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(54) Title: GRANULAR COMPOSITION

(57) Abstract: The dissolution rate of a therapeutically active compound in an aqueous liquid is increased by: i) preparing an essentially dry mixture consisting essentially of a) a therapeutically active compound and b) a cellulose ether, ii) compacting the resulting mixture under pressure and iii) comminuting the compacted mixture.

GRANULAR COMPOSITION

This invention relates to a novel granular composition which comprises a therapeutically active compound and a cellulose ether as well as to the use of the novel granular composition in a pharmaceutical composition for oral administration.

Background of the Invention

In designing pharmaceutical compositions for oral administration, achieving the desired bioavailability of the therapeutically active compound is important for efficacy and safety reasons. The aqueous solubility of the therapeutically active compound and permeation of the dissolved compound across the walls of the gastrointestinal tract and into the blood stream are known to be important factors influencing the bioavailability of therapeutically active compounds. Particularly regarding a poorly water-soluble therapeutically active compound, it is generally acknowledged that the rate of dissolution can be the rate-determining step of absorption.

Accordingly, much research has been undertaken to improve the bioavailability of therapeutically active compounds and particularly to improve the dissolution rate of poorly water-soluble drugs.

U.S. Patent No. 5,093,372 discloses a pharmaceutical composition comprising a physical mixture of exifone and a water-soluble hydroxypropyl methyl cellulose ether, a hydroxypropyl cellulose ether or a methyl cellulose ether. The U.S. Patent discloses that by coexistence of exifone and the mentioned water-soluble polymer the drawback that exifone is sparingly soluble in water is improved and high bioavailability can be attained upon oral administration. According to one way of producing the pharmaceutical composition, exifone is dissolved in an organic solvent, such as ethanol, then the cellulose ether is dissolved in this solution and the solvent is evaporated. Conventional additives can be incorporated in the solution or compounded with the solid dispersion obtained upon evaporation of the solvent. According to another way of producing the pharmaceutical composition, exifone is mixed with the water soluble cellulose ether and the mixed powder is kneaded with a suitable kneading solvent. However, especially in large scale processes the use of an

organic solvent is not desired because the recycling and/or disposal of large volumes of organic solvents is disadvantageous. The use of an organic solvent for preparing compositions intended for oral applications might also cause environmental or health concerns.

U.S. Patent No. 6,045,829 discloses formulations of nanoparticulate HIV protease inhibitors comprising a cellulosic surface stabilizer. The nanoparticulate formulations are said to have an increased rate of dissolution in vitro and an increased rate of absorption in vivo. The nanoparticulate HIV protease inhibitors have a cellulosic surface stabilizer absorbed thereon in an amount sufficient to maintain an effective average particle size of less than about 1000 nm. The nanoparticulate HIV protease inhibitor particles are prepared by wet milling of an HIV protease inhibitor. The HIV protease inhibitor can be milled in the presence of the cellulosic surface stabilizer or the drug particles can be contacted with the cellulosic surface stabilizer following the milling process. Unfortunately, this wet-milling procedure may require several days to complete, requires a large amount of grinding media, such as zirconium oxide or polymeric beads, and poses significant difficulties when scaling up from laboratory-scale to a production-scale.

U.S. Patent No. 5,861,172 discloses compacted granulates of a mixture of 99.9-90 weight percent, most preferably 98.75-96.5 weight percent of an antibiotic and 0.1 to 10 weight percent, most preferably 1.25-3.5 weight percent of an intragranular disintegrant selected from starches, such as maize starch, rice starch, cross-linked N-vinyl-2-pyrrolidone, sodium starch glycollate, croscarmellose sodium and formaldehyde-casein. The U.S. patent teaches that the intimate contact between the antibiotic and the intragranular disintegrant in the granulate appears to assist in improved disintegration and dispersion of the granulate in contact with water to release antibiotic particles and to provide finely dispersed suspensions. The compacted granules can be used in encapsulated formulations or can be compacted together into a tablet form together with a wide variety of extra-granular disintegrants and optionally also an extra-granular lubricant. In the tablet formulation the granulate amounts to 70 percent or more, most preferably 95 percent or more of the total tablet weight. Unfortunately, the U.S patent does not teach how to increase the dissolution rate of sparingly water-soluble drugs.

