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(54) Title: A SUSTAINED RELEASE COMPOSITION COMPRISING A HYDROXYPROPYL METHYLCELLULOSE ACETATE SUCCINATE

(57) Abstract: A sustained release composition comprises an active ingredient mixed with a hydroxypropyl methylcellulose acetate succinate having a total degree of substitution of acetyl and succinoyl groups, DSAc + DSS, of at least 0.75, wherein the concentration of hydroxypropyl methylcellulose acetate succinate is from 0.1 to 20 % by weight of the active ingredient, and wherein the active ingredient has a solubility in water of at least 1 mg/ml. The sustained release composition is useful for preparing oral dosage form where a drug is formulated with a reduced amount of excipient(s) to permit a reduction in the overall size of the dosage form and improve the swallowability without compromising the sustained release properties thereof.



A SUSTAINED RELEASE COMPOSITION COMPRISING A HYDROXYPROPYL METHYLCELLULOSE ACETATE SUCCINATE

5 FIELD

The present invention relates to a novel sustained release composition, preferably for oral administration, comprising an active ingredient and a hydroxypropyl methylcellulose acetate succinate.

10 INTRODUCTION

Sustained release dosage forms have found wide application in a variety of technology areas such as in personal care and agricultural applications, water treatment and in particular pharmaceutical applications. Sustained release dosage forms are designed to release a finite quantity of an active ingredient into an aqueous environment over an extended period of
15 time. Sustained release pharmaceutical dosage forms are desirable because they provide a method of delivering a long-lasting dose in a single application without overdosing. Known sustained release pharmaceutical dosage forms contain a drug or a vitamin whose release is controlled by a polymeric matrix which, for instance, may comprise one or more water-soluble cellulose ethers. Water-soluble cellulose ethers hydrate on the surface of a tablet to
20 form a gel layer. A fast formation of the gel layer is important to prevent wetting of the interior and disintegration of the tablet core. Once the gel layer is formed, it controls the penetration of additional water into the tablet. As the outer layer fully hydrates and dissolves, an inner layer must replace it and be sufficiently cohesive and continuous to retard the influx of water and control drug diffusion.

25 A commonly used cellulose ether for providing sustained release of an active ingredient from an oral dosage form is hydroxypropyl methylcellulose (HPMC). For instance, US 4,734,285 discloses that the release of an active ingredient can be prolonged by employing a fine particle sized HPMC as an excipient in a solid tablet. HPMC is used in commercial oral pharmaceutical formulations as a component of a polymeric matrix
30 providing sustained release of a drug usually at a concentration of 30% to 60% by weight of the oral dosage form.

It is a well-known problem in the pharmaceutical art that some patients, especially children or the elderly, or patients with dysphagia, find it difficult to swallow conventional oral dosage forms such as capsules or tablets. In particular, this is the case if the drug administered in the dosage form is a highly dosed drug which, when the drug is formulated with pharmaceutical excipients in the typical amounts included in commercial dosage forms, either makes each dosage form very large or requires the dose to be divided among two or more dosage forms that have to be swallowed at the same time.

It would therefore be desirable to develop a new sustained release composition for oral administration where a drug is formulated with a reduced amount of excipient(s) to permit a reduction in the overall size of the dosage form and improve the swallowability without compromising the sustained release properties thereof.

SUMMARY OF THE INVENTION

It has surprisingly been found that when a water-insoluble hydroxypropyl methylcellulose acetate succinate (HPMCAS) having a certain degree of substitution of acetyl and succinoyl groups is used as an excipient in admixture with an active ingredient, it is capable to provide sustained release of the active ingredient in the stomach of an individual ingesting the dosage form. This finding is very surprising because HPMCAS is known as enteric polymer. Enteric polymers are those that are resistant to dissolution in the acidic environment of the stomach. Dosage forms coated with HPMCAS are known to protect the drug from release in the acidic environment of the stomach but release the drug in the small intestine.

