable form as defined herein and 2) an erodable layer or combination of erodable layers, as defined in claim 1, after a lag-time (A), defined as described herein, of at least 60 minutes during which at the most 30% by weight of the inherently substantially freely releasable active substance contained in the core is released, releases at least 70% by weight of the inherently substantially freely releasable active substance contained in the core within a burst-period (B), defined as described herein, of at the most 45 minutes, the said releases being measured as mean data determined by dissolution testing in purified water at 37°C and in 0.1 N hydrochloric acid at 37°C in accordance with Ph.Eur. V.5.4. (1991 edition), using a dissolution apparatus equipped with baskets rotating at 100 rpm.

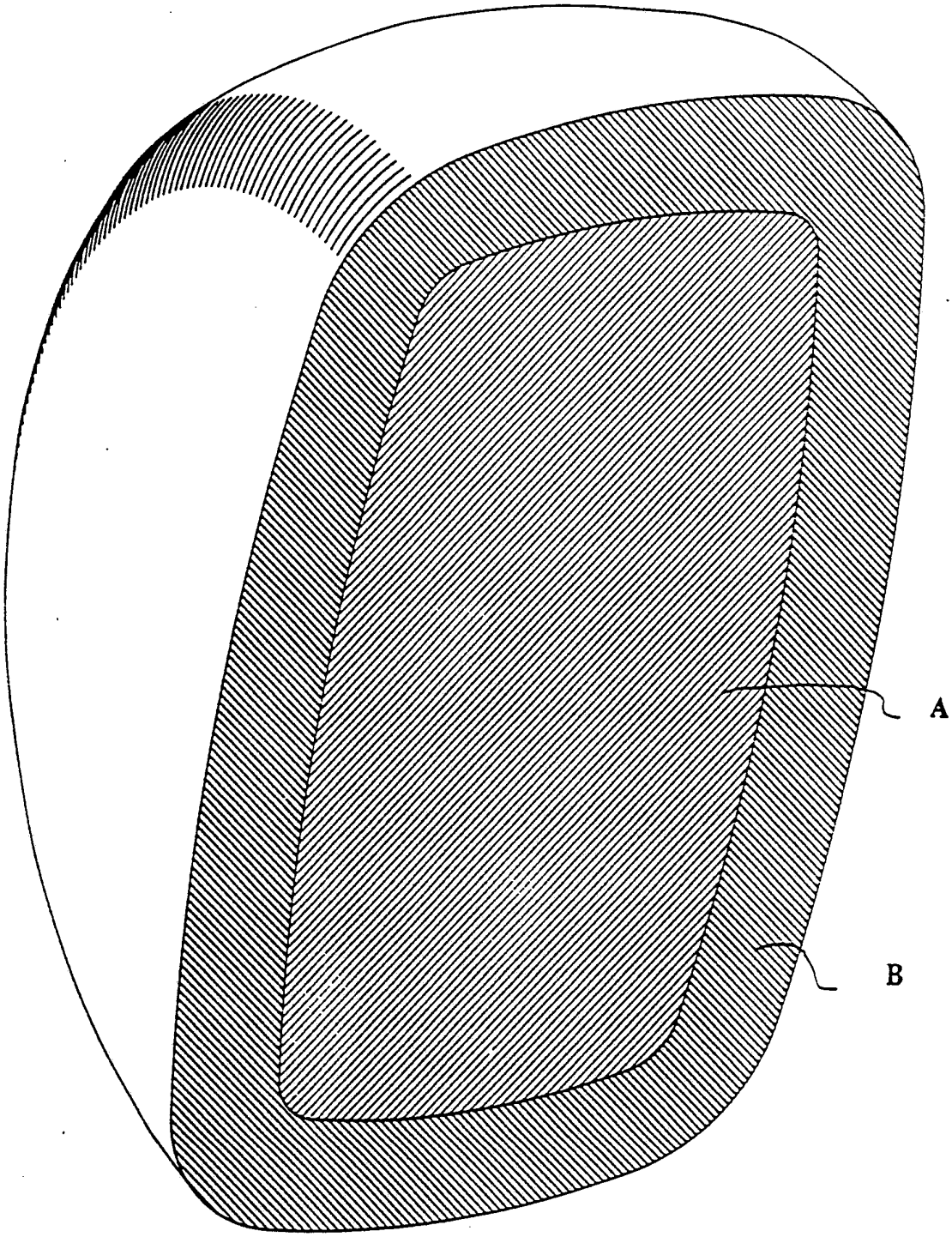


Fig. 1

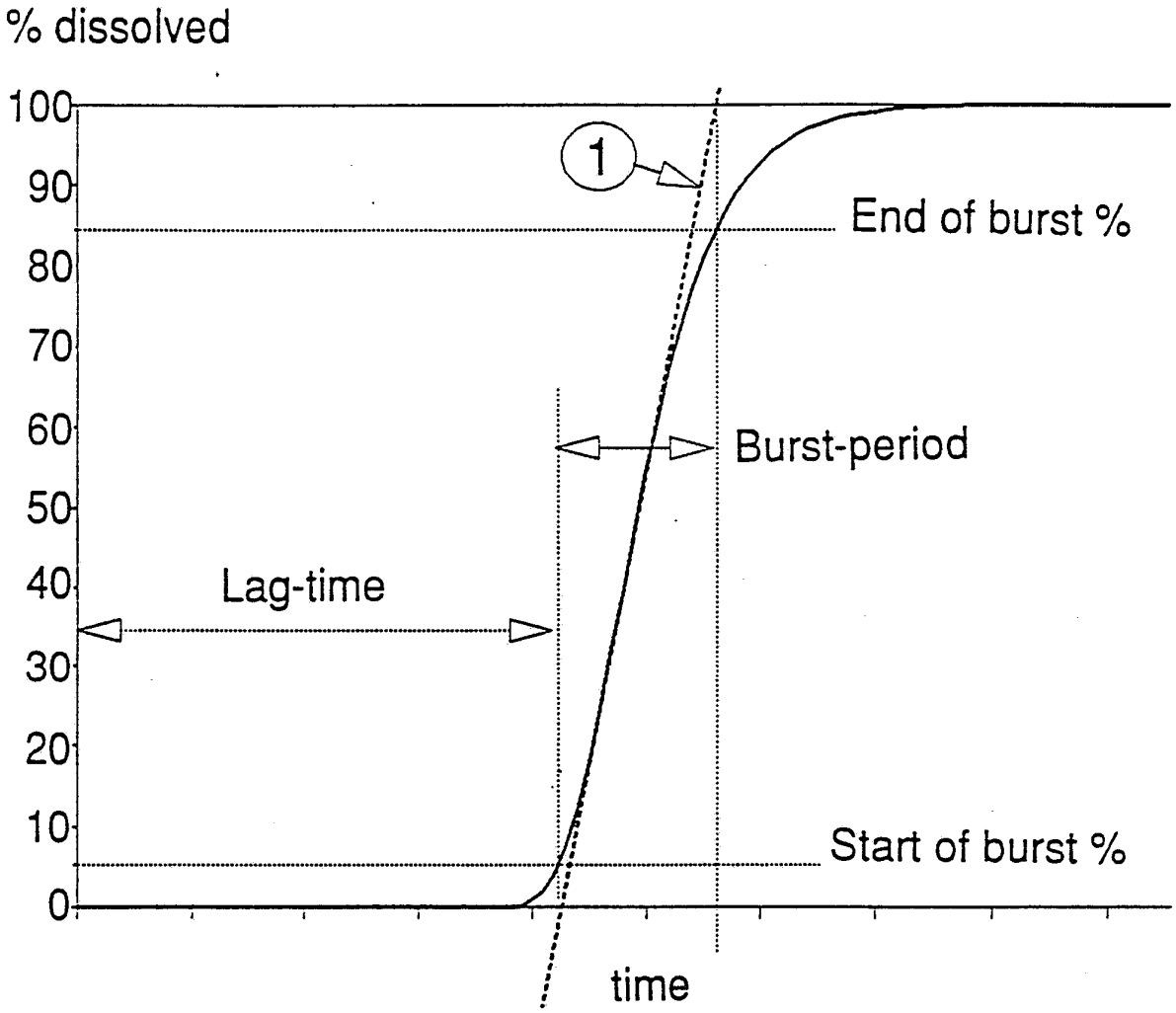

% dissolved
100
90
80
70
60
50
40
30
20
10
0
1
End of burst %
Burst-period
Lag-time
Start of burst %
time