U.S. Patent No. 5,340,591 discloses a method of producing a solid dispersion of the sparingly water-soluble drug nilvadipine in a water-soluble polymer, such as hydroxypropyl

methyl cellulose or methyl cellulose, wherein the drug and the water-soluble polymer are mixed and heated below the melting points of the two components. However, heating of a drug is often undesirable because it increases the risk of drug decomposition or degradation.

Accordingly, it would be desirable to find a new method of increasing the dissolution rate of a therapeutically active compound in an aqueous liquid. It would be particularly desirable to find a new method which is efficient, can be readily scaled up from laboratory scale to production scale, and does not make use of an organic solvent or of heat.

Summary of the Invention

One aspect of the present invention is a method of increasing the dissolution rate of a therapeutically active compound in an aqueous liquid which comprises the steps of
i) preparing an essentially dry mixture consisting essentially of a) a therapeutically active compound and b) a cellulose ether,
ii) compacting the resulting mixture under pressure and
iii) comminuting the compacted mixture.

It has surprisingly been found that the dissolution rate of poorly water-soluble therapeutically active compounds can be substantially more increased by the method of the present invention than by preparing a corresponding dry-blended, non-compressed physical mixture of the therapeutically active compound a) and the cellulose ether b).

Another aspect of the present invention is a dry-granulated composition which consists essentially of
a) a therapeutically active compound and
b) a cellulose ether,
wherein the dry-granulated composition comprises agglomerates of the compound a) and the cellulose ether b) and at least 10 weight percent of the dry-granulated composition has a particle size of greater than 425 micrometers.

Yet another aspect of the present invention is the use of an above-mentioned dry-granulated composition for preparing a pharmaceutical composition for oral administration.

Yet another aspect of the present invention is a method of preparing a pharmaceutical composition for oral administration wherein an above-mentioned dry-granulated composition is blended with a liquid or solid excipient and compounded to produce the pharmaceutical composition.

Yet another aspect of the present invention is a pharmaceutical composition for oral administration which comprises the above-mentioned dry-granulated composition.

Detailed Description of the Invention

The dry-granulated composition of the present invention consists essentially of the therapeutically active compound a) and the cellulose ether b). The term "consists essentially of" means that the combined weights of a) and b) are at least 80 weight percent, preferably at least 90 weight percent, more preferably at least 95 weight percent, most preferably at least 98 weight percent, based on the total weight of the dry-granulated composition.

The present invention is particularly suitable for poorly water-soluble drugs, that means drugs with a low solubility in water resulting in a poor bioavailability after oral administration. The term "low solubility" is meant to encompass all drugs in which the aqueous solubility of the drug hinders its oral administration. Poorly water-soluble drugs generally have an aqueous solubility of less than 33 mg/mL, typically less than 10 mg/mL, more typically less than 1 mg/mL. The term "poorly water-soluble" is used herein synonymously to other terms known in the art, such as "sparingly water-soluble", "water-insoluble" or "practically water-insoluble". Examplary of poorly water-soluble drugs are exifone, phenacetin, phenytoin, digitoxin, nilvadipine, diazepam, griseofulvin, chloramphenicol, danazol, cyclosporine, or, preferably, naproxen, nifedipine or carbamazepine.

