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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| A61K 9/20 | |
| (21) International Application Number: PCT/US93/01410 |
| (22) International Filing Date: 22 February 1993 (22.02.93) |
| (30) Priority data: 4/044136 29 February 1992 (29.02.92) JP |
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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: PHARMACEUTICAL PREPARATION FOR SUSTAINED RELEASE OF A DRUG AND PROCESS FOR PRODUCING THE SAME |

(57) Abstract

The object of the present invention is to provide a polymer matrix type pharmaceutical preparation for sustained release of a drug which can realize the desired release properties and a process for producing the same. A pharmaceutical preparation for sustained release of a drug which comprises as a main base hydroxypropylmethylcellulose, wherein the drug is released according to the prescribed formula. Control of release is done by regulating the substitution degree and mean molecular weight of hydroxypropylmethylcellulose and appropriately containing therein the water-soluble additive. Such the pharmaceutical preparation can be obtained by applying the partial wet granulation process thereto in which a drug is wet-granulated using a binder and thereafter this is dried to obtain a drug granule, and thereafter mixing hydroxypropylmethylcellulose and water-soluble ingredient therein and compressing the mixture.
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PHARMACEUTICAL PREPARATION FOR SUSTAINED RELEASE OF A DRUG AND PROCESS FOR PRODUCING THE SAME

DETAILED EXPLANATION OF THE INVENTION

The present invention relates to a polymer matrix type pharmaceutical preparation for sustained release of a drug and a process for producing the same. More particularly, it relates to a polymer matrix type pharmaceutical preparation for sustained release of a drug in which the drug release can be regulated arbitrarily by controlling the swelling and disintegrating properties of the polymer matrix which is formed by hydroxypropylmethylcellulose (HPMC) as a base and a process for producing the same.

There is a method for clinically reducing the administration times, or inhibiting the rapid increase in the blood concentration of the drug to inhibit the manifestation of the side effect by controlling the sustained release or dissolution of the drug using the pharmaceutical preparation techniques to maintain the blood concentration of the drug at the appropriate level for a long period of time upon administration. This method is shown to be useful in oral pharmaceutical preparations from a view point of the simplicity of the administration.

INFORMATION DISCLOSURE

Pharmaceutical preparations for sustained release of a drug comprising as a base hydroxypropylmethylcellulose are known. However, there have been reported only ones which are prepared by the direct compression process [see J.E.Hogan, Drug Dev.Ind.Pharm., 15, 975 (1985)]. The process by such the direct compression process is simple in respect of steps, but the release properties depend upon the physical properties of the drug which is the subject of the sustained release, as well as 1) deterioration during mixing, 2) deterioration due to the properties of the mixed powder, and 3) problems from compression (adhesion to a die or punch, insufficiency in the hardness of the tablets and the like) are observed frequently. These phenomena appear markedly in the case, particularly, where the amount of the subject drug contained in one pharmaceutical preparation grows larger.

PROBLEMS TO BE SOLVED BY THE INVENTION

Although the pharmaceutical preparations for sustained release of a drug are useful as described above, the pharmaceutical preparations design concept which does not depend upon the physical properties of the subject drug and therefore can be applied more extensively has not been hitherto established by the mechanical proof. The object of the present invention is to realize such the establishment in a polymer matrix type oral pharmaceutical preparation for sustained release of a drug which comprises as a main base hydroxypropylmethylcellulose and to provide a pharmaceutical preparation in which the desired release properties can be arbitrarily given.

In addition, another object of the present invention is to provide a pharmaceutical
preparation for sustained release of a drug in which the various obstacles arising from the previous direct compression process can be solved, the release properties do not depend upon the physical properties of the subject drug and, even when the amount of the drug contained in one pharmaceutical preparation is large, the above-described deterioration of the mixing and the like can be avoided, and further the application is possible to more extensive drugs.

MEANS OF SOLVING THE PROBLEMS

Hydroxypropylmethylecellulose is a non-ionic cellulosic ether and has the methoxy group and hydroxypropoxy group as a substituent. According to The Pharmacopoeia of Japan, hydroxypropylmethylecellulose is classified into 2910 (methoxy group; 28 to 30 %, hydroxypropoxy group; 7 to 12 %), 2906 (methoxy group; 27 to 30 %, hydroxypropoxy group; 4 to 7.5 %) and 2208 (methoxy group; 19 to 24 %, hydroxypropoxy group; 4 to 12 %) depending upon the substitution degree of each substituent, and the viscosity of the solution in water is shown as the index of the mean molecular weight. And since hydroxypropylmethylecellulose is generally hydrophilic and highly viscous, it has the higher water retention. When hydroxypropylmethylecellulose is used as a base for the oral pharmaceutical preparations for sustained release of a drug, it is essential for establishing the above pharmaceutical preparations design concept to make clear the influence of the above properties on the drug release properties.

For that reason, the present inventors have been studying intensively in order to make clear 1) the control of the swelling and disintegrating properties of the polymer matrix by changing the substitution degree of hydroxypropylmethylecellulose contained in the pharmaceutical preparation, and the drug release properties, 2) the control of the swelling and disintegrating properties of polymer matrix by changing the viscosity of hydroxypropylmethylecellulose contained in the pharmaceutical preparation, and the drug release properties, 3) control of the swelling and disintegrating properties of the polymer matrix by containing and dispersing the water-soluble ingredient such as lactose and the like into the matrix formed by hydroxypropylmethylecellulose, and the drug release properties.

As the result, the present inventors have obtained the findings that, when hydroxypropylmethylecellulose is used as a base which forms the polymer matrix, a pharmaceutical preparation for sustained release of a drug in which the desired release properties can be realized arbitrarily by appropriately selecting the substitution degree and mean molecular weight and, if necessary, containing therein the water-soluble additive (lactose etc.) so that the drug can be released according to the constant formula.

The present invention was done based on such the findings and is to provide a polymer matrix type pharmaceutical preparation for sustained release of a drug which comprises as a main base hydroxypropylmethylecellulose, wherein the drug is released according to the
following formula:

(a) in the case where \( V_1 C_s > A \),

\[
Q_s = S_4 \left[ \frac{D V_1}{r} t \right]^{\frac{1}{2}}
\]

(b) in the case where \( V_1 C_s \leq A \),

\[
Q_s = S_4 \left[ \frac{2 D V_1}{r} A C_s t \right]^{\frac{1}{2}}
\]

(c) in the case where \( V_1 C_s \ll A \),

\[
Q_s = Q \cdot \left( 1 - (1 - k_2 t)^3 \right)
\]

wherein \( C_s \) is the solubility of the drug, \( A \) is the total amount of the drug present in the unit volume of the matrix, \( V_1 \) is the effective volume in the interior of the matrix, \( Q_s \) is the drug releasing amount after \( t \) hours, \( S_4 \) is the total surface area, \( D \) is the diffusion coefficient, \( r \) is the tortuosity of the capillary tube system, \( Q \) is the total drug releasing amount, \( Q_s \) is the content of the drug contained in one pharmaceutical preparation, \( k_2 \) is the apparent rate constant for releasing the drug from a drug granule. The intended drug release properties can be realized by the present invention.