Fig. 2

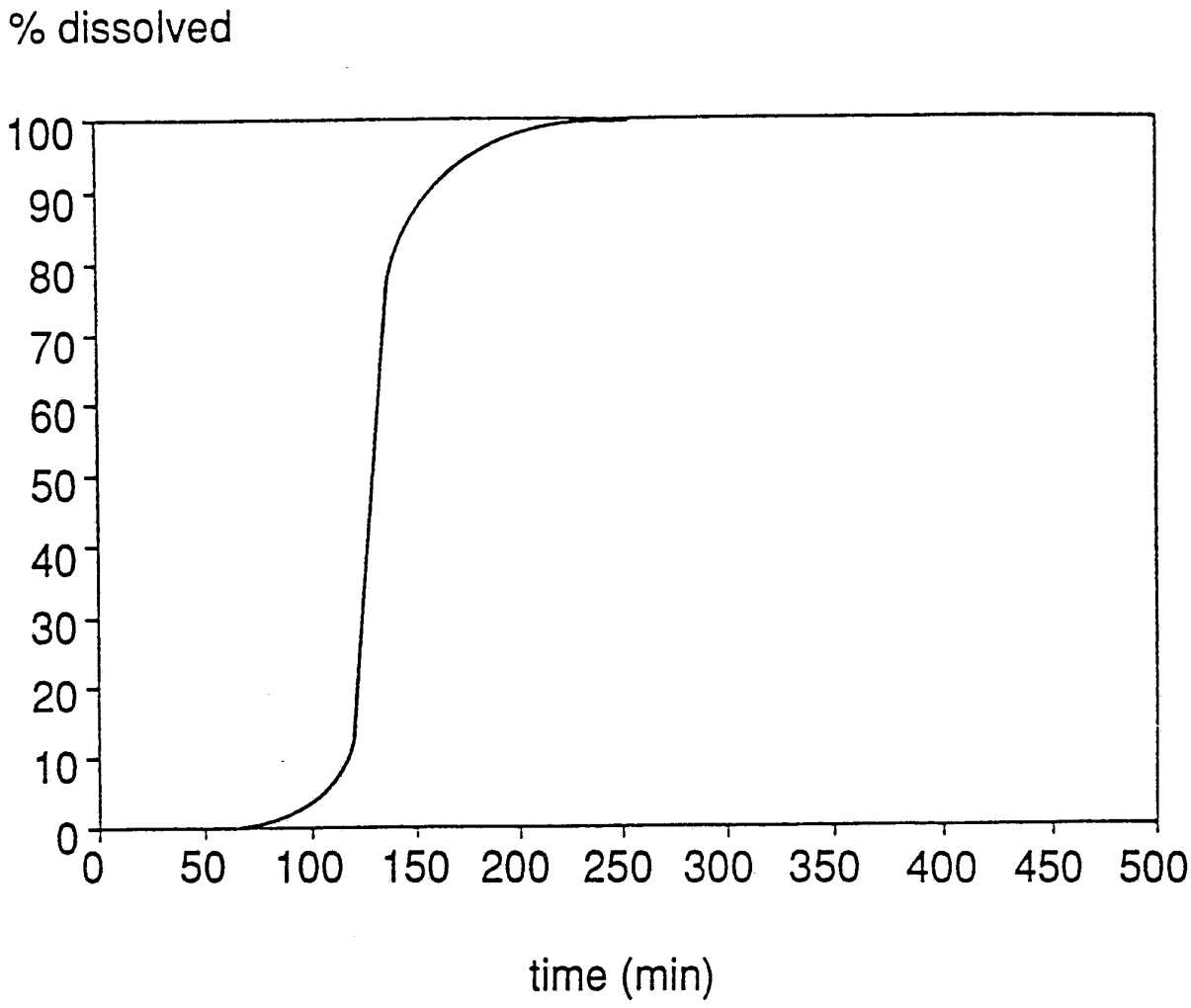

% dissolved
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
300
350
400
450
500
time (min)

Fig. 3

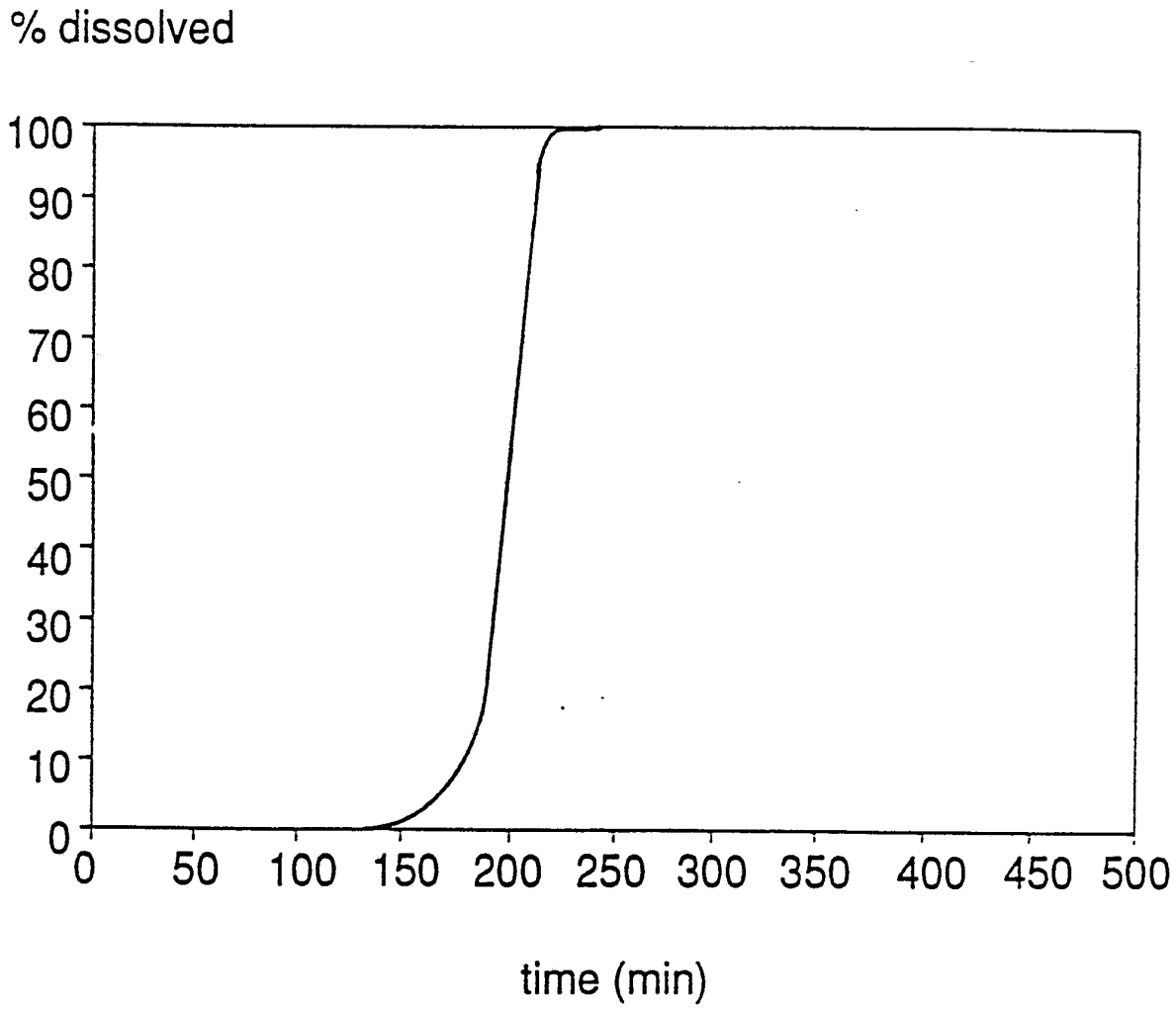

% dissolved
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
300
350
400
450
500
time (min)