Furthermore, the dry-granulated composition of the present invention comprises a cellulose ether b). The cellulose ether is preferably water-soluble at a temperature of up to 40°C. Generally, suitable cellulose ethers are alkyl cellulose ethers, preferably methyl cellulose ethers; or alkyl hydroxyalkyl cellulose ethers, preferably C_1-C_3-alkyl hydroxy-C_{1-3}-alkyl cellulose ethers, more preferably hydroxypropyl methyl cellulose ethers; or hydroxyalkyl cellulose ethers, preferably hydroxy-C_{1-3}-alkyl cellulose ethers, more preferably hydroxypropyl cellulose ethers; or mixed hydroxyalkyl cellulose ethers, preferably mixed hydroxy-C_1-C_3-alkyl cellulose ethers. Methyl cellulose ethers and hydroxypropyl methyl cellulose ethers are particularly preferred. The most preferred cellulose ethers are methyl cellulose ethers with a methoxyl substitution of from 21 to 42 percent, more preferably from 26 to 33 percent, and methyl hydroxypropyl cellulose ethers with a methoxyl substitution of from 16 to 33 percent, more preferably from 19 to 30 percent, and a hydroxypropoxyl substitution of from 1 to 32 percent, preferably from 3 to 12 percent. Methylcellulose ethers generally will have a non-methoxyl substitution content of about 5% or less, more preferably about 1 percent or less, if they contain any measurable non-methoxyl substitution. The viscosity of the cellulose ether preferably is up to 4000 mPa·s, more preferably up to 100 mPa·s, most preferably up to 10 mPa·s, measured as a 2 weight percent aqueous solution at 20 °C using an Ubbelohde viscosimeter. The viscosity of the cellulose ether is generally 0.1 mPa·s or more, typically 3 mPa·s or more, measured as indicated above.

The dry-granulated composition generally comprises a) from 9 to 91 weight percent, preferably from 16 to 84 weight percent, more preferably from 25 to 75 weight percent, most preferably from 40 to 60 weight percent of the therapeutically active compound, b) from 9 to 91 weight percent, preferably from 16 to 84 weight percent, more preferably from 25 to 75 weight percent, most preferably from 40 to 60 weight percent of the cellulose ether, and c) from 0 to 20 weight percent, preferably from 0 to 10 weight percent, more preferably from 0 to 5 weight percent, most preferably from 0 to 2 weight percent of an excipient other than the cellulose ether b), the amounts of a), b) and c) being based on the total weight of the dry-granulated composition. The total amount of a) and b) is at least 80 weight percent, preferably at least 90 weight percent, more preferably at least 95 weight

percent, most preferably at least 98 weight percent, based on the total weight of the dry-granulated composition.

Excipients other than cellulose ethers which can be incorporated in the dry-granulated composition of the present invention as component c) are generally solid at room temperature and pharmaceutically inert. Their amount should be low enough that the excipient does not substantially decrease the effect of the cellulose ether b) on the dissolution rate of the therapeutically active compound a). Suitable amounts of the excipient, if present, are indicated above. Exemplary of pharmaceutically inert excipients are diluents, such as crystalline cellulose, starch, D-mannitol or lactose; surfactants such as sodium laurel sulfate, polyethylene glycols, or polysorbates; binders; lubricants such as magnesium stearate; or desintegrants, such as hydroxypropyl starch or starch-glycolate.

If the dry-granulated composition of the present invention comprises more than one type of therapeutically active compounds a) or cellulose ethers b) or excipients c), the weight amounts of the total of compounds a), the total of cellulose ethers b) and the total of excipients c) is generally within the ranges indicated above.

At least 10 weight percent, preferably at least 20 weight percent, more preferably at least 30 weight percent of the dry-granulated composition has a particle size of greater than 425 micrometers. Generally at least 20 weight percent, preferably at least 30 weight percent, more preferably at least 40 weight percent of the dry-granulated composition has a particle size of greater than 250 micrometers. Preferably less than 30 weight percent, more preferably less than 25 weight percent of the dry-granulated composition has a particle size of less than 75 micrometers. By "particle size" is meant the size of the sieve mesh on which the particles are excluded. The average particle size of the dry-granulated composition of the present invention is preferably at least 5 micrometers, more preferably at least 10 micrometers.

The above-described composition of the present invention is dry-granulated. By the term "dry-granulated" is meant that not more than about 10 percent, preferably not more than about 5 percent, more preferably not more than about 2 percent of a liquid has been

added prior to or during granulation, based on the total weight of the composition, if any liquid has been added at all. Some liquid can be added to the composition to be granulated, for example to reduce dust, however the presence of liquid is not required and its amount should be within the limits indicated above. Most preferably, the dry-granulated composition of the present invention is free from solvent residues. By visual comparison of the composition under the microscope, it is discernible whether the composition is dry-granulated or whether it has been produced by a conventional wet granulation method requiring the presence of a liquid, such as water or an organic solvent.