Firstly, the physiologically active drugs used in the present invention which are the subject of the sustained release are not limited to specific ones. As in the previous techniques, particularly remarkable effects can be obtained in the case of the drugs whose effective and safe areas of the blood concentration after administration into the body are near from each other and the drugs which are administered frequently with difficulty. As representative examples of the drugs whose effective area and safe area are near from each other, there are theophyllin and aminophyllin which are xanthine derivatives and the like. And as the drugs which are administered frequently with difficulty, there are psychopharmaceuticals (adinazolam methanesulfonate, 3-(5-cycloproun-1,2,4-oxadiazol-3-yl)-5-(1-methyllethyl)imidazo[1,5-a]-quinoxalin-4(5H)-one (U-78,875) or panadiplon, alprazolam, triazolam, (3aR-cis)-2,3,3a,4,5,9b-Hexahydro-9-carboxamido-3-(n-propyl)-1H-benz[e]indole, and the like.

And water-very soluble drugs, for example, synthetic local anesthetics (procainamide), antipyretic analgesics (sodium salicylate, aspirin, salicylamide, ethoxybenzamide, sasapyrine, aspirin aluminum, methyl salicylate, ethenamide, antipyrine, sulpyrine, aminopyrine, phenylbutazone, isopropylantipyrine, acetanilide, phenacetin, acetaminophen, ibuprofen, flurbiprofen) and the like are also used. On the other hand, water-slightly soluble drugs, for
example, fibrinolytic agent itazigrel (The Upjohn Company), antineoplastic agent menogaril (The Upjohn Company), bropirimine (The Upjohn Company) and vitamin agent (coenzyme type vitamin B12) and the like can be also used.

Further, the sustained release techniques of the present invention can be applied to p-hydroxybenzoic esters (methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate, propyl p-hydroxybenzoate, isopropyl p-hydroxybenzoate, butyl p-hydroxybenzoate and isobutyl p-hydroxybenzoate) which are used extensively as an antiseptic for food and are not aiming at direct application to the human body. Antiseptics, and other pharmaceuticals for animals, agricultural chemicals (herbicides, insect repellents, antifungals) and the like in which the release of the above compounds are sustained are contained in the pharmaceutical preparations for sustained release of a drug of the present invention.

In the present invention, not only one of but also more than two of these drugs can be used in the pharmaceutical preparations for sustained release of a drug, and the amount thereof can be appropriately selected depending upon the purpose of the sustained release.

In the present pharmaceutical preparations for sustained release of a drug, hydroxypropylmethylcellulose is contained therein as a main ingredient of a base. The sustained release properties can be regulated by selecting hydroxypropylmethylcellulose depending upon the substitution degree (methoxyl group, hydroxypropoxyl group) and mean molecular weight (viscosity grade). And the sustained release can be also regulated by containing therein water-soluble ingredients such as lactose, sucrose, D-mannose and D-sorbitol and the like and changing the content ratio of these relative to hydroxypropylmethylcellulose. Other ingredients such as excipient, binder, lubricant, stabilizer and the like can be appropriately contained therein as in the conventional pharmaceutical preparations.

Such the selection and containing of these ingredients are done so that the release according to the above formula can be obtained. This can be easily done by repeating the dissolution test on the given drugs.

A process for producing a polymer matrix type pharmaceutical preparation for sustained release of a drug of the present invention is explained below.

The process of the present invention can be named as "partial wet granulation process".

In this process, the subject drug is wet-granulated using a binder such as corn starch, hydroxypropylcellulose and the like, and dried to obtain a drug granule. Further hydroxypropylmethylcellulose and a water-soluble ingredient are added to the resulting granule to obtain the pharmaceutical preparations. By employing such the granulation step, firstly, the obstacles at compression molding based on the physical properties of the subject drug is masked and, secondly, the dispersibility of the subject drug is increased and thereby the applicable scope of the subject medicine can be extremely expanded.
In addition, these granules can be appropriately graded so that they have the intended mean particle size and size distribution depending upon the purpose thereof, and to this are added hydroxypropylmethylcellulose and the water-soluble ingredient such as lactose and the like so that the desired release can be obtained. Upon this, the known lubricant such as precipitated aluminum silicate, magnesium stearate and the like can be appropriately contained therein in order to improve the flowability and moldability of the mixture.

These ingredients are mixed and dispersed well, and the mixture is converted into the compressed tablets having the desired weight using a tablet machine. The compression conditions can be appropriately selected depending upon the kind and content of the subject drug as well as the content ratio relative to hydroxypropylmethylcellulose and water-soluble ingredient such as lactose and the like.

A process for producing a pharmaceutical preparation for sustained release of a drug which releases the drug according to the above formula which comprises using such the partial wet granulation process is also within the scope of the present invention.

As the drug release properties of the pharmaceutical preparation of the present invention thus obtained, there are those based on two mechanisms of the following cases, that is, 1) where the drug release is controlled mainly by infiltration of the solvent into the interior of the matrix, dissolution of the medicine in the interior of the matrix and subsequent diffusion, and 2) where the drug release is controlled mainly by disintegration of the matrix and subsequent release from the drug granule.