Fig. 4

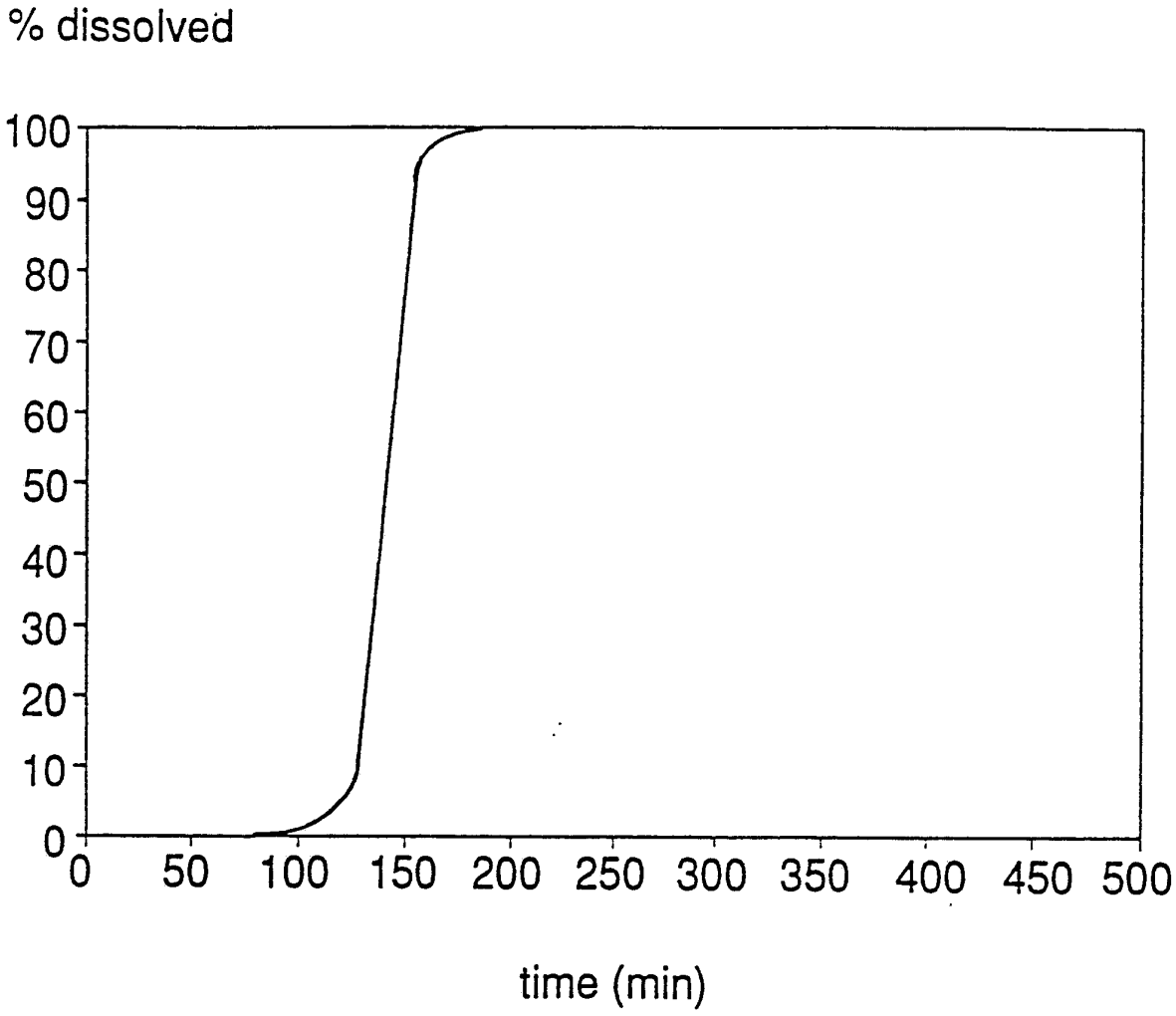

% dissolved
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
300
350
400
450
500
time (min)

Fig. 5

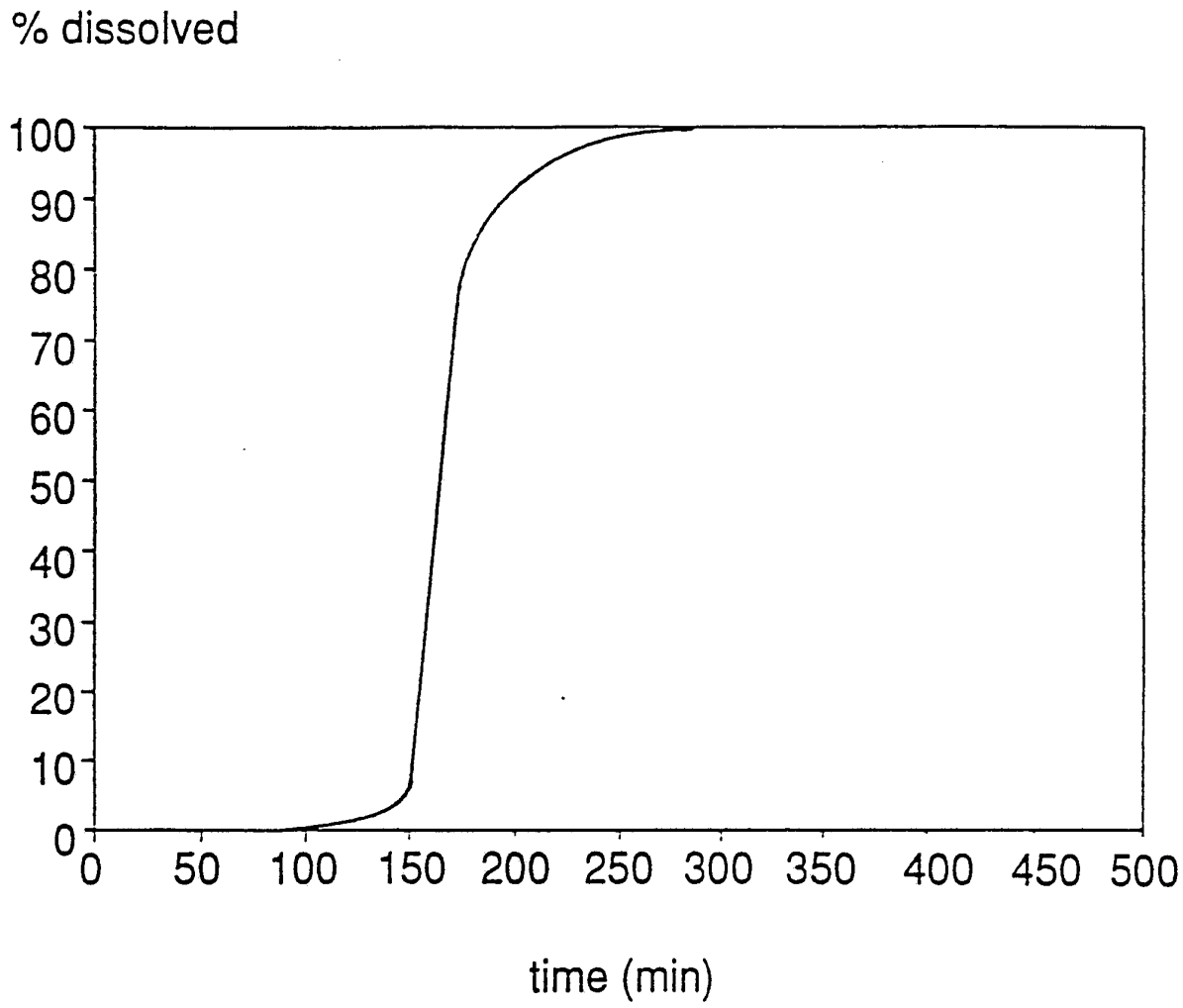

% dissolved
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
300
350
400
450
500
time (min)

Fig. 6

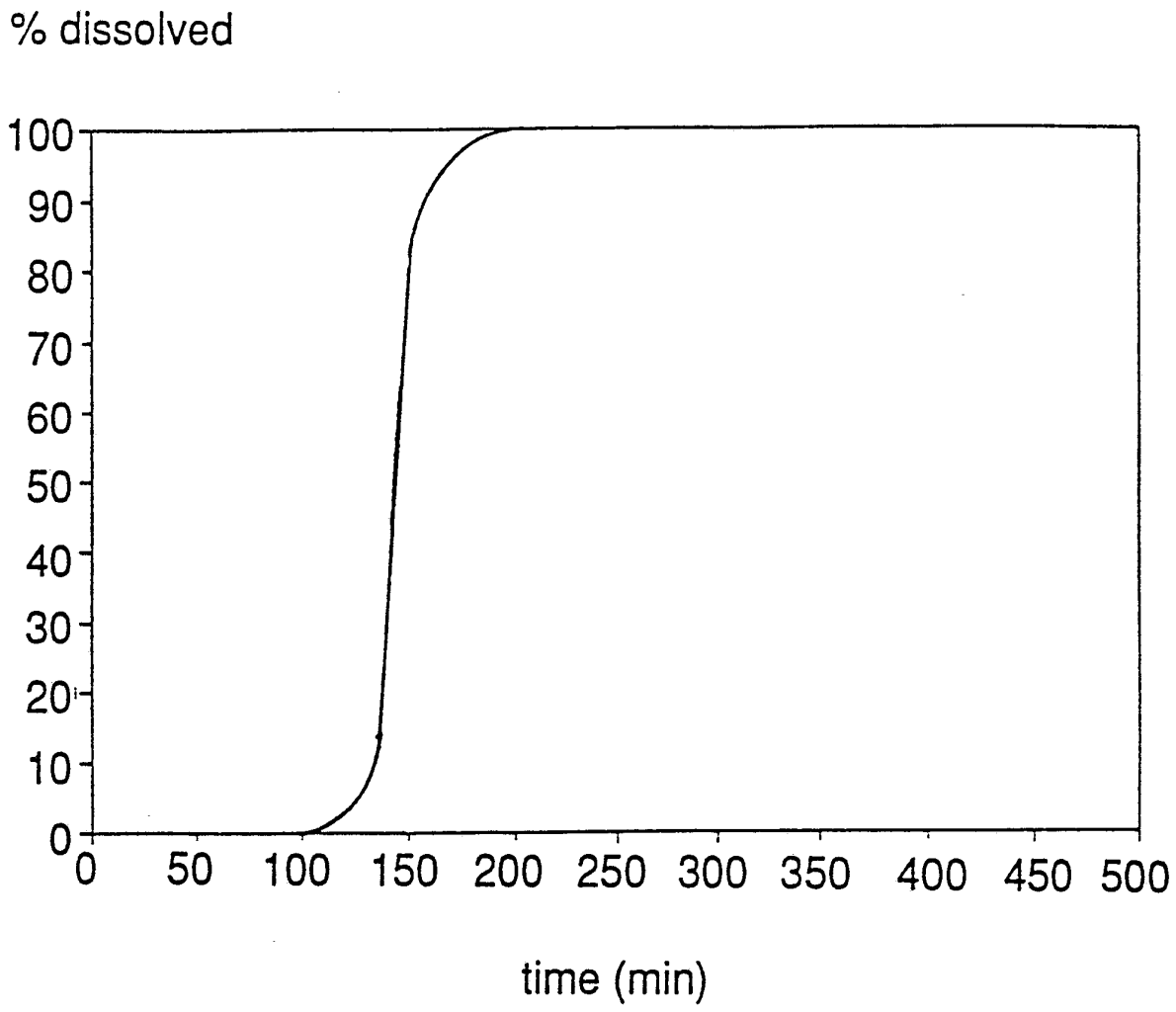

% dissolved
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
300
350
400
450
500
time (min)