Surprisingly, it has been found that by the method of the present invention described in detail below the dissolution rate of the therapeutically active compound a) in an aqueous liquid can be substantially increased.

In step i) of the method of the present invention, an essentially dry mixture of components a) and b) and optionally c) may be mixed in a known mixing device, such as a V-blender. An "essentially dry mixture" means that not more than about 10 percent, preferably not more than about 5 percent, more preferably not more than about 2 percent of a liquid, based on the total weight of the mixture, has been added to the mixture if any liquid has been at all. Preferred therapeutically active compounds a), preferred cellulose ethers b), optional excipients c) and preferred weight ranges of the components a) and b) and the optional excipient c) are indicated above. The mixing is preferably carried out at room temperature.

In step ii) of the method of the present invention, the resulting mixture is compacted under pressure. The pressure generally is at least 1,000 psi (6.9 MPa), preferably at least 5,000 psi (34.5 MPa), more preferably at least 10,000 psi (69 MPa). Any conventional methods and devices for compacting the mixture known in the art can be used. A preferred method is by slugging on a tablet press, such as a rotary tablet press. The most preferred method is by roller compaction. The compacted mixture typically has a coherent structure, such as a ribbon or a slug.

In step iii) of the method of the present invention, the compacted mixture is comminuted to a granular composition. Generally at least 10 weight percent, preferably at least 20 weight percent, most preferably at least 30 weight percent of the granular

composition has a particle size of greater than 425 micrometers and/or generally at least 20 weight percent, preferably at least 30 weight percent, more preferably at least 40 weight percent has a particle size of greater than 250 micrometers and/or preferably less than 30 weight percent, more preferably less than 25 weight percent of the granular composition has a particle size of less than 75 micrometers. Any conventional comminution method and device may be used, including bill mills, co-mills, or other communition devices known in the art.

Some liquid can be added to the essentially dry mixture obtained in step i) prior to or during the compacting and comminuting steps ii) and iii), for example to reduce dust, however the presence of liquid is not required and its total amount should be within the limits indicated further above. Preferably, no substantial amount of heat is added to the essentially dry mixture obtained in step i) prior to or during the compacting and comminuting steps ii) and iii). By "no substantial amount" is meant that the mixture is not subjected to an external heat source with the purpose to raise the temperature of the mixture. Most preferably, steps i), ii) and iii) of the method of the present invention are carried out without addition of a liquid and without use of an external heat source.

The dry-granulated composition prepared as described above has a drug dissolution rate which is considerably higher than I) the drug dissolution rate of the same, but non-diluted therapeutically active compound a) and II) the drug dissolution rate of a corresponding dry-blended, non-compressed physical mixture of the therapeutically active compound a) and the cellulose ether b) and an optional excipient c). The difference in dissolution rate depends on various factors, such as the characteristics of the therapeutically active compound a) and the type and viscosity of the cellulose ether b). However, after 2.5 minutes typically at least 10 times as much, in most cases even at least 15 times as much therapeutically active compound a) is dissolved in water when the dry-granulated composition prepared as described above is contacted with water, than when the therapeutically active compound a) alone is contacted with water. Moreover, after 2.5 minutes typically at least 1.5 times as much, in most cases at least 2 times as much, in the most preferred cases even at least 5 times as much therapeutically active compound a) is dissolved in water when the dry-granulated composition prepared from a) and b) and optionally c) as described above is contacted with water than when a corresponding dry-

blended, non-compressed physical mixture of a) and b) and optionally c) is contacted with water.

The dry-granulated composition prepared as described above is useful for preparing a pharmaceutical composition for oral administration. The dry-granulated composition can be blended with a liquid or solid excipient and compounded to a pharmaceutical composition in a known manner. For example, the dry-granulated composition can be combined with known excipients, such as those listed further above, and compounded to tablets. However, the dry-granulated composition is particularly useful in the preparation of capsules which are filled with the dry-granulated composition of the present invention.