Accordingly, one aspect of the present invention is a sustained release composition, preferably for oral administration, which comprises an active ingredient mixed with a hydroxypropyl methylcellulose acetate succinate having a total degree of substitution of acetyl and succinoyl groups, DS_{Ac} + DS_S, of at least 0.75, wherein the concentration of hydroxypropyl methylcellulose acetate succinate is from 0.1 to 20 % by weight of the active ingredient, and wherein the active ingredient has a solubility in water of at least 1 mg/ml.

Another aspect of the present invention is a unit dosage form comprising or produced from a sustained release composition as specified above.

Yet another aspect of the present invention is the use of a hydroxypropyl methylcellulose acetate succinate having a total degree of substitution of acetyl and succinoyl groups, $DS_{Ac} + DS_S$, of at least 0.75 as an excipient of a polymeric matrix providing sustained release of an active ingredient from a solid oral dosage form.

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BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 is a graph showing the release over time of acetaminophen (APAP) from compositions of the invention comprising different concentrations of hydroxypropyl methylcellulose acetate succinate when HPMC capsules size 00 containing the compositions are immersed in 900 ml of 0.1 N HCl pH 1.1.

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DESCRIPTION OF EMBODIMENTS

In the present invention, a specific hydroxypropyl methylcellulose acetate succinate (HPMCAS) is an essential component of the composition to provide sustained release of the active ingredient on oral administration of the composition even when the HPMCAS is present in a very low amount relative to the active ingredient.

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HPMCAS polymers which are suitable for use in the sustained release composition of this invention are described in US 4,226,981 mentions the use of these HPMCAS polymers for enteric film coating of solid dosage forms. US Patent No. 4,365,060 discloses enterosoluble capsules prepared from, e.g., HPMCAS. WO 2913/164122 discloses the use of HPMCAS polymers for production of enteric capsules providing release of an active ingredient in the small intestine. EP 3006049 describes the use of HPMCAS to prepare a solid dispersion of an active ingredient by hot melt extrusion. However these dosage forms are not suggested to provide sustained release of the active ingredient over a period of several hours in an acidic environment.

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The HPMCAS has a cellulose backbone having β -1,4 glycosidically bound D-glucopyranose repeating units, designated as anhydroglucose units in the context of this invention. At least a part of the hydroxyl groups of the anhydroglucose units are substituted by a combination of methoxyl and hydroxypropoxyl groups.

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The degree of the substitution of hydroxyl groups of the anhydroglucose units by hydroxypropoxyl groups is expressed by the molar substitution of hydroxypropoxyl groups,

the MS(hydroxypropoxyl). The MS(hydroxypropoxyl) is the average number of moles of hydroxypropoxyl groups per anhydroglucose unit in the esterified cellulose ether. It is to be understood that during the hydroxypropylation reaction the hydroxyl group of a hydroxypropoxyl group bound to the cellulose backbone can be further etherified by a methylation agent, and/or a hydroxypropylation agent. Multiple subsequent hydroxypropylation etherification reactions with respect to the same carbon atom position of an anhydroglucose unit yields a side chain, wherein multiple hydroxypropoxyl groups are covalently bound to each other by ether bonds, each side chain as a whole forming a hydroxypropoxyl substituent to the cellulose backbone.

The term “hydroxypropoxyl groups” thus has to be interpreted in the context of the MS(hydroxypropoxyl) as referring to the hydroxypropoxyl groups as the constituting units of hydroxypropoxyl substituents, which either comprise a single hydroxypropoxyl group or a side chain as outlined above, wherein two or more hydroxyalkoxy units are covalently bound to each other by ether bonding. Within this definition it is not important whether the terminal hydroxyl group of a hydroxypropoxyl substituent is further methylated, or not; both methylated and non-methylated hydroxypropoxyl substituents are included for the determination of MS(hydroxypropoxyl). The HPMCAS utilized in the sustained release composition of this invention generally has a molar substitution of hydroxypropoxyl groups in the range 0.05 to 1.00, preferably 0.08 to 0.70, more preferably 0.15 to 0.60, most preferably 0.15 to 0.40, and particularly 0.20 to 0.40.