Fig. 7

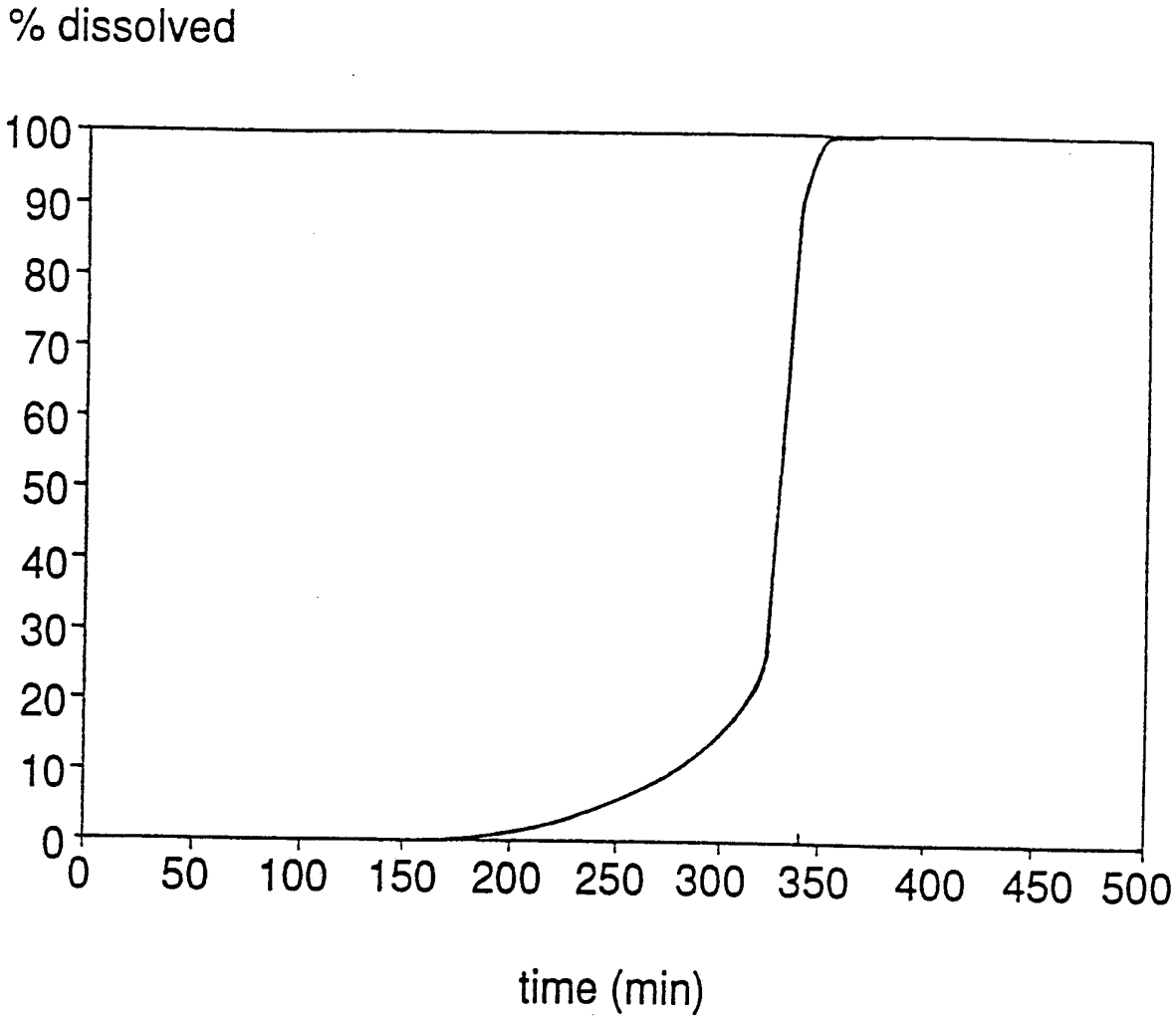

% dissolved
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
300
350
400
450
500
time (min)

Fig. 8

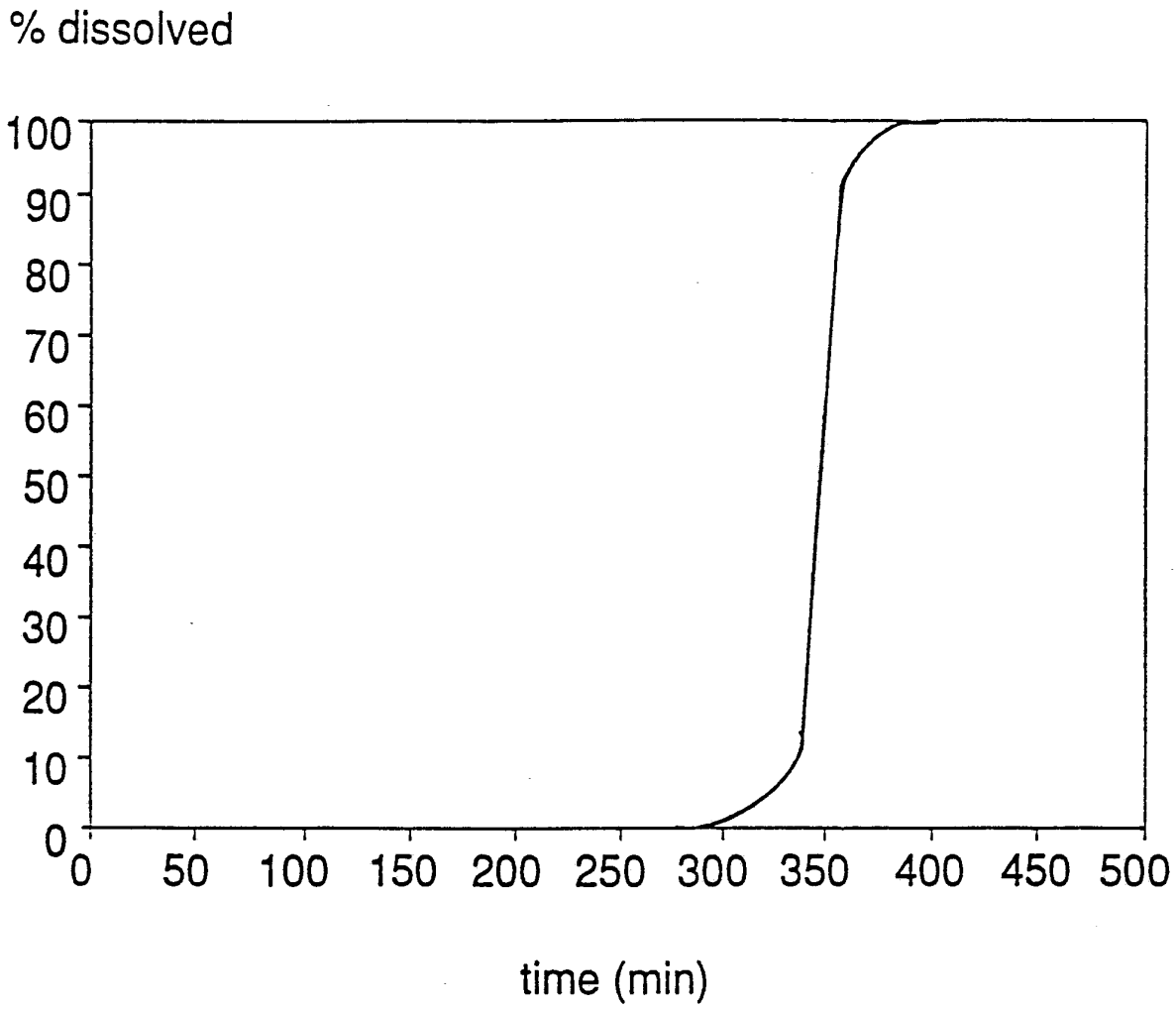

% dissolved
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
300
350
400
450
500
time (min)