The present invention is further illustrated by the following examples which should not be construed to limit the scope of the present invention. All parts and percentages are by weight unless otherwise indicated. The viscosities are indicated as a 2 percent by weight aqueous solution at 20°C, measured using an Ubbelohde viscosimeter.

EXAMPLE 1

200 g of the drug naproxen and 200 g of a hydroxypropyl methyl cellulose ether, commercially available from The Dow Chemical Company under the Trademark METHOCEL K3PLV cellulose ether are dry blended in a V-blender for 20 minutes. The hydroxypropyl methyl cellulose ether has a methoxyl substitution of 19-24 percent, a hydroxypropoxyl substitution of 7-12 percent and a viscosity of 3 mPa·s. The resulting physical mixture is roller compacted using smooth rolls on a Freund roller compactor, Model mini, commercially available from Vector Corporation, Marion, Iowa under the following conditions:

Screw Motor: 8.0 RPM, 0.6 amps
Roll Motor: 2.0 RPM, 1.3 amps
Roll Force: 3 tons (29.4 kN).

The resulting ribbons are milled with a CoMil, Model 197S from Quadro Engineering, Waterloo, Ontario, Canada at 1000 RPM.

EXAMPLE 2

Example 1 is repeated except that nifedipine is used as a drug instead of naproxen.

EXAMPLE 3

150 g of carbamazepine and 150 g of METHOCEL K3PLV cellulose ether are dry blended as described in Example 1. The resulting physical mixture is roller compacted and milled as described in Example 1 except that the Freund roller compactor is run under the following conditions.

Screw Motor: 4.0 RPM, 0.3 amps

Roll Motor: 2.0 RPM, 1.3 amps

Roll Force: 3 tons (29.4 kN)

EXAMPLE 4

25.0 g of naproxen and 25.0 g of METHOCEL K3PLV cellulose ether are dry blended in a glass jar for 10 minutes. Slugs are compressed from the resulting physical mixture on a commercially available Carver Press (Model C) using the following conditions:

Punch and Die:	0.8755 in (22.2 mm) diameter, round, flat faced
Compression Force:	10,200 lb_f (45.4 kN)
Dwell Time:	10 sec
Slug Weight:	500-600 mg

The resulting slugs are milled as described in Example 1 except that the mill is run at 1450 RPM instead of at 1000 RPM.

EXAMPLE 5

Example 4 is repeated except that nifedipine is used as a drug instead of naproxen.

EXAMPLE 6

Example 4 is repeated except that carbamazepine is used as a drug instead of naproxen.

Comparative Examples A to C

10 g METHOCEL K3PLV cellulose ether is dry blended with 10 g of the drug naproxen (Comparative Example A) or with 10 g of the drug nifedipine (Comparative Example B) or with 10 g of the drug carbamazepine (Comparative Example C) in a glass jar for 20 minutes.

EXAMPLE 7

Example 4 is repeated, except that 20.0 g of the drug naproxen from a different lot than in Example 4 is dry blended with 20.0 g of a hydroxypropyl methyl cellulose ether, commercially available from The Dow Chemical Company under the Trademark METHOCEL E3PLV cellulose ether. The hydroxypropyl methyl cellulose ether has a methoxyl substitution of 28-30 percent, a hydroxypropoxyl substitution of 7-12 percent and a viscosity of 3 mPa·s.

Comparative Example E

Comparative Example A is repeated except that the drug naproxen from the same lot as in Example 7 and the same hydroxypropyl methyl cellulose ether as in Example 7 are used.

EXAMPLE 8

Example 7 is repeated, except that a hydroxypropyl methyl cellulose ether, commercially available from The Dow Chemical Company under the Trademark METHOCEL E5PLV cellulose ether is used. The hydroxypropyl methyl cellulose ether has a methoxyl substitution of 28-30 percent, a hydroxypropoxyl substitution of 7-12 percent and a viscosity of 5 mPa·s.

Comparative Example F

Comparative Example E is repeated except that the same methyl cellulose ether as in Example 8 is used.