Now, the influence of change of the substitution degree of hydroxypropylmethylcellulose contained in the pharmaceutical preparation on the swelling properties of the polymer matrix, that is, 1) the drug release properties, and on the disintegrating properties of the matrix, that is, 2) the drug release properties have been made clear. That is, hydroxypropylmethylcellulose 2910 and hydroxypropylmethylcellulose 2208 in the pharmaceutical preparation have comparatively high water retention and are effective for aiming at the above drug release mechanism 1). On the other hand, hydroxypropylmethylcellulose 2906 in the pharmaceutical preparation shows comparatively rapid disintegrability and, therefore, is effective for aiming at the above drug release mechanism 2). In addition, the influence of change of the mean molecular weight (whose parameter is viscosity grade) on the drug release properties has been also made clear. That is, hydroxypropylmethylcellulose high viscosity grade has high water retention as the fundamental physical properties and, therefore, is effective for aiming at the above drug release mechanism 1). On the other hand, hydroxypropylmethylcellulose low viscosity grade in the pharmaceutical preparation shows rapid disintegrability and, therefore, is effective for aiming at the above drug release mechanism 2). Further, the influence of containing of water-very soluble ingredient such as lactose and the like in the matrix formed by
hydroxypropylmethylcellulose has been also made clear. That is, when aiming at the above
drug release mechanism 1), expansion of the interior water paths increases the drug release rate
and, when aiming at the above drug release mechanism 2), promotion of the matrix
disintegrability increases the drug release rate. It has been found that the linearity between the
content ratio of hydroxypropylmethylcellulose and water-very soluble ingredient such as lactose
and the like and the release rate is recognized in a certain range. Based on this findings, it has
been become possible to predict the content ratio for accomplishing the desired release rate.
In addition, it has been found that, regarding the subject drug itself, the solubility
thereof and the amount thereof in the tablet is the most important influencing factor on the drug
release properties. That is, when the drug is in the condition where it can dissolve well in the
atmospheric interior of the swollen hydroxypropylmethylcellulose matrix, the above drug release
mechanism 1) becomes predominant and, when the drug is not in the condition where it cannot
dissolve well in the atmospheric interior swollen hydroxypropylmethylcellulose matrix, the
above drug release mechanism 2) becomes predominant. Specifically, it can be deduced that the
release mechanism is determined depending upon 1) $V_fC_s>A$ and $V_fC_s\leq A$, 2) $V_fC_s<A$, wherein
$C_s$ is the solubility of the drug, $A$ is the amount of the drug in one pharmaceutical preparation
and $V_f$ is the effective volume in the interior of the matrix.
The above-described formulas were derived from these findings.
Thus, in the pharmaceutical preparation of the present invention, the release properties
can be controlled by the contained ingredients and the amount thereof and the like and shows
the release properties based on the pharmaceutical preparations design in the digestive tract upon
oral administration.

The following Examples further illustrate the present invention in detail.

**Example 1**

14 G of corn starch and 1 g of hydroxypropylcellulose were added to 5 g of adinazolam
methanesulfonate, and the partial wet-granulation was applied thereto. Lactose/hydroxy-
propylmethylcellulose 2910 4000cps was added to the granule in the content ratio of 0.47 to
obtain 500 tablets of the pharmaceutical preparation for sustained release of a drug of the
present invention containing 5 mg of adinazolam methanesulfonate in 190 mg of the tablet.

**Example 2**

14 G of corn starch and 1 g of hydroxypropylcellulose were added to 5 g of adinazolam
methanesulfonate, and the partial wet-granulation was applied thereto. Lactose/hydroxy-
propylmethylcellulose 2208 4000 cps was added to the granule in the content ratio of 0.47 to
obtain 500 tablets of the pharmaceutical preparation for sustained release of a drug of the
present invention containing 5 mg of adinazolam methanesulfonate in 190 mg of the tablet.

**Example 3**
14 G of corn starch and 1 g of hydroxypropylcellulose were added to 5 g of adinazolam methanesulfonate, and the partial wet-granulation was applied thereto. Lactose/hydroxypropylmethylcellulose 2906 4000 cps was added to the granule in the content ratio of 0.47 to obtain 500 tablets of the pharmaceutical preparation for sustained release of a drug of the present invention containing 5 mg of adinazolam methanesulfonate in 190 mg of the tablet.

Example 4

14 G of corn starch and 1 g of hydroxypropylcellulose were added to 5 g of adinazolam methanesulfonate, and the partial wet-granulation was applied thereto. Lactose/hydroxypropylmethylcellulose 2910 50 cps was added to the granule in the content ratio of 0.47 to obtain 500 tablets of the pharmaceutical preparation for sustained release of a drug of the present invention containing 5 mg of adinazolam methanesulfonate in 190 mg of the tablet.

Example 5

14 G of corn starch and 1 g of hydroxypropylcellulose were added to 15 g of adinazolam methanesulfonate, and the partial wet-granulation was applied thereto.

Lactose/hydroxypropylmethylcellulose 2910 4000 cps was added to the granule in the content ratio of 0.61 to obtain 500 tablets of the pharmaceutical preparation for sustained release of a drug of the present invention containing 15 mg of adinazolam methanesulfonate in 200 mg of the tablet.

Example 6

14 G of corn starch and 1 g of hydroxypropylcellulose were added to 15 g of adinazolam methanesulfonate, and the partial wet-granulation was applied thereto.

Lactose/hydroxypropylmethylcellulose 2910 4000 cps was added to the granule in the content ratio of 0.47 to obtain 500 tablets of the pharmaceutical preparation for sustained release of a drug of the present invention containing 15 mg of adinazolam methanesulfonate in 200 mg of the tablet.

Example 7

14 G of corn starch and 1 g of hydroxypropylcellulose were added to 15 g of adinazolam methanesulfonate, and the partial wet-granulation was applied thereto.

Lactose/hydroxypropylmethylcellulose 2910 4000 cps was added to the granule in the content ratio of 0.35 to obtain 500 tablets of the pharmaceutical preparation for sustained release of a drug of the present invention containing 15 mg of adinazolam methanesulfonate in the 200 mg of the tablet.

Example 8

14 G of corn starch and 1 g of hydroxypropylcellulose were added to 15 g of adinazolam methanesulfonate, and the partial wet-granulation was applied thereto.

Lactose/hydroxypropylmethylcellulose 2910 4000 cps was added to the granule in the content
ratio of 0.25 to obtain 500 tablets of the pharmaceutical preparation for sustained release of a
drug of the present invention containing 15 mg of adinazolam methanesulfonate in 200 mg of
the tablet.

Example 9

14 G of corn starch and 1 g of hydroxypropylcellulose were added to 10 g of
adinazolam methanesulfonate, and the partial wet-granulation was applied thereto.
Lactose/hydroxy-propylmethylcellulose 2910 4000 cps was added to the granule in the content
ratio of 0.47 to obtain 500 tablets of the pharmaceutical preparation for sustained release of a
drug of the present invention containing 15 mg of adinazolam methanesulfonate in 200 mg of
the tablet.

Example 10

14 G of corn starch and 1 g of hydroxypropylcellulose were added to 20 g of
adinazolam methanesulfonate, and the partial wet-granulation was applied thereto.
Lactose/hydroxy-propylmethylcellulose 2910 4000 cps was added to the granule in the content
ratio of 0.47 to obtain 500 tablets of the pharmaceutical preparation for sustained release of a
drug of the present invention containing 15 mg of adinazolam methanesulfonate in 200 mg of
the tablet.