The average number of hydroxyl groups substituted by methoxyl groups, per anhydroglucose unit, is designated as the degree of substitution of methoxyl groups, DS(methoxyl). In the above-given definition of DS, the term “hydroxyl groups substituted by methoxyl groups” is to be construed within the present invention to include not only methylated hydroxyl groups directly bound to the carbon atoms of the cellulose backbone, but also methylated hydroxyl groups of hydroxypropoxyl substituents bound to the cellulose backbone. The HPMCAS utilized in the sustained release composition of this invention generally has a DS(methoxyl) in the range of 1.0 to 2.5, preferably from 1.2 to 2.2, more preferably from 1.6 to 2.05, and most preferably from 1.7 to 2.05.

An essential feature of the HPMCAS utilized in the sustained release composition of this invention is its total degree of substitution of acetyl and succinoyl groups, $DS_{Ac} + DS_s$.

The total degree of substitution of acetyl and succinoyl groups, $DS_{Ac} + DS_S$, is at least 0.75, preferably at least 0.80. The total degree of substitution of acetyl and succinoyl groups, $DS_{Ac} + DS_S$, is not more than 1.5, preferably not more than 1.0, more preferably not more than 1.0. In one aspect of the present invention a HPMCAS having a $DS_{Ac} + DS_S$ of from
5 0.75 to 1.0 and particularly from 0.80 to 0.95 is preferred.

The HPMCAS utilized in the sustained release composition of this invention has a degree of substitution of acetyl groups of generally at least 0.1, preferably at least 0.3. The HPMCAS generally has a degree of substitution of acetyl groups of up to 0.9, preferably up to 0.70. In one embodiment of the invention the HPMCAS has a degree of substitution of
10 acetyl groups of from 0.1 to 0.9 or from 0.3 to 0.7.

The HPMCAS utilized in the sustained release composition of this invention has a degree of substitution of succinoyl groups of generally at least 0.1. The HPMCAS generally has a degree of substitution of succinoyl groups of up to 0.9, preferably up to 0.60, more preferably up to 0.55, and most preferably up to 0.50 or up to 0.45. In one aspect of the
15 invention the HPMCAS has a degree of substitution of succinoyl groups of from 0.15 to 0.45.

The content of the acetate and succinate ester groups is determined according to “Hydromellose Acetate Succinate, United States Pharmacopeia and National Formulary, NF 29, pp. 1548-1550”. Reported values are corrected for volatiles (determined as described in
20 section “loss on drying” in the above HPMCAS monograph).

The content of the ether groups, i.e., the methoxyl and hydroxypropoxyl groups, in the HPMCAS is determined in the same manner as described for “Hydromellose”, United States Pharmacopeia and National Formulary, USP 35, pp 3467-3469.

The contents of ether and ester groups obtained by the above analyses are converted to DS and MS values of individual substituents according to the formulas below.

% cellulose backbone

$$= 100 - \left(\% \text{MeO} * \frac{M(\text{OCH}_3) - M(\text{OH})}{M(\text{OCH}_3)} \right) \\ - \left(\% \text{HPO} * \frac{M(\text{OCH}_2\text{CH}(\text{OH})\text{CH}_3) - M(\text{OH})}{M(\text{OCH}_2\text{CH}(\text{OH})\text{CH}_3)} \right) \\ - \left(\% \text{Acetyl} * \frac{M(\text{COCH}_3) - M(\text{H})}{M(\text{COCH}_3)} \right) \\ - \left(\% \text{Succinoyl} * \frac{M(\text{COC}_2\text{H}_4\text{COOH}) - M(\text{H})}{M(\text{COC}_2\text{H}_4\text{COOH})} \right)$$

$$\text{DS}(\text{Me}) = \frac{\frac{\% \text{MeO}}{M(\text{OCH}_3)}}{\frac{\% \text{cellulose backbone}}{M(\text{AGU})}}$$

$$\text{MS}(\text{HP}) = \frac{\frac{\% \text{HPO}}{M(\text{HPO})}}{\frac{\% \text{cellulose backbone}}{M(\text{AGU})}}$$