EXAMPLE 9

Example 4 is repeated, except that a methyl cellulose ether, commercially available from The Dow Chemical Company under the Trademark METHOCEL A4M cellulose ether is used. The methyl cellulose ether has a methoxyl substitution of 27.5-31.5 percent and a viscosity of 4,000 mPa·s. The methyl cellulose ether is subjected to a molecular weight reduction with anhydrous hydrochloric acid whereby the viscosity is reduced from 4,000 mPa.s to 5.5 mPa.s. 30.0 g of the thus treated cellulose ether material is blended with 30.0 g

of naproxen, originating from the same lot as in Example 4, and the process of Example 4 is performed.

Comparative Example D

Comparative Example A is repeated except that the same methyl cellulose ether as in Example 9 with a viscosity of 5.5 mPa.s is used.

The particle size distributions of the dry-granulated compositions of Examples 1-9 and of the physical blends of Comparative Examples A to C were evaluated by sieving. Table I lists the weight percentage of the dry-granulated composition in each sieve cut.

Table I

	> 425 µm sieve cut	250-425 µm sieve cut	150-250 µm sieve cut	75-150 µm sieve cut	< 75 µm sieve cut
Comparative Example A (Physical Mixture)	2%	4%	18%	21%	55%
Example 1 (Roller compacted)	57%	10%	9%	8%	16%
Example 4 (Slugged)	31%	13%	22%	13%	20%
Example 7 (Slugged)	43%	11%	10%	17%	18%
Example 8 (Slugged)	32%	14%	19%	21%	14%
Example 9 (Slugged)	33%	10%	12%	26%	18%
Comparative Example B (Physical Mixture)	7%	12%	18%	23%	39%
Example 2 (Roller compacted)	58%	9%	8%	11%	14%
Example 5 (Slugged)	30%	12%	19%	18%	22%
Comparative Example C (Physical Mixture)	3%	19%	27%	18%	32%
Example 3 (Roller compacted)	57%	8%	7%	9%	19%
Example 6 (Slugged)	34%	12%	14%	16%	24%

The dissolution rates of commercially available drugs and of drugs in the compositions of Examples 1 to 9 and Comparative Examples A to F were tested in a DisTek dissolution apparatus II (paddles) at 100 RPM (revolutions per minute) using a method set forth in the United States Pharmacopeia. 100 mg of drug equivalent (100 mg or 200 mg of

powder) were added to 900 mL of deionized water at 37°C. Each value in Tables II and III below is the mean concentration (mg/L) of drug dissolved in the dissolution media at the indicated times for three trials. Where two values are shown for a time point, the entire run was repeated on a separate day with fresh deionized water to assess the reproducibility of the data. High performance liquid chromatography (HPLC) assay for drug content was performed to characterize the product.

For preparing Examples 1, 4 and 9 and Comparative Examples A and D naproxen from the same lot was used. The dissolution rates in Examples 1, 4 and 9 and in Comparative Examples A and D were compared with the dissolution rate of pure naproxen from the same lot. These results are listed in Table II below.

A considerably different dissolution rate of the pure drug was observed when naproxen originating from a different lot was used. The data presented in Table III below are all based on naproxen originating from one lot, which is different from the lot used to prepare the data presented in Table II.

Table II

	Mean concentration of dissolved drug (mg/L) after x minutes (min.)					
Elapsed Time	2.5 min.	5 min.	10 min.	15 min.	30 min.	60 min.
Naproxen, as received	0.2	0.7	2.6	5.2	14.7	27.7
Comparative Example A (Physical Mixture)	3.0, 2.5	9.1, 8.2	18.0, 17.4	23.0, 22.3	29.3, 28.5	32.2, 31.3
Example 1 (Roller compacted)	7.1, 6.7	16.4, 16.8	25.5, 26.4	29.1, 29.8	32.7, 33.0	34.4, 34.6
Example 4 (Slugged)	8.8, 7.3	18.2, 17.1	26.1, 26.7	29.1, 29.7	32.1, 32.5	33.8, 34.0
Comparative Example D (Physical Mixture)	10.6	20.4	27.7	30.9	35.9	37.7
Example 9 (Slugged)	19.3	27.6	33.4	35.8	38.7	39.6
Nifedipine, as received	0.1	0.4	1.2	2.1	5.1	9.8
Comparative Example B (Physical Mixture)	0.3	0.8	1.9	2.7	4.6	6.6
Example 2 (Roller compacted)	3.3	7.8	10.9	12.0	12.9	13.2
Example 5 (Slugged)	2.3, 2.2	5.2, 5.5	7.5, 8.2	8.4, 9.2	9.5, 10.3	9.8, 10.9
Carbamazepine, as received	1.2	3.3	8.3	13.4	28.6	> 40*)