Example 11

14 G of corn starch and 1 g of hydroxypropylcellulose were added to 30 g of
adinazolam methanesulfonate, and the partial wet-granulation was applied thereto.
Lactose/hydroxy-propylmethylcellulose 2910 4000 cps was added to the granule in the content
ratio of 0.47 to obtain 500 tablets of the pharmaceutical preparation for sustained release of a
drug of the present invention containing 15 mg of adinazolam methanesulfonate in 200 mg of
the tablet.

Example 12

14 G of corn starch and 1 g of hydroxypropylcellulose were added 15 g of procain
hydrochloride, and the partial wet-granulation was applied thereto.
Lactose/hydroxypropylmethyl-cellulose 2910 4000 cps was added to the granule in the content
ratio of 0.47 to obtain 500 tablets of the pharmaceutical preparation for sustained release of a
drug of the present invention containing 15 mg of procain hydrochloride in 200 mg of the
tablet.

Example 13

14 G of corn starch and 1 g of hydroxypropylcellulose were added to 15 g of
acetaminophen, and the partial wet-granulation was applied thereto. Lactose/hydroxypropyl-
methylcellulose 2910 4000 cps was added to the granule in the content ratio of 0.47 to obtain
500 tablets of the pharmaceutical preparation for sustained release of a drug of the present
invention containing 15 mg of acetaminophen in 200 mg of the tablet.

Example 14

14 G of corn starch and 1 g of hydroxypropylcellulose were added to 15 g of theophylline, and the partial wet-granulation was applied thereto. Lactose/hydroxypropylmethylcellulose 2910 4000 cps was added to the granule in the content ratio of 0.47 to obtain 500 tablets of the pharmaceutical preparation for sustained release of a drug of the present invention containing 15 mg of theophylline in 200 mg of the tablet.

Example 15

14 G of corn starch and 1 g of hydroxypropylcellulose were added to 15 g of methyl p-hydroxybenzoate, and the partial wet-granulation was applied thereto. Lactose/hydroxypropylmethylcellulose 2910 4000 cps was added to the granule in the content ratio of 0.47 to obtain 500 tablets of the pharmaceutical preparation for sustained release of a drug of the present invention containing 15 mg of methyl p-hydroxybenzoate in 200 mg of the tablet.

Example 16

14 G of corn starch and 1 g of hydroxypropylcellulose were added to 15 g of ethyl p-hydroxybenzoate, and the partial wet-granulation was applied thereto. Lactose/hydroxypropylmethylcellulose 2910 4000 cps was added to the granule in the content ratio of 0.47 to obtain 500 tablets of the pharmaceutical preparation for sustained release of a drug of the present invention containing 15 mg of ethyl p-hydroxybenzoate in 200 mg of the tablet.

Example 17

14 G of corn starch and 1 g of hydroxypropylcellulose were added to 15 g of propyl p-hydroxybenzoate, and the partial wet-granulation was applied thereto. Lactose/hydroxypropylmethylcellulose 2910 4000 cps was added to the granule in the content ratio of 0.47 to obtain 500 tablets of the pharmaceutical preparation for sustained release of a drug of the present invention containing 15 mg of propyl p-hydroxybenzoate in 200 mg of the tablet.

Example 18

14 G of corn starch and 1 g of hydroxypropylcellulose were added to 15 g of U-78875, and the partial wet-granulation was applied thereto. Lactose/hydroxypropylmethylcellulose 2910 4000 cps was added to the granule in the content ratio of 0.47 to obtain 500 tablets of the pharmaceutical preparation for sustained release of a drug of the present invention containing 15 mg of U-78875 in 200 mg of the tablet.

Example 19

14 G of corn starch and 1 g of hydroxypropylcellulose were added to 1.5 g of alprazolam, and the partial wet-granulation was applied thereto. Lactose/hydroxypropylmethylcellulose 2910 4000 cps was added to the granule in the content ratio of 0.47 to obtain 500 tablets of the pharmaceutical preparation for sustained release of a drug of the present invention
containing 1.5 mg of alprazolam in 186.5 mg of the tablet.

**Example 20**

14 G of corn starch and 1 g of hydroxypropylcellulose were added to 1.5 g of triazolam, and the partial wet-granulation was applied thereto. Lactose/hydroxypropylmethylcellulose 2910 4000 cps was added to the granule in the content ratio of 0.47 to obtain 500 tablets of the pharmaceutical preparation for sustained release of a drug of the present invention containing 1.5 mg of triazolam in 186.5 mg of the tablet.

**Example 21**

14 G of corn starch and 1 g of hydroxypropylcellulose were added to 1.5 g of ibuprofen, and the wet-granulation was applied thereto. Lactose/hydroxypropylmethylcellulose 2910 4000 cps was added to the granule in the content ratio of 0.47 to obtain 500 tablets of the pharmaceutical preparation for sustained release of a drug of the present invention containing 1.5 mg of ibuprofen in 186.5 mg of the tablet.

**Example 22**

14 G of corn starch and 1 g of hydroxypropylcellulose were added to 1.5 g of U-78875, and the wet-granulation was applied thereto. Lactose/hydroxypropylmethylcellulose 2910 4000 cps was added to the granule in the content ratio of 0.47 to obtain 500 tablets of the pharmaceutical preparation for sustained release of a drug of the present invention containing 1.5 mg of U-78875 in 186.5 mg of the tablet.

The following Experiments further illustrate the effects of sustained release and preparations design concept of the present invention in detail.

**Experiment 1**

The influence of the change in the substitution degree and viscosity grade of hydroxypropylmethylcellulose on the drug dissolution properties

Pharmaceutical preparations of the present invention obtained in Example 1 to 4 were examined.

Using adinazolam methanesulfonate as the subject drug, the sustained release tablets comprising as a main base hydroxypropylmethylcellulose 2910 4000 cps, hydroxypropylmethylcellulose 2208 4000 cps or hydroxypropylmethylcellulose 2906 4000 cps were prepared according to the above process, and the influence of the fundamental physical properties of hydroxypropylmethylcellulose in the pharmaceutical preparation on the dissolution properties of adinazolam methanesulfonate was examined. And, the influence of the viscosity grade on the release properties was compared and examined using the sustained release tablets comprising as a main base hydroxypropylmethylcellulose 2910 50 cps. In addition, the content ratio of hydroxypropylmethylcellulose present in the formulations was maintained constant at 60.5 % in any cases. Swelling properties (water retention) and disintegrability (disintegration rate) of the
matrix formed by each hydroxypropylmethylcellulose were calculated from the wet and dry weights after immersion of the tablets into a dissolution medium for a predetermined time according to the following formulas:

Water retention = (wet weight-dry weight)/wet weight X 100

(formula 1)

Disintegration rate = (initial dry weight-dry weight)/initial dry weight

(formula 2)

wherein initial dry weight indicates the weight of the tablet before immersion.