Fig. 9

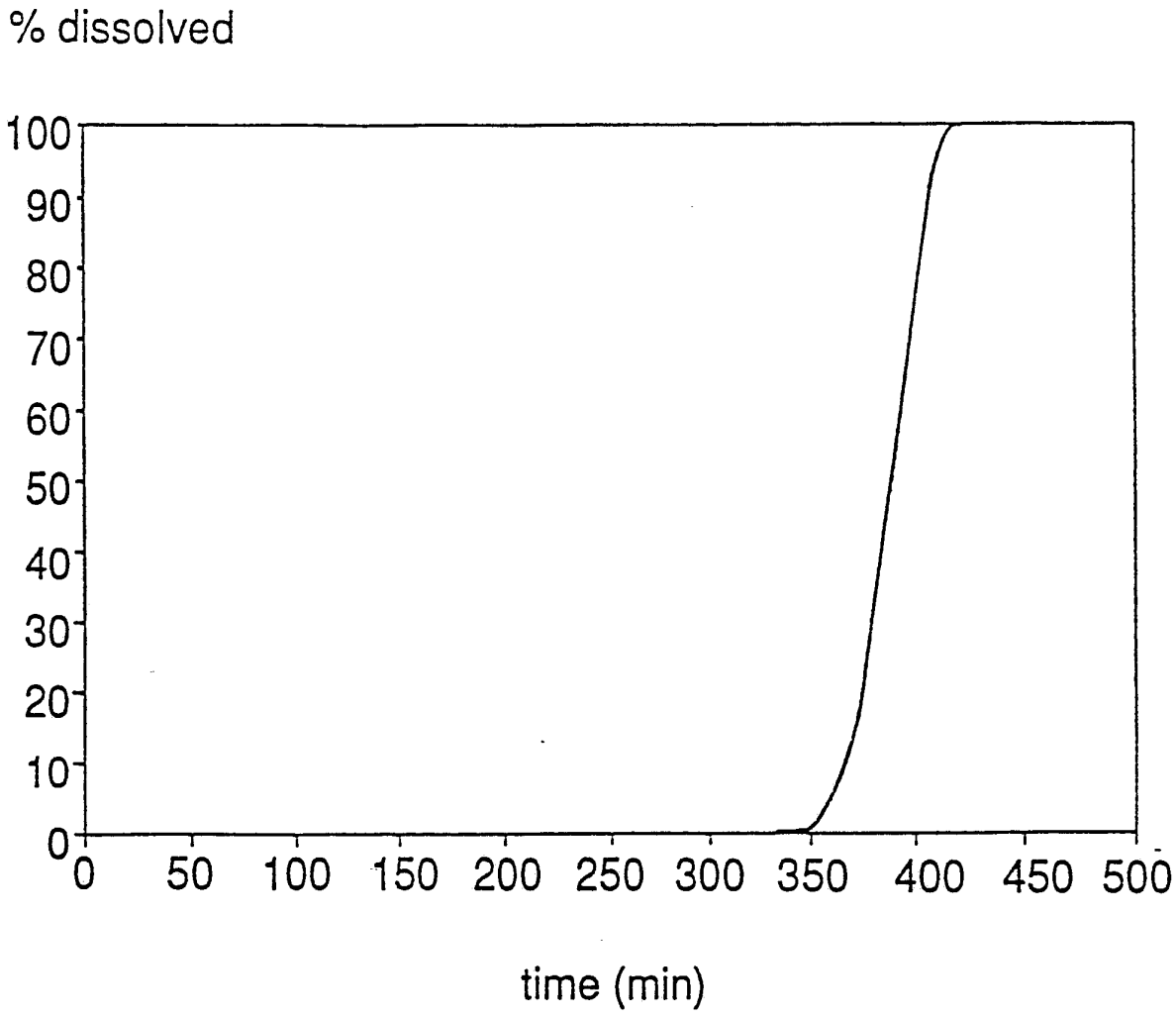

% dissolved
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
300
350
400
450
500
time (min)

Fig. 10

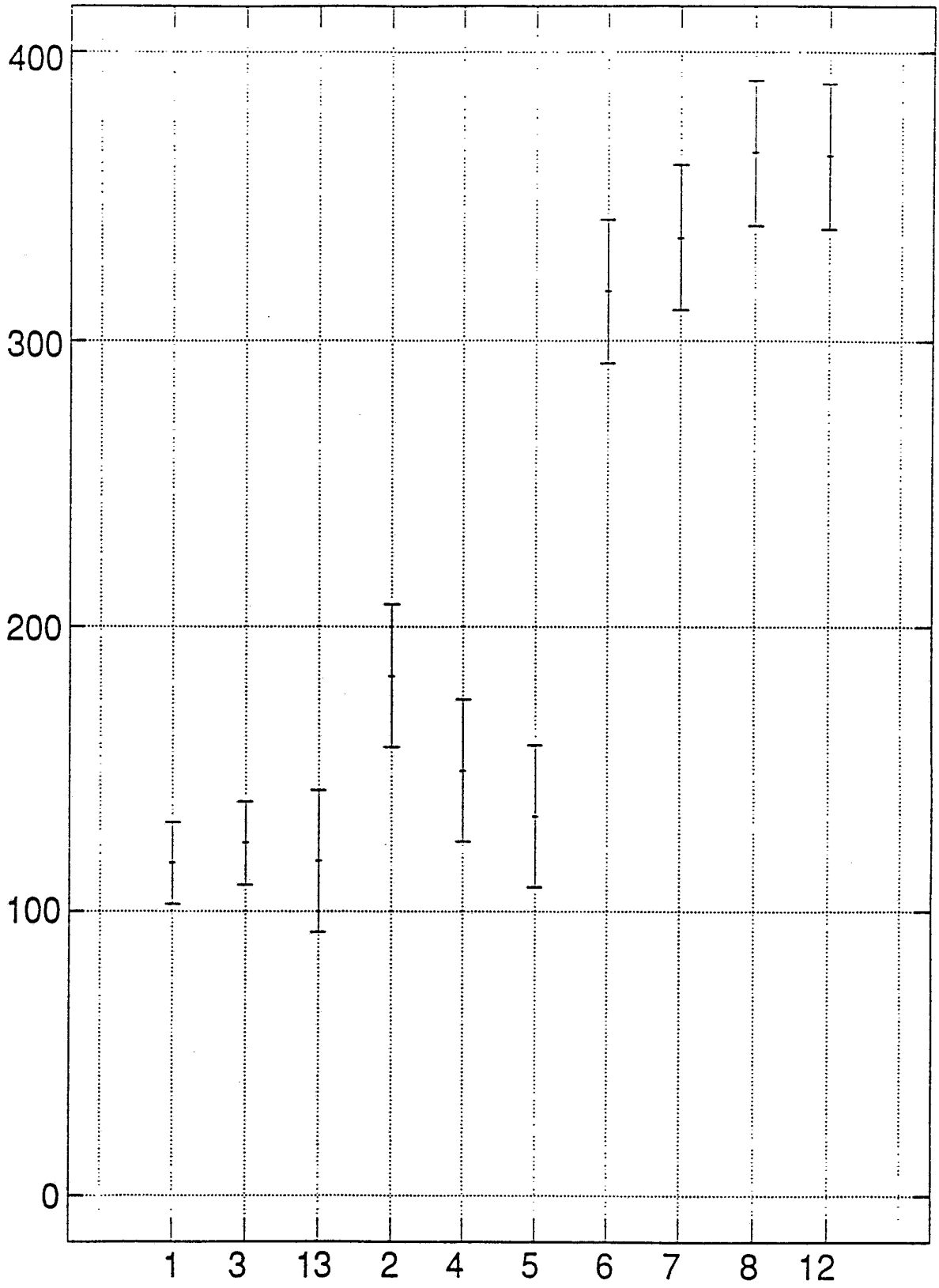


Fig. 11

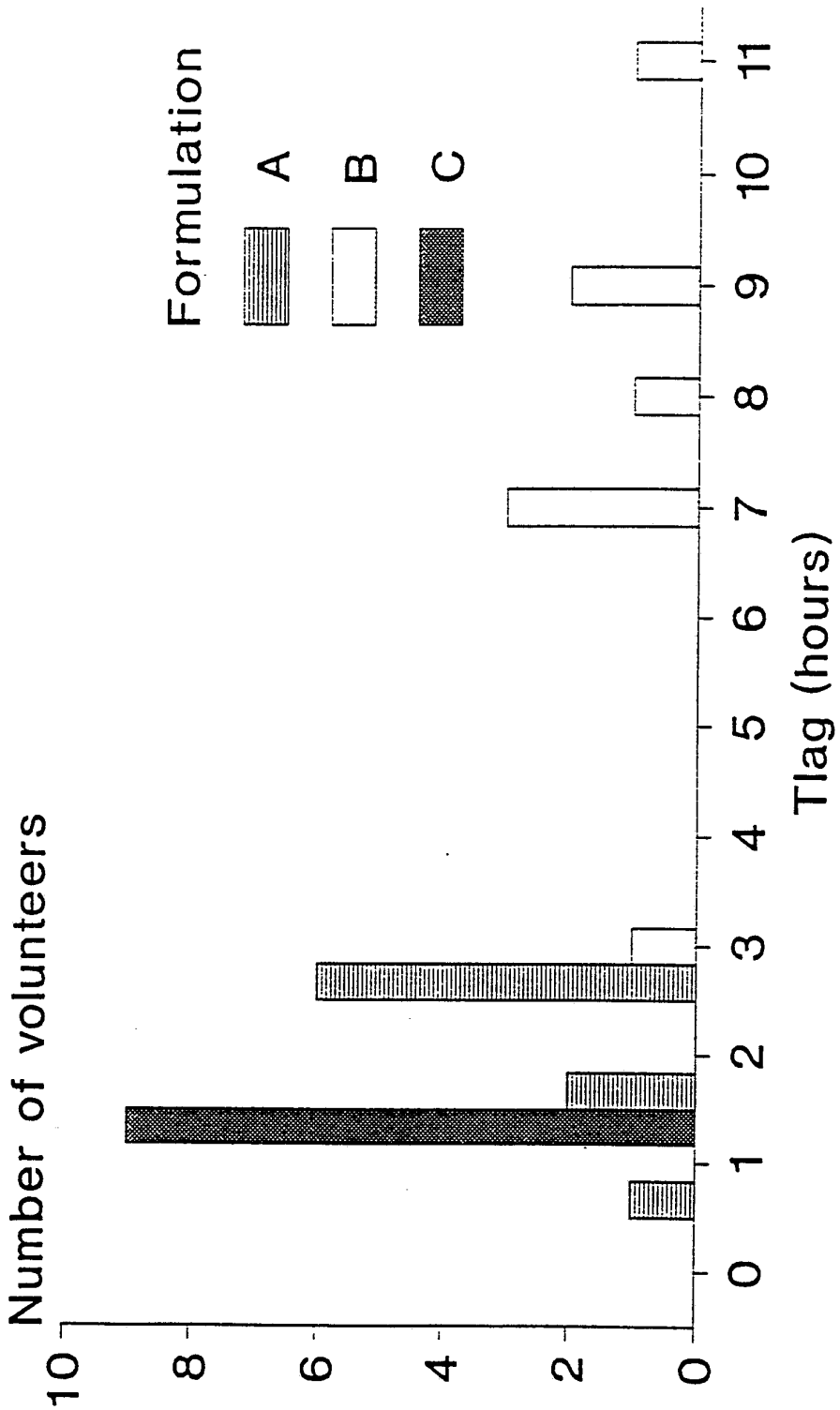

Formulation
A
B
C
Number of volunteers
0
2
4
6
8
10
Tlag (hours)
0
1
2
3
4
5
6
7
8
9
10
11