	Mean concentration of dissolved drug (mg/L) after x minutes (min.)					
Elapsed Time	2.5 min.	5 min.	10 min.	15 min.	30 min.	60 min.
Comparative Example C (Physical Mixture)	1.7	5.8	15.1	23.1	39.1	> 40*)
Example 3 (Roller compacted)	24.8	> 40*)	> 40*)	> 40*)	> 40*)	> 40*)
Example 6 (Slugged)	19.4, 18.6	39.7, 39.1	> 40*)	> 40*)	> 40*)	> 40*)

*) The measuring device is only capable of measuring a carbamazepine concentration of up to 40 mg/L. The listed concentration is higher.

Table III

	Mean concentration of dissolved drug (mg/L) after x minutes (min.)					
Elapsed Time	2.5 min.	5 min.	10 min.	15 min.	30 min.	60 min.
Naproxen, as received, different lot than in Table II	2.2, 1.7	6.1, 6.9	15.3, 19.2	23.0, 27.2	37.2, 39.6	45.5, 45.1
Comparative Example E (Physical Mixture)	8.5	19.4	31.5	36.8	41.3	43.0
Example 7 (slugged)	16.7	30.2	39.3	41.9	43.9	44.8
Comparative Example F (Physical Mixture)	7.9	18.3	29.5	34.8	40.0	42.6
Example 8 (slugged)	14.6	27.7	37.5	40.5	43.2	44.4

Tables II and III illustrate that a dry-granulated composition prepared according to the present invention has a drug dissolution rate which is considerably higher than i) the drug dissolution rate of the same, but non-diluted therapeutically active compound and ii) the drug dissolution rate of a corresponding dry-blended, non-compressed physical mixture of the therapeutically active compound a) and a cellulose ether b).

Examples 10 to 16: Use of the dry-granulated compositions for preparing pharmaceutical compositions

EXAMPLE 10

5.0 g of the dry-granulated composition produced according to Example 1, 1.0 g of microcrystalline cellulose, 0.5 g of cross-linked sodium carboxymethylcellulose (trademark

Ac-Di-Sol), and 3.5 g of Fast-Flo lactose (#316) are blended in a glass jar for 10 minutes. 25 mg of magnesium stearate is added and the formulation is blended for an additional 1 minute. Tablets are compressed from the resulting mixture on a Carver Press (Model C) using the following conditions:

Punch and Die:	13/32 inch (10.3 mm) diameter, round, flat faced/beveled edge
Compression Force:	4000 lb_f (17.8 kN)
Dwell Time:	7 seconds
Tablet Weight:	400 mg.

EXAMPLE 11

2.0 g of the dry-granulated composition produced according to Example 2, 0.4 g of microcrystalline cellulose, 0.2 g of cross-linked sodium carboxymethycellulose (trademark Ac-Di-Sol), and 1.4 g of Fast-Flo lactose (#316) are blended in a glass jar for 10 minutes. 10 mg of magnesium stearate is added and the formulation is blended for an additional 1 minute. Tablets are compressed from the resulting mixture exactly as described in Example 10.

EXAMPLE 12

Example 11 is repeated, except that the dry-granulated composition produced according to Example 3 is used instead of the dry-granulated composition produced according to Example 2.

EXAMPLE 13

Example 10 is repeated, except that 5.0 g of the dry-granulated composition produced according to Example 9 is used instead of the dry-granulated composition produced according to Example 1.

EXAMPLE 14

200 mg of the dry-granulated composition produced according to Example 1 is hand-filled into a size 0 two-piece gelatin capsule, commercially available from Now Foods, Bloomingdale, Illinois.