Figure 1 shows the change as a function of time in the wet and dry weights of the sustained release tablets comprising as a main base each hydroxypropylmethylcellulose. In the cases of hydroxypropylmethylcellulose 2910 4000 cps and 2208 4000 cps, it is shown that the wet weight is increased and the decrease in the dry weight is comparatively delayed. On the other hand, in the cases of hydroxypropylmethylcellulose 2906 4000 cps and 2910 50 cps, it is shown that, after the wet weight is increased transiently, it is decreased and the dry weight is comparatively rapidly decreased.

Figure 2 shows the water retention and disintegration rate as a function of time which were calculated according to formulas 1 and 2. From figure 2, it was shown that the water retention is more significantly influenced by the viscosity grade than the substitution degree. That is, as the mean molecular weight of hydroxypropylmethylcellulose is increased, the water retention grows higher and thereby it was made clear that the mean molecular weight is dominant over the swelling properties of the matrix when formulated into the pharmaceutical preparations. And, it was made clear from the change of the disintegration rate that the intermolecular force in the matrix which determines the disintegrating properties is controlled by substitution balance of methoxyl and hydroxypropoxyl groups as well as the mean molecular weight.

From the fundamental physical properties of hydroxypropylmethylcellulose herein when it forms the matrix, in the case where the above drug release mechanism 1), that is, diffusion controlling type drug release mechanism is intended, high viscosity grade of 2910 or 2208 should be selected as a base and, in the case where the above drug release mechanism 2), that is, disintegration controlling type disintegrating mechanism is intended, low viscosity grade of 2906, 2910 or 2208 should be selected as a base.

**Experiment 2**

Drug release control by changing the content ratio of hydroxypropylmethylcellulose and lactose

The pharmaceutical preparations of the present invention obtained in Examples 5 to 8 were examined.

In this Experiment, pharmaceutical preparations having four stage release properties
(dissolution rate) were prepared by containing lactose as a water-very soluble ingredient, in various content ratios, in a sustained release tablet comprising as a main base hydroxypropylmethylcellulose and as a subject drug adinazolam methanesulfonate. The content ratio of lactose/hydroxypropylmethylcellulose in the formulation was varied from 0.25 to 0.60.

From Figure 3, it was made clear that, as the content ratio of lactose/hydroxypropylmethylcellulose is increased, the dissolution is accelerated and thereby the drug release control is possible by changing the content ratio. In addition, as is shown in Figure 4, when the drug dissolution rate is estimated as the mean dissolution time, good correlation is recognized between said time and content ratio of lactose/hydroxypropylmethylcellulose. This means that the content ratio of lactose/hydroxypropylmethylcellulose can be inversely predicted from the intended dissolution rate.

Experiment 3

The influence of the change in the drug potency on the drug release properties

The pharmaceutical preparations of the present invention obtained in Example 1 and Examples 9 to 11 were examined.

In this Experiment, the influence of the change in the drug potency of one tablet on the drug release properties from the matrix formed by hydroxypropylmethylcellulose 2910 4000 cps was examined using adinazolam methanesulfonate as the subject drug. As shown in the below Table 1, it was made clear that the pharmaceutical preparations of the present invention obtained in Example 1 and Examples 9 to 11 are not extremely influenced by the drug potency in one tablet. However, the application of this relation is considered to be limited to atmosphere where $V_iC_s = A$ is effected wherein $C_s$ is the solubility of the drug, $A$ is the amount of the drug in one tablet and $V_i$ is the effective volume in the interior of the matrix.

[Table 1]

Experiment 4

The influence of the solubility of the subject drug on the drug release properties

The pharmaceutical preparations of the present invention obtained in Example 1 and Examples 12 to 18 were examined.

In this Experiment, the dissolution properties of the model compounds having the various degrees of the solubility were examined using hydroxypropylmethylcellulose 2910 4000 cps as a main base which forms the matrix. As the model compounds, the following compounds were examined: adinazolam methanesulfonate (the solubility in Disintegrating Test 2nd Medium of The Pharmacopoeia of Japan; 0.59 mg/ml), procain hydrochloride (the solubility in Disintegrating Test 2nd Medium of The Pharmacopoeia of Japan; 453 mg/ml), acetaminophen (the solubility in Disintegrating Test 2nd Medium of The Pharmacopoeia of Japan; 18.9 mg/ml), theophylline (the solubility in Disintegrating Test 2nd Medium of The Pharmacopoeia of Japan;
10.6 mg/ml), methyl p-hydroxybenzoate (the solubility in Disintegrating Test 2nd Medium of The Pharmacopoeia of Japan; 3.11 mg/ml), ethyl p-hydroxybenzoate (the solubility in Disintegrating Test 2nd Medium of The Pharmacopoeia of Japan; 1.27 mg/ml), propyl p-hydroxybenzoate (the solubility in Disintegrating 2nd Medium of The Pharmacopoeia of Japan; 0.53 mg/ml) and U-78875 (the solubility in Disintegrating Test 2nd Medium of The Pharmacopoeia of Japan; 0.07 mg/ml) were examined.

As shown Figure 5, it is clear that drug dissolution properties from the matrix having the same composition is remarkably influenced by the solubility of the subject drug itself. When the mean release time of the drug is plotted relative to the solubility of the drug itself in order to make clear the above phenomenon, the relation shown in Figure 6 is obtained. When this relation is expressed more generally, the relation in Figure 7 is derived. That is, when the solubility of the subject drug and the amount of the drug in one tablet are given, the drug release mechanism which is intended by the pharmaceutical preparation of the present invention is determined inevitably and, therefore, the substitution degree of hydroxypropylmethylcellulose and mean molecular weight (viscosity grade) which are appropriate for the release mechanism can be selected as described above.

The pharmaceutical preparation and process of the present invention are useful from a viewpoint that the optimum formulation can be selected in shorter period of time.

Mechanism of drug release

Then, the formulas with which drug release of the present pharmaceutical preparation accords are explained.