$$\text{DS}(\text{Acetyl}) = \frac{\frac{\% \text{Acetyl}}{M(\text{Acetyl})}}{\frac{\% \text{cellulose backbone}}{M(\text{AGU})}}$$

$$\text{DS}(\text{Succinoyl}) = \frac{\frac{\% \text{Succinoyl}}{M(\text{Succinoyl})}}{\frac{\% \text{cellulose backbone}}{M(\text{AGU})}}$$

$$\begin{array}{ll} M(\text{MeO}) = M(\text{OCH}_3) = 31.03 \text{ Da} & M(\text{HPO}) = M(\text{OCH}_2\text{CH}(\text{OH})\text{CH}_3) = 75.09 \text{ Da} \\ M(\text{Acetyl}) = M(\text{COCH}_3) = 43.04 \text{ Da} & M(\text{Succinoyl}) = M(\text{COC}_2\text{H}_4\text{COOH}) = 101.08 \text{ Da} \\ M(\text{AGU}) = 162.14 \text{ Da} & M(\text{OH}) = 17.008 \text{ Da} \quad M(\text{H}) = 1.008 \text{ Da} \end{array}$$

By convention, the weight percent is an average weight percentage based on the total weight of the cellulose repeat unit, including all substituents. The content of the methoxyl group is reported based on the mass of the methoxyl group (i.e., -OCH₃). The content of the hydroxypropoxyl group is reported based on the mass of the hydroxypropoxyl group (i.e., -O-CH₂CH(CH₃)-OH). The content of the acetyl groups is reported based on the mass of acetyl (-C(O)-CH₃). The content of the succinoyl group is reported based on the mass of succinoyl groups (i.e., -C(O) - CH₂ - CH₂ - COOH).

The HPMCAS utilized in the sustained release composition of this invention generally has a weight average molecular weight M_w of up to 500,000 Dalton, preferably up to 250,000 Dalton, more preferably up to 200,000 Dalton, most preferably up to 150,000 Dalton, and particularly up to 100,000 Dalton. Generally the HPMCAS has a weight average molecular weight M_w of at least 10,000 Dalton, preferably at least 12,000 Dalton, more preferably at least 15,000 Dalton, and most preferably at least 20,000 Dalton, and particularly at least 30,000 Dalton.

The HPMCAS utilized in the sustained release composition of this invention generally has a Polydispersity M_w/M_n , i.e., a ratio of weight average molecular weight M_w to number average molecular weight M_n , of at least 1.5, typically at least 2.1 and often at least 2.9. Moreover, the HPMCAS generally has a Polydispersity of up to 4.1, preferably of up to 3.9, and most preferably of up to 3.7.

M_w and M_n are measured according to Journal of Pharmaceutical and Biomedical Analysis 56 (2011) 743 using a mixture of 40 parts by volume of acetonitrile and 60 parts by volume of aqueous buffer containing 50 mM NaH_2PO_4 and 0.1 M NaNO_3 as mobile phase. The mobile phase is adjusted to a pH of 8.0. The measurement of M_w and M_n is described in more details in the Examples.

The HPMCAS utilized in the sustained release composition of this invention generally has a viscosity of up to 200 mPa·s, preferably up to 100 mPa·s, more preferably up to 50 mPa·s, measured as a 2.0 wt.-% solution of the HPMCAS in 0.43 wt.-% aqueous NaOH at 20 °C. Generally the viscosity is at least 1.2 mPa·s, more typically at least 1.8 mPa·s, even more typically at least 2.4 mPa·s, and most typically at least 2.8 mPa·s, measured as a 2.0 wt.-% solution of the HPMCAS in 0.43 wt.-% aqueous NaOH at 20 °C. The 2.0 % by weight solution of the HPMCAS is prepared as described in "Hypromellose Acetate Succinate, United States Pharmacopeia and National Formulary, NF 29, pp. 1548-1550", followed by an Ubbelohde viscosity measurement according to DIN 51562-1:1999-01 (January 1999).