Fig. 12

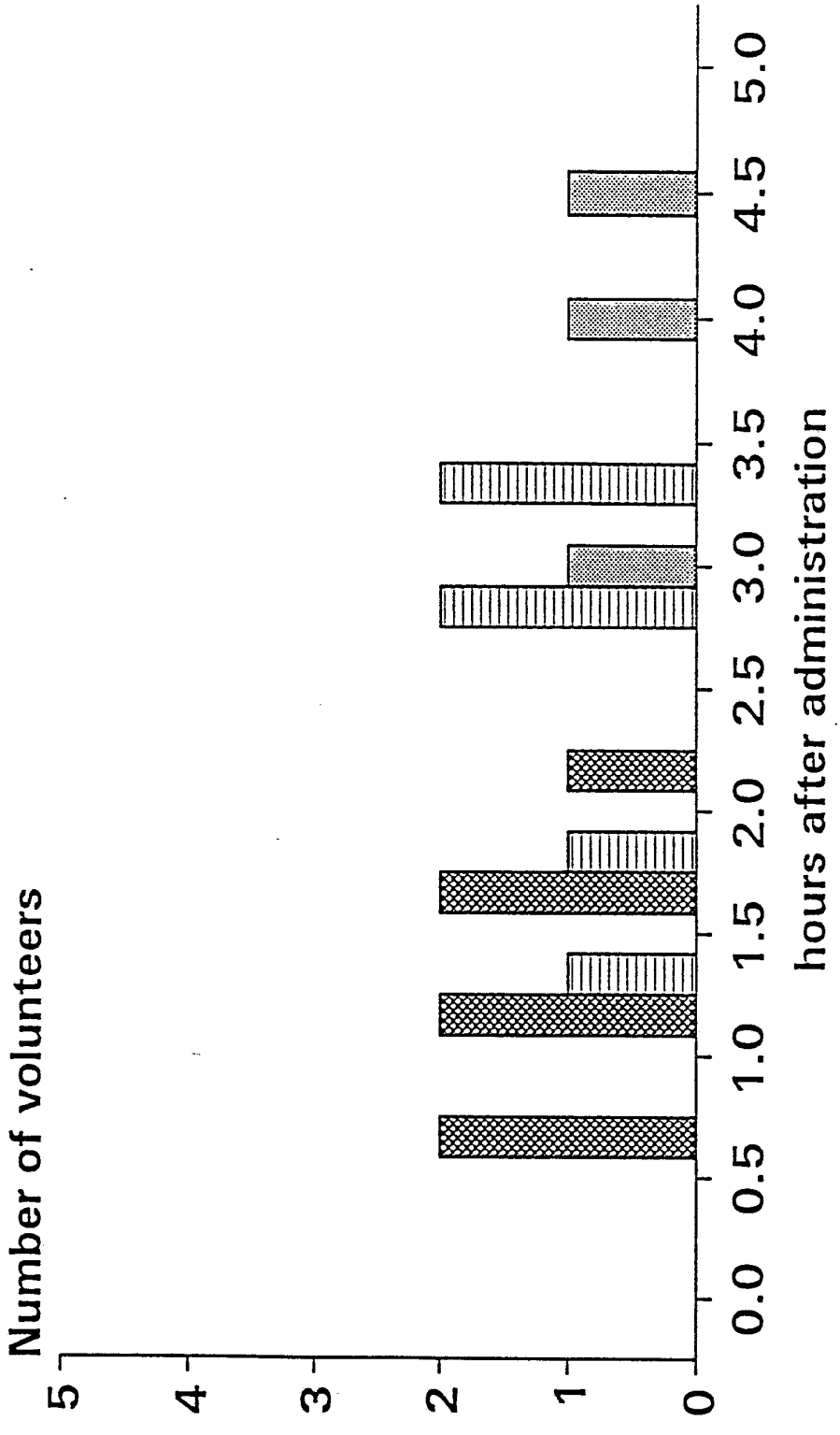

Number of volunteers
0
1
2
3
4
5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
hours after administration

Fig. 13

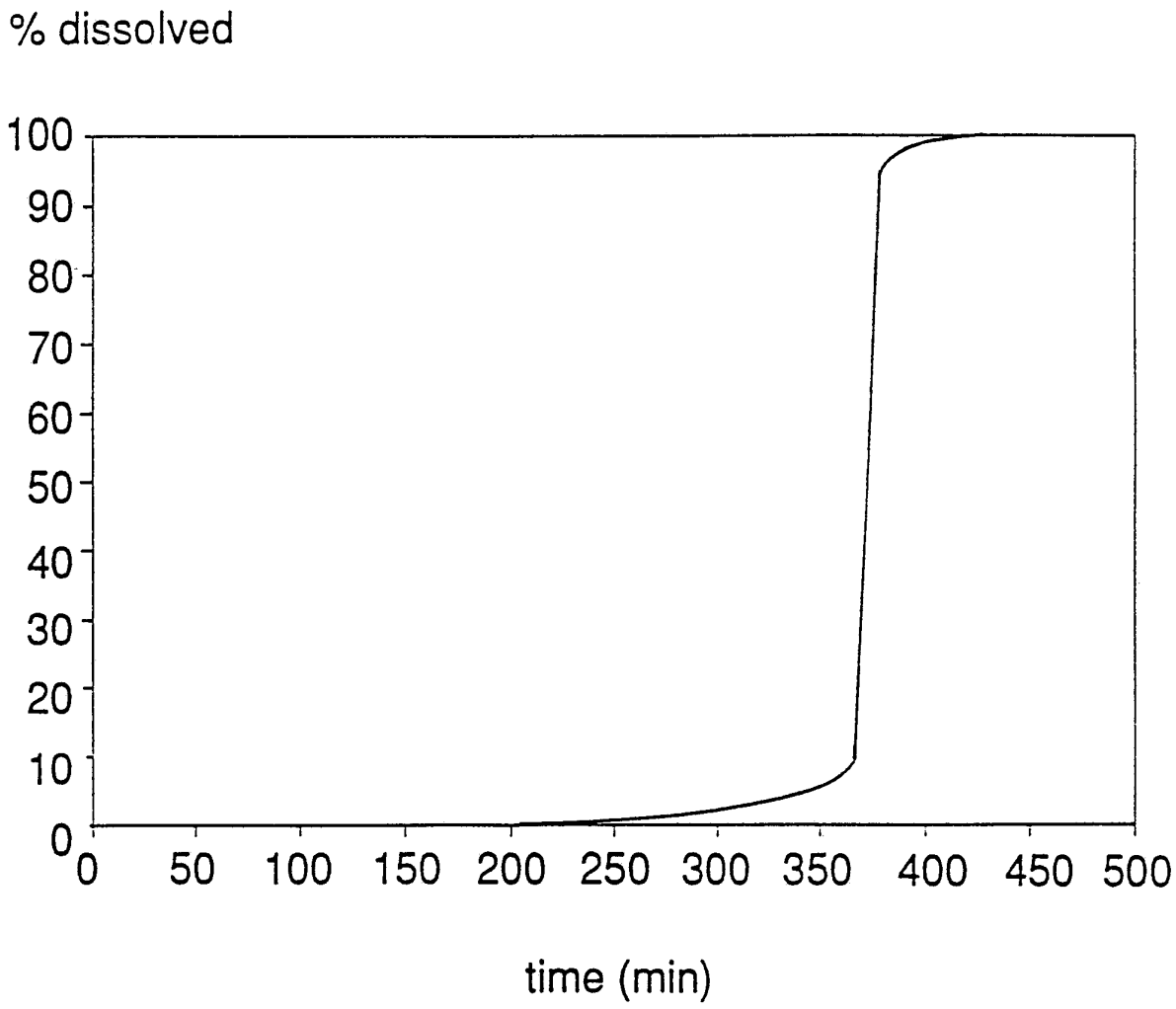

% dissolved
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
300
350
400
450
500
time (min)