Drug release from the matrix which dose not disintegrate is expected to accord with the theoretical formula proposed by Higuchi [see T. Higuchi, J.Pharm.Sci., 52, 1145 (1989)].

\[ Q_d = S \left( \frac{D V_1}{r} \left( 2 A - V_1 C_s \right) C_s t \right)^{1/2} \]

wherein \( Q_d \): the drug releasing amount after \( t \) hours,
\( D \): the diffusion coefficient of the drug in the matrix,
\( r \): tortuosity in the capillary tube system,
\( A \): the total amount of the drug present in the unit volume of the matrix,
\( C_s \): the solubility of the drug,
\( V_1 \): the effective volume in the interior of the matrix,
\( S \): the total surface area.

Accordingly, when drug release occurs before disintegration of the matrix type pharmaceutical preparation, the following conclusion can be drawn (see Figure 7).

Firstly, depending upon the total drug amount (A) in the unit volume of the matrix, the
effective volume ($V_e$) in the interior of the matrix and the solubility ($C_s$) of the drug, the cases are classified as follows:

(a) $V_eC_s > A$ and (b) $V_eC_s \leq A$

That is, the cases are classified into those where (a) the drug in the matrix dissolves promptly in a dissolution medium which infiltrates therein and (b) a part of the drug dissolves therein.

In the case of (a), since $V_eC_s$ is sufficiently larger than $A$, the formula I can be replaced by the following formula II.

$$Q_d = S \left[ \frac{D V_i}{r} \cdot t \right]^{\frac{1}{2}}$$

(Formula II)

In this case, the drug in the matrix dissolves rapidly in a dissolution medium which infiltrates therein without reaching the saturation and is subsequently released by the diffusion. That is, after a dissolution medium infiltrates into the matrix, the drug release is controlled only by the diffusion coefficient ($D$) of the drug.

In the case of (b), that is, where $A$ is larger or $C_s$ is smaller and $V_eC_s < A$, the formula I can be replaced by the following formula III.

$$Q_d = S \left[ \frac{2 D V_i}{r} \cdot A \cdot C_s \cdot t \right]^{\frac{1}{2}}$$

(Formula III)

In this case, drug release is controlled by the solubility ($C_s$) and the diffusion coefficient ($D$).

And the drug release rate shows intermediate between the infiltration rate of a dissolution medium into the matrix and the disintegrating rate of the matrix.

In the case of (c) where the solubility of the drug is extremely small or the drug content is extremely large, that is, the extremely small part of the drug dissolves in a dissolution medium which infiltrates into the matrix, not dissolution in the matrix but disintegration of the matrix drives the drug release.

(c) $V_eC_s < A$

That is, the drug dose not dissolve in the matrix, the drug granule is released by disintegration of the matrix, and subsequently release from the drug granule occurs.

The amount of the remaining drug in the matrix at time $T_{n-1}$ and $T_n$ are shown by the following formula IV or V, respectively.

$$W_e(T_{n-1}) / W_i = (1 - k_i T_{n-1})^3$$ formula IV

$$W_e(T_n) / W_i = (1 - k_i T_n)^3$$ formula V

wherein $W_e(T_{n-1})$ and $W_e(T_n)$ are the amount of the drug which remains in the matrix at time $T_{n-1}$ and $T_n$, $W_i$ is the total drug amount at the initial stage and $k_i$ is the apparent matrix disintegration rate.
integration constant.

Accordingly, the releasing amount of the drug granule for a time from \( T_{n+1} \) to \( T_n \) by disintegration of the matrix can be expressed by the following formulas:

\[
X_R = W(T_{n+1}) - W(T_n)
\]

\[
W_i[(1-k_iT_{n+1})^3 - (1-k_iT_n)^3]
\]  
formula VI

And the releasing amount \( (Q_R) \) of the drug from the drug granule which was released by disintegration of the matrix accords with cubic root rule by Hixon Crowell [see A.W.Hixon and J.H.Crowell, Ind.Eng.Chem.), 23, 923 (1931)].

\[
Q_R = X_R[1-(1-k_R t)^3]
\]  
formula VII

wherein \( k_R \) is the apparent releasing rate constant from the drug granule.

Accordingly, the total drug releasing amount \( (Q_o) \) accords with the following formula:

\[
Q_o = \sum Q_R = \sum X_R[1-(1-k_R t)^3]
\]  
formula VIII

As can be understood from the formula VIII, the release rate depends upon the release rate from the drug granule by disintegration of the matrix.

When the release rate of the drug from the drug granule is extremely small in comparison with the disintegration rate of the matrix, the formula VIII can be expressed as follows:

\[
Q_o = Q_o[1-(1-k_o t)^3]
\]  
formula IX

wherein \( Q_o \) is the drug amount contained in one pharmaceutical preparation.

When the preceding theory is schematically shown, the relation in Figure 8 can be deduced. That is, the point of inflection \( (C_o') \) in the drug solubility curve in the cases of (a) and (b) satisfies with:

\[
(2A-V_oC_o')C_o' = 0
\]  
formula X

in the formula I. From this, this point of inflection can be defined as:

\[
C_o' = \frac{2A}{V_o}
\]  
formula XI

and, when the composition of the matrix is constant, that is, \( V_o \) is constant, the point of inflection is changed proportionally by the drug content. This relation is shown schematically as in Figure 8. That is, when the solubility of the subject drug and the drug content are given, the release properties thereof can be predicted. In particular, Figure 8 shows the case of lactose/hydroxypropylmethylcellulose (the content ratio: 0.47) shown in Examples. Accordingly, when the content ratio of lactose/hydroxypropylmethylcellulose is changed, that is, the lactose content in the formulation is increased, \( V_o \) in the formula XI grows larger and a point of inflection \( C_o' \) shifts in the direction toward the smaller. Inversely, when the hydroxypropylmethylcellulose content in the formulation is increased, \( V_o \) in the formula XI grows smaller and a point of inflection \( C_o' \) shifts in the direction toward the larger.

Prediction of release properties from the drug release mechanism.
Prediction of release properties from the drug release mechanism

The preceding cases are where the amount of the subject drug is 15 mg (principal agent content; 7.5 %) in 200 mg of the tablet. Water-slightly soluble drug (solubility: 0.1 mg/ml) is illustrated in view of the relation between the mean release time and the solubility and content of principal agent.

A preparation which contains 1.5 mg of U-78875 in 200 mg of the tablet (principal agent content: 0.75 %) has the release properties shown in Figure 8.

Similarly, alprazolam, triazolam, ibuprofen and the like show the release properties shown in Table 2.