EXAMPLE 15

Controlled release tablets are prepared as follows: 4.0 g of the dry-granulated composition produced according to Example 1, 2.0 g of a hydroxypropyl methyl cellulose ether, commercially available from The Dow Chemical Company under the Trademark METHOCEL K4MP CR cellulose ether, and 2.0 g of Fast-Flo lactose (#316) are blended in a glass jar for 10 minutes. The hydroxypropyl methyl cellulose ether has a methoxyl substitution of 19-24 percent, a hydroxypropoxyl substitution of 7-12 percent and a viscosity of 4,000 mPa·s. 25 mg of magnesium stearate is added and the formulation is blended for an additional 1 minute. Tablets are compressed from the resulting mixture exactly as described in Example 10.

EXAMPLE 16

Controlled release tablets are prepared as follows: 0.4 g of the dry-granulated composition produced according to Example 1, 1.2 g of METHOCEL K4MP CR cellulose ether, and 2.4 g of Fast-Flo lactose (#316) are blended in a glass jar for 10 minutes. 10 mg of magnesium stearate is added and the formulation is blended for an additional 1 minute. Tablets are compressed from the resulting mixture exactly as described in Example 10.

WHAT IS CLAIMED IS:

1. A dry-granulated composition consisting essentially of
a) a therapeutically active compound and
b) a cellulose ether,
wherein the dry-granulated composition comprises agglomerates of the compound a) and the cellulose ether b) and at least 10 weight percent of the dry-granulated composition has a particle size of greater than 425 micrometers.

2. The dry-granulated composition of Claim 1 comprising
a) from 9 to 91 weight percent of a therapeutically active compound,
b) from 9 to 91 weight percent of a cellulose ether, and
c) from 0 to 20 percent of an excipient other than the cellulose ether b),
the amounts of a), b) and c) being based on the total weight of the dry-granulated composition.

3. The dry-granulated composition of Claim 1 or Claim 2 wherein at least 30 weight percent of the dry-granulated composition has a particle size of greater than 425 micrometers.

4. The dry-granulated composition of any one of Claims 1 to 3 wherein less than 30 weight percent of the dry-granulated composition has a particle size of less than 75 micrometers.

5. The dry-granulated composition of any one of Claims 1 to 4 being free of solvent residues.

6. The dry-granulated composition of any one of Claims 1 to 5 wherein the cellulose ether has a viscosity of up to 4000 mPa·s as a 2 weight percent aqueous solution at 20°C.

7. The dry-granulated composition of any one of Claims 1 to 6 wherein the cellulose ether is a hydroxypropyl methyl cellulose ether or a methyl cellulose ether.

8. The dry-granulated composition of any one of Claims 1 to 7 wherein the therapeutically active compound a) is a poorly water-soluble drug.

9. The dry-granulated composition of any one of Claims 1 to 8 wherein the therapeutically active compound a) is naproxen, nifedipine, or carbamazepine.

10. Use of the dry-granulated composition of any one of Claims 1 to 9 for preparing a pharmaceutical composition for oral administration.

11. A method of preparing a pharmaceutical composition for oral administration wherein the dry-granulated composition of any one of Claims 1 to 9 to is blended with a liquid or solid excipient and compounded to produce the pharmaceutical composition.

12. A pharmaceutical composition for oral administration comprising the dry-granulated composition of any one of Claims 1 to 9.

13. The pharmaceutical composition of Claim 12 in the form of capsules filled with the dry-granulated composition of any one of Claims 1 to 9.

14. A method of increasing the dissolution rate of a therapeutically active compound in an aqueous liquid comprising the steps of
i) preparing an essentially dry mixture consisting essentially of a) a therapeutically active compound and b) a cellulose ether,
ii) compacting the resulting mixture under pressure and
iii) comminuting the compacted mixture.

15. The method of Claim 14 wherein the mixture is compacted at a pressure of at least 1,000 psi (6.9 MPa).

16. The method of Claim 14 or 15 wherein the mixture is compacted by slugging on a tablet press or by roller compaction.

17. The method of any one of Claims 14 to 16 wherein the dry-granulated composition of any one of Claims 1 to 10 is prepared.