Fig. 14

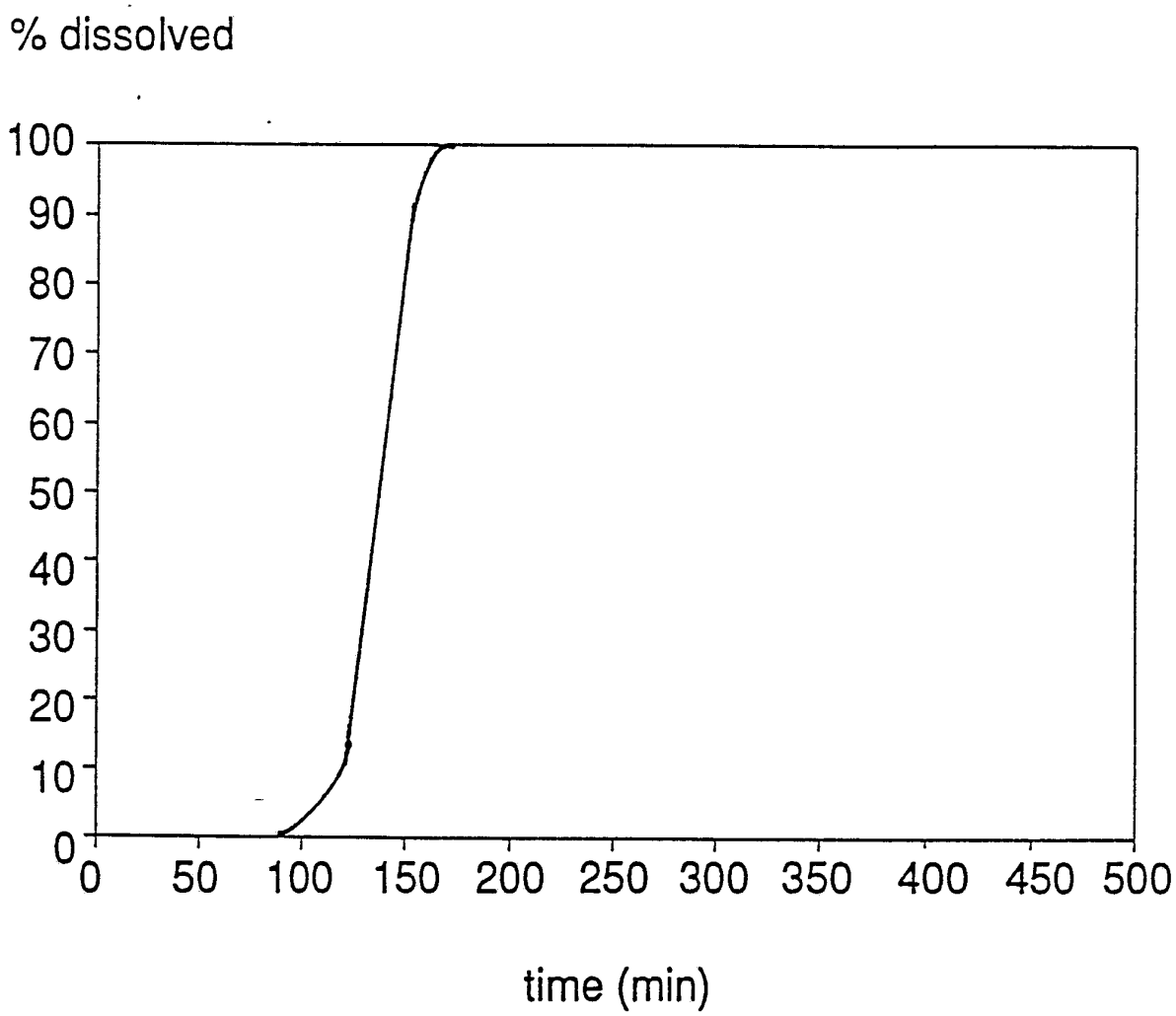

% dissolved
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
300
350
400
450
500
time (min)

Fig. 15

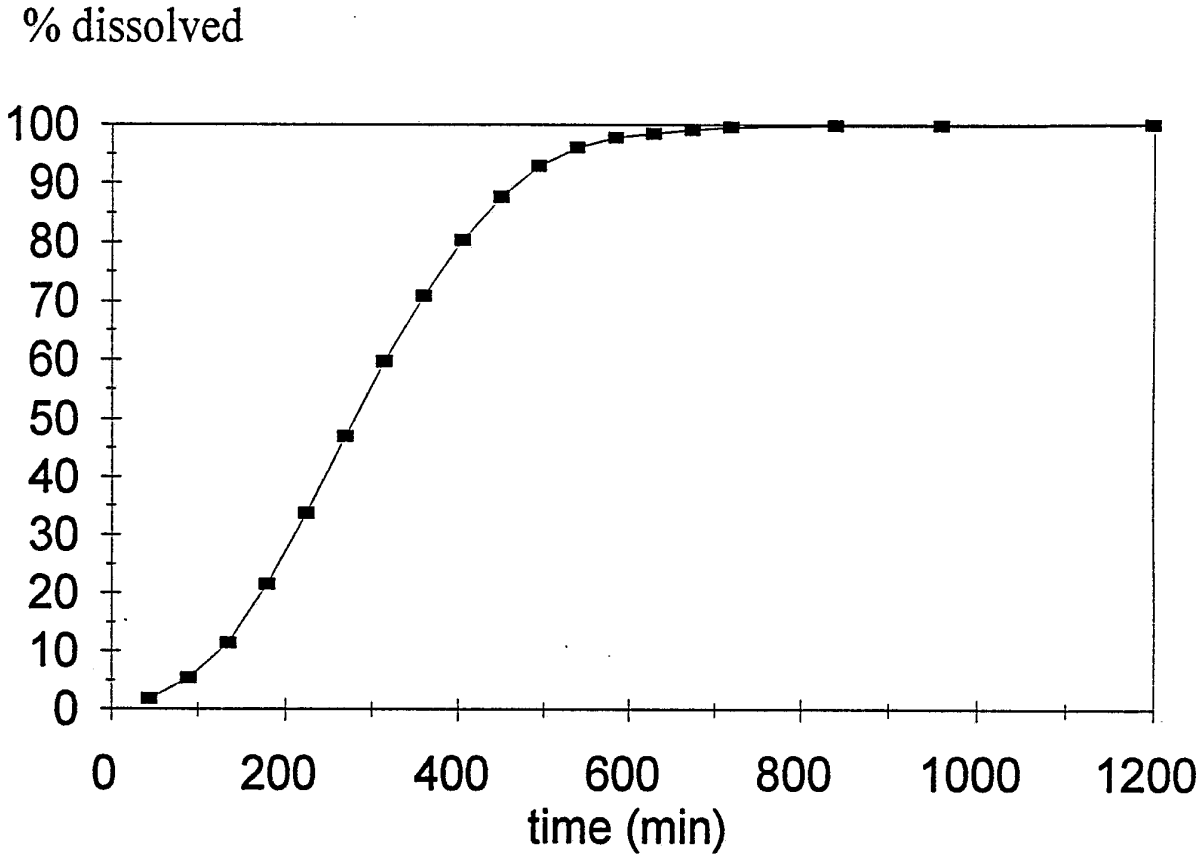

% dissolved
100
90
80
70
60
50
40
30
20
10
0
0
200
400
600
800
1000
1200
time (min)

Fig. 16

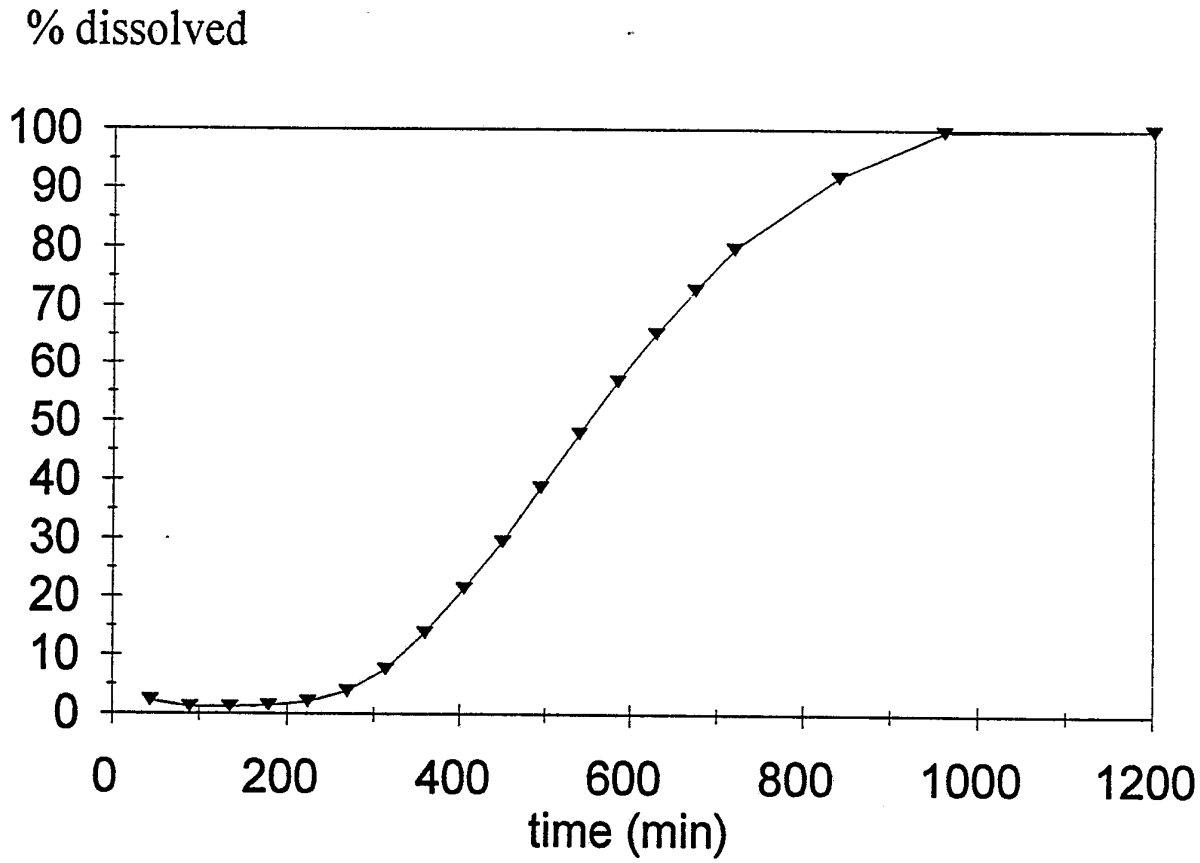

% dissolved
100
90
80
70
60
50
40
30
20
10
0
0
200
400
600
800
1000
1200
time (min)