Experiment 5

Drug absorption test from sustained release pharmaceutical preparation which uses hydroxypropylmethylcellulose in beagle dogs

In the following test, after the pharmaceutical preparation of the present invention obtained in Example 1 containing 15 mg of adinazolam methanesulfonate as a drug and the control preparation also containing 15 mg of the same were orally administered to beagle dogs, respectively, the plasma concentration of adinazolam was measured as a function of time. Figure 10 shows the change in the plasma concentration of adinazolam methanesulfonate after administration of respective pharmaceutical preparations. From these, the maximum blood concentration of drug (C_{max}) is 130 ng/ml in the rapid release type pharmaceutical preparation, while 43.1 ng/ml in the present pharmaceutical preparation and is about one third of the above. The mean absorption time (MAT) calculated by the conventional method is 0.87 hours in the rapid release pharmaceutical preparation, while 7.12 hours in the pharmaceutical preparation of the present invention and shows about eight times absorption time of the above. From this, it is demonstrated that the pharmaceutical preparation of the present invention can control the blood concentration of a drug by formulation thereof, and it can be used for inhibiting the rapid increase in blood concentration of a drug and manifestation of the side effect and clinically decreasing the administration times.

EFFECT OF THE INVENTION

According to the present invention, there is provided a polymer matrix type pharmaceutical preparation for sustained release of a drug which comprises as a main base hydroxypropylmethylcellulose and the release properties of a principal agent can be controlled arbitrarily and a process for producing the same.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1

A graph which indicates the change as a function of time in the weight of the pharmaceutical preparation for sustained release of a drug of the present invention comprising as
a main base hydroxypropylmethylcellulose. Figure 1 (a) indicates the change in the wet weight and Figure 1 (b) indicates the change in the dry weight as a function of time.

**Figure 2**

A graph which indicates the release properties of the pharmaceutical preparation for sustained release of a drug of the present invention. Figure 2 (a) indicates the change in water retention and Figure 2 (b) indicates the change in disintegrating rate as a function of time.

**Figure 3**

A graph which indicates the change in the drug release from the pharmaceutical preparation for sustained release of a drug of the present invention. Figure 3 (a) indicates the case of Disintegrating Medium of The Pharmacopoeia of Japan, pH 1.2, Figure 3 (b) 0.1 M phosphate buffer, pH 4.0, and Figure 3 (c) Disintegrating Medium of The Pharmacopoeia of Japan, pH 6.8.

**Figure 4**

A graph which indicates the relation between the lactose/HPMC content ratio and mean dissolution time.

**Figure 5**

A graph which indicates dissolution properties of the drugs having various degrees of the solubility. Figure 5 (a) shows the case of procain hydrochloride, acetaminophen and theophylline, Figure 5 (b) shows the case of methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate and propyl p-hydroxybenzoate, and Figure 5 (c) shows the case of adinazolam methanesulfonate and U-78875.

**Figure 6**

A graph which indicates the relation between the drug solubility and mean dissolution time.

**Figure 7**

A graph which indicates the relation between the drug solubility and mean dissolution time.

**Figure 8**

A graph which schematically indicates that a point of inflection in the relation of solubility-mean dissolution time is varied by the drug content.

**Figure 9**

A graph which indicates a release curve in which a drug having the solubility of 0.1 mg/ml is released from the pharmaceutical preparation for sustained release of a drug containing 1.5 mg of the said medicine.

**Figure 10**

A graph which indicates the change as a function of time in the plasma concentration of
adinazolam methanesulfonate in beagle dogs.
<table>
<thead>
<tr>
<th>Example</th>
<th>Content ratio (lactose/HPMC)</th>
<th>Mean dissolution time</th>
<th>pH 6.8&lt;sup&gt;a&lt;/sup&gt;</th>
<th>pH 4.0&lt;sup&gt;b&lt;/sup&gt;</th>
<th>pH 1.2&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0.61</td>
<td>5.68±0.27</td>
<td>3.91±0.31</td>
<td>2.96±0.04</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.47</td>
<td>6.32±0.11</td>
<td>4.17±0.31</td>
<td>3.38±0.02</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0.35</td>
<td>7.05±0.12</td>
<td>4.54±0.23</td>
<td>3.82±0.26</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0.25</td>
<td>7.75±0.12</td>
<td>4.54±0.23</td>
<td>3.86±0.15</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>0.47</td>
<td>6.70±0.15</td>
<td>4.25±0.01</td>
<td>3.42±0.10</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0.47</td>
<td>6.60±0.34</td>
<td>4.14±0.04</td>
<td>3.20±0.13</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>0.47</td>
<td>6.19±0.08</td>
<td>4.06±0.05</td>
<td>3.11±0.04</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> : Disintegrating Test 2nd Medium of the Pharmacopoeia of Japan  <br>
<sup>b</sup> : 0.1 M phosphate buffer  <br>
<sup>c</sup> : Disintegrating Test 2nd Medium of The Pharmacopoeia of Japan  <br>
Each values are mean ± S.D. (n=6).
TABLE 2

<table>
<thead>
<tr>
<th>Subject Drug</th>
<th>T 25%</th>
<th>% 50%</th>
<th>T 75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>alprazolam</td>
<td>1.0–2.0</td>
<td>3.5–4.5</td>
<td>8.0–9.0</td>
</tr>
<tr>
<td>triazolam</td>
<td>1.0–2.0</td>
<td>3.5–4.5</td>
<td>8.0–9.0</td>
</tr>
<tr>
<td>ibuprofen</td>
<td>1.0–2.0</td>
<td>3.5–4.5</td>
<td>8.0–9.0</td>
</tr>
</tbody>
</table>

T 25%, T 50% and T 75% represent the time necessary for dissolving 25%, 50% and 75% of the total drug, respectively.
CLAIMS

1. A polymer matrix type pharmaceutical preparation for sustained release of a drug which comprises as a main base hydroxypropylmethylcellulose, wherein the drug is released according to the following formula:

   \( Q_d = S_s \left( \frac{D V_1}{r} t \right)^{\frac{1}{2}} \)

   \( Q_d = S_s \left( \frac{2D V_1}{r} \frac{A C_s}{t} \right)^{\frac{1}{2}} \)

   \( Q_r = Q \cdot \left( 1 - (1 - k_2 t)^{1/3} \right) \)

   wherein \( C_s \) is the solubility of the drug, \( A \) is the total amount of the drug present in the unit volume of the matrix, \( V_1 \) is the effective volume in the interior of the matrix, \( Q_d \) is the drug releasing amount after \( t \) hours, \( S_s \) is the total surface area, \( D \) is the diffusion coefficient of the drug in the matrix, \( \tau \) is the tortuosity in the capillary tube system, \( Q_r \) is the total drug releasing amount, \( Q_o \) is the amount of the drug contained in one pharmaceutical preparation, \( k_2 \) is the apparent rate constant for releasing the drug from a drug granule.