Fig. 17

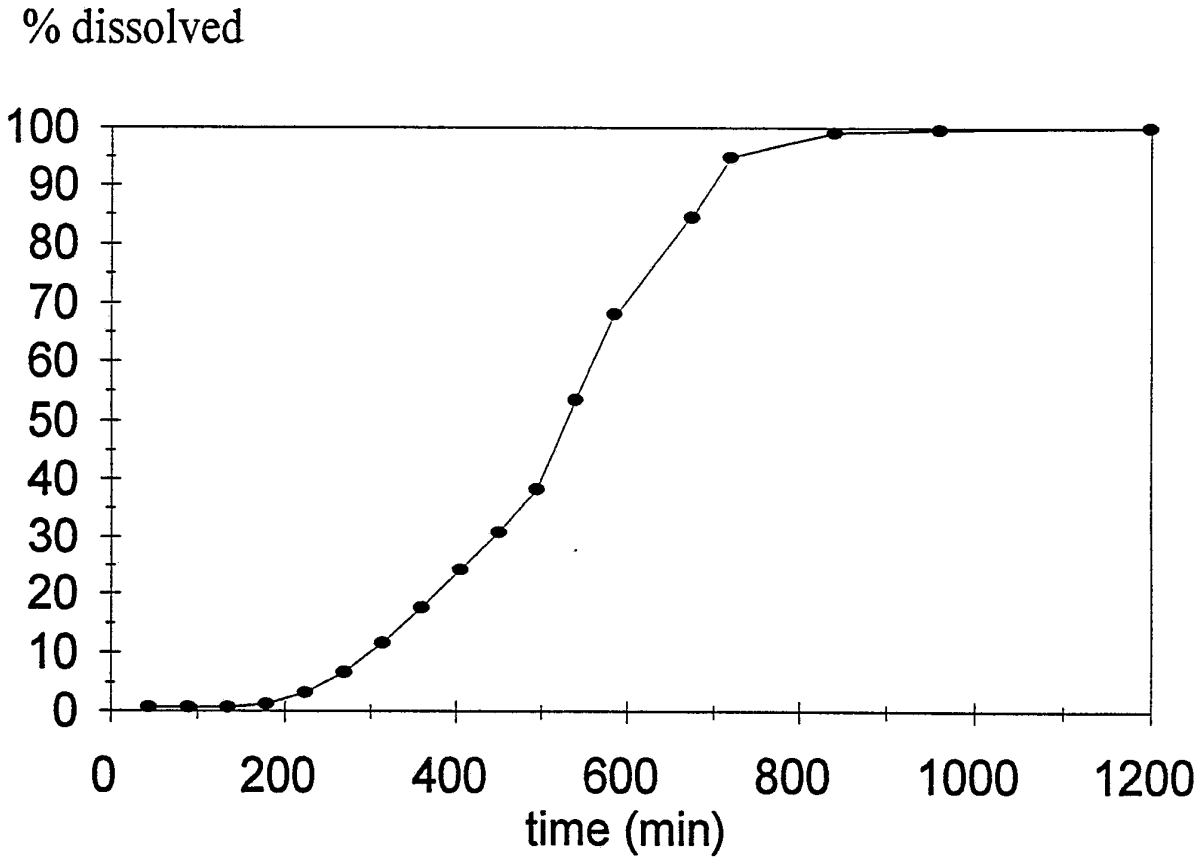

% dissolved
100
90
80
70
60
50
40
30
20
10
0
0
200
400
600
800
1000
1200
time (min)

Fig. 18

INTERNATIONAL SEARCH REPORT

International Application No PCT/DK 93/00117

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K9/28

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	GB,A,2 245 492 (ZAMBON GROUP SPA) 8 January 1992 cited in the application	1-11, 13-16, 20, 23-25, 28,32, 35,36
Y	see page 1, line 4 - line 7 see page 13, line 10 - line 23 see page 17, line 20 - line 25 see page 18 - page 20; example 2 see page 23 - page 26; examples 4,5 see claims 12,15,16 --- -/--	12, 17-19, 26-31, 33,34

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
23 JULY 1993	[illegible]
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	BOULOIS D.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	DE,A,3 013 059 (SANDOZ PATENT GMBH) 8 October 1981 cited in the application see page 5 - page 7; example 1	31,34
Y	EP,A,0 411 590 (ARNOLD J.D.) 6 February 1991 cited in the application see page 8; examples 1,2	30
Y	EP,A,0 384 514 (NORWICH EATON PHARMACEUTICALS INC) 29 August 1990 cited in the application see page 3, line 31 - line 35 see page 5 - page 6; example 1	27
Y	GB,A,793 808 (BARDANI F. M.) 23 April 1958 cited in the application see page 4, line 128 - page 5, line 19	26,29,33
Y	FR,A,2 276 108 (SHIN-ETSU CHEMICAL CO LTD) 23 January 1976 cited in the application see page 16 - page 18; example 3	17-19
A	GB,A,2 212 396 (THE PROCTER & GAMBLE COMPANY) 26 July 1989 cited in the application see page 13 - page 16; example 1	1-36
Y	EP,A,0 013 131 (MUNDIPHARMA AG) 9 July 1980 cited in the application see page 5 - page 7; example 1	12, 17-19, 28,31
X	EP,A,0 210 540 (FUJISAWA PHARMACEUTICAL CO LTD) 4 February 1987 cited in the application see page 2, column 1, line 1 - line 27 see page 4, column 2, line 1 - line 20 see page 5; table 1 see page 6; tables 4,5 see page 7; table 6 see page 10, column 1; examples 9,10 see claims 1,3,5,8-10	1-8,11, 12,17, 21,24

-/--

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	PHARM. IND. vol. 41, no. 8, 1979, pages 799 - 802 SALOMON J.L. ET AL 'sustained release of a water soluble drug from hydrophilic compressed dosage form' cited in the application see page 799, column 2, paragraph 2.2 see page 800; figures 1,3 see page 801, column 2, paragraph 3 see page 802, paragraph 3.2; figure 5	1-36
X	US,A,4 775 536 (MAHESH K.P.) 4 October 1988 cited in the application see column 1, line 5 - line 18 see column 2, line 47 - line 65 see column 5 - column 6; example 2 see column 7 - column 8; table 1	1,8,11, 13-16, 17,20-25
A	EP,A,0 299 211 (BAYER AG) 18 January 1989 see page 3, line 57 - line 58 see page 5 - page 6; example 1	1

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

DK 9300117
SA 72995

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 23/07/93

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
GB-A-2245492	08-01-92	AU-A-	8019991	09-01-92
		BE-A-	1004882	16-02-93
		CA-A-	2044398	05-01-92
		DE-A-	4122039	09-01-92
		FR-A-	2664163	10-01-92
		LU-A-	87964	03-03-92
		NL-A-	9101161	03-02-92
		SE-A-	9102072	05-01-92
DE-A-3013059	08-10-81	CH-A-	652926	13-12-85
EP-A-0411590	06-02-91	AU-B-	632602	07-01-93
		AU-A-	5997190	07-02-91
		CA-A-	2022422	03-02-91
		JP-A-	3141224	17-06-91
EP-A-0384514	29-08-90	US-A-	5032406	16-07-91
		AU-B-	632793	14-01-93
		AU-A-	4997090	30-08-90
		CA-A-	2010037	21-08-90
		JP-A-	3200724	02-09-91
GB-A-793808		None		
FR-A-2276108	23-01-76	JP-A-	50160418	25-12-75
		JP-B-	56024648	08-06-81
		JP-A-	51029220	12-03-76
		AT-B-	342204	28-03-78
		AU-B-	499055	05-04-79
		BE-A-	830570	16-10-75
		DE-A,B	2528190	15-01-76
		GB-A-	1444890	04-08-76
		NL-A-	7507511	30-12-75
		SE-A-	7506993	29-12-75
GB-A-2212396	26-07-89	None		
EP-A-0013131	09-07-80	None		
EP-A-0210540	04-02-87	AU-B-	592581	18-01-90

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 23/07/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0210540		AU-A- 5979186	22-01-87
		CA-A- 1282698	09-04-91
		DE-A- 3682135	28-11-91
		JP-A- 62030709	09-02-87
		US-A- 4871549	03-10-89
US-A-4775536	04-10-88	None	
EP-A-0299211	18-01-89	DE-A- 3720757	05-01-89
		DE-A- 3870338	27-05-92
		JP-A- 1022822	25-01-89
		US-A- 4892741	09-01-90