2. The pharmaceutical preparation for sustained release of a drug according to claim 1, wherein the drug is adinazolam methanesulfonate, alprazolam or triazolam.

3. A process for producing a pharmaceutical preparation for sustained release of a drug which comprises wet-granulating a drug using a binder, and drying it to obtain a granule, mixing the granule with hydroxypropylmethylcellulose and a water-soluble ingredient, then compressing it to obtain a polymer matrix type pharmaceutical preparation for sustained release of a drug comprising as a main base hydroxypropylmethylcellulose so that the drug is released according to the following formula:
(a) in the case where \( V_t C_s > A \),

\[
Q_s = S_s \left[ \frac{D V_i}{\tau} t \right]^{\frac{1}{2}}
\]

(b) in the case where \( V_t C_s \leq A \),

\[
Q_s = S_s \left[ \frac{2 D V_i}{\tau} A C_s t \right]^{\frac{1}{2}}
\]

(c) in the case where \( V_t C_s \ll A \),

\[
Q_t = Q_s \{ 1 - (1 - k_2 t)^2 \}
\]

wherein \( C_s \) is the solubility of the drug, \( A \) is the total amount of the drug present in the unit volume of the matrix, \( V_i \) is the effective volume in the interior of the matrix, \( Q_s \) is the drug releasing amount after \( t \) hours, \( S_s \) is the total surface area, \( D \) is the diffusion coefficient of the drug in the matrix, \( \tau \) is tortuosity of the capillary tube system, \( Q_t \) is the total drug releasing amount, \( Q_s \) is the amount of the drug contained in one preparation, \( k_2 \) is the apparent rate constant for releasing the drug from a drug granule.
(a) Change as a function of time in wet weight (mean±S.D. (n=5))

(b) Change as a function of time in dry weight (mean±S.D. (n=3))
FIGURE 2

(a) Change as a function of time in water retention

(b) Change as a function of time in disintegration rate
FIGURE 3

Drug dissolution (Disintegrating Medium of the Pharmacopoeia of Japan, p81.2)

(a) Lactose/HPMC (w/v): 0.61
    Lactose/HPMC (w/v): 0.47
    Lactose/HPMC (w/v): 0.35
    Lactose/HPMC (w/v): 0.25

(b) Drug dissolution (0.1M phosphate buffer, p84.0)

(c) Drug dissolution (Disintegrating Medium of the Pharmacopoeia of Japan, p85.8)
Relation between content ratio of lactose/HPMC and mean dissolution time (mean±S.D. (n=6))

- Disintegrating medium of the Pharmacopoeia of Japan, pH 1.2
- 0.1M phosphate buffer, pH 4.0
- Disintegrating medium of the Pharmacopoeia of Japan, pH 6.8
FIGURE 5

(a) Relation between the solubility of the drug and dissolution rate (mean ± S.D. (n=3))
- procaïn hydrochloride
- acetoaminophen
- theophylline

(b) Relation between the solubility of the drug and dissolution rate (mean ± S.D. (n=3))
- methyl p-hydroxybenzoate
- ethyl p-hydroxybenzoate
- propyl p-hydroxybenzoate

(c) Relation between the solubility of the drug and dissolution rate (mean ± S.D. (n=3))
- adinaolamine methanesulfonate
- U-78875
Relation between the solubility of the drug and mean dissolution time.

- Propyl p-hydroxybenzoate
- Adinazolam methanesulfonate
- Ethyl p-hydroxybenzoate
- Theophylline
- Acetaminophen
- Methyl p-hydroxybenzoate
- Procain hydrochloride

Axes:
- Mean dissolution time (h) on the y-axis
- Solubility (mg/ml) on the x-axis
Relation between the solubility of the drug and mean dissolution time

\[ V_1 C_s < A \quad V_1 C_s < A \quad V_1 C_s > A \]

solubility
Influence of the amount of the drug contained in one pharmaceutical preparation in the solubility of the drug — mean dissolution time

- 1.875 %
- 3.750 %
- 7.500 %
- 15.00 %
- 30.00 %
Release curve from a pharmaceutical preparation for sustained release of a drug which contains 1.5mg of a drug having 0.1mg/ml of the solubility.
Change in plasma concentration of adinazolam methanesulfonate in beagle dogs as a function of time after administration of the rapid release preparation.

- ○: after normal oral administration
- ●: after oral administration of the sustained release preparation
- ▲: after oral administration of the rapid release preparation

Plasma concentration of adinazolam methanesulfonate (mg/mL)

(hour)
### I. CLASSIFICATION OF SUBJECT MATTER

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

Int.Cl. 5 A61K9/20

### II. FIELDS SEARCHED

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### III. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of Document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to Claim No.</th>
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</table>
| X        | JOURNAL OF CONTROLLED RELEASE vol. 5, no. 2, September 1987, AMSTERDAM (NL) pages 159 - 172  
R.M. FRANZ ET AL. *in vitro evaluation of a mixed polymeric sustained release matrix using response surface methodology*  
see page 160, paragraph "materials"  
see page 163; figure 1 | 1,2 |

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* Special categories of cited documents:
  - 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
  - I: 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

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

* V: 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.

* A: document member of the same patent family

### IV. CERTIFICATION

Date of the Actual Completion of the International Search  
14 JUNE 1993

Date of Mailing of this International Search Report

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

BENZ K.F.
<table>
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<td>X</td>
<td>JOURNAL OF CONTROLLED RELEASE&lt;br&gt;vol. 14, no. 1, September 1990, AMSTERDAM (NL)&lt;br&gt;pages 1 - 10, XP150659&lt;br&gt;T.C. DAHL ET AL. 'influence of physico-chemical properties of hydroxypropyl methylcellulose on naproxen release from sustained release matrix tablets'&lt;br&gt;see the whole document</td>
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<td>JOURNAL OF CONTROLLED RELEASE&lt;br&gt;vol. 9, no. 2, July 1989, AMSTERDAM (NL)&lt;br&gt;pages 169 - 175, XP29272&lt;br&gt;A.C. SHAH ET AL. 'gel-matrix systems exhibiting bimodal controlled release for oral drug delivery'&lt;br&gt;SEE PAGE 170, PARAGRAPH &quot;MATERIALS&quot;&lt;br&gt;see page 171; table 1</td>
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<tr>
<td>X</td>
<td>EP,A,0 440 462 (MERCK &amp; CO. INC.)&lt;br&gt;7 August 1991&lt;br&gt;see the whole document</td>
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