Details of the production of the HPMCAS utilized in the sustained release composition of this invention are described in EP 2888293 B1 and in the example below.

The sustained release composition of the present invention comprises the HPMCAS described above mixed with an active ingredient. In the sustained release composition of the present invention the concentration of the HPMCAS is only from 0.1 to 20 weight percent, preferably from 0.5 to 15 weight percent, more preferably from 1 to 10 weight percent, and most preferably from 4 to 8 weight percent, by weight of the active ingredient.

The sustained release composition comprises one or more active ingredients, typically one or more physiologically active ingredients, preferably one or more drugs, one or more diagnostic agents, or one or more physiologically active ingredients which are useful for cosmetic or nutritional purposes, such as vitamins, herbals and mineral

supplements. The term "drug" denotes a compound having beneficial prophylactic and/or therapeutic properties when administered to an individual, typically a mammal, especially a human individual.

5 The combined amount of the HPMCAS and the active ingredient(s) is preferably at least 50 weight percent, more preferably at least weight 70 percent, and most preferably at least 90 weight percent, based on the total dry weight of the sustained release composition. The combined amount of the HPMCAS and the active ingredient(s) is up to 100 percent, preferably up to 98 percent or up to 95 percent, based on the total dry weight of the sustained release composition.

10 The sustained release composition may comprise optional adjuvants, such as coloring agents, pigments, opacifiers, flavor and taste improvers, antioxidants, surfactants and any combination thereof. Preferred surfactants are described further below. The total amount of optional adjuvants preferably is not more than 50 weight percent, more preferably not more than 30 weight percent, and most preferably not more than 10 weight
15 percent, based on the total dry weight of the sustained release composition.

The HPMCAS described above is useful as an excipient for a sustained release dosage form which means that it has the function to regulate the release of an active ingredient from the dosage form over an extended period of time. The term "sustained release" is used herein synonymously with the term "controlled release". Sustained release
20 is an approach by which active ingredients such as physiologically active compounds are made available at a rate and duration designed to accomplish an intended effect. The HPMCAS is useful for forming all or part of a polymeric matrix in which the active ingredient is embedded. The polymeric matrix may additionally comprise one or more other polymers capable of providing sustained release of the active ingredient from the dosage
25 form. The HPMCAS typically constitutes at least 50%, preferably 60-100%, more preferably 70-100%, even more preferably 80-100%, and most preferably 90-100% by weight of the polymeric matrix. When one or more other polymers are included as components of the polymeric matrix, they may be selected from cellulose ethers such as hydroxypropyl methylcellulose, hydroxyethyl methylcellulose, methylcellulose,
30 hydroxypropyl cellulose or carboxymethyl cellulose, or they may be selected from other

polysaccharides such as sodium alginate or calcium alginate. It is generally preferred that HPMCAS constitutes 100% by weight of the polymeric matrix.

The HPMCAS may be included in sustained release dosage forms intended for oral administration of drugs or other physiologically active ingredients and release thereof into the gastrointestinal tract so as to control the absorption rate of the active ingredient to achieve a desired blood plasma profile. The dosage form is designed to provide a constant or nearly constant level of the active ingredient in plasma with reduced fluctuation via a slow, continuous release of the active ingredient over an extended period of time such as a period of between 4 and 30 hours, preferably between 8 and 24 hours to release all or almost all of the active ingredient from the dosage form.

It has been found that sustained release dosage forms such as tablets and capsules wherein the polymer matrix is formed partially or completely from HPMCAS remains intact over an extended time period such as at least 4 hours, preferably at least 6 hours and under optimized conditions at least 8 hours. Without wanting to be bound by theory, it is believed that the HPMCAS is hydrated to form a strong swollen layer on the outer surface of the dosage form upon contact with an aqueous liquid at body temperature. The strong swollen layer minimizes the release of the active ingredient caused by erosion of the dosage form. Since the tablets or capsule contents do not disintegrate (i.e. do not fall apart to any significant degree), the release of the active ingredient is controlled by the slow diffusion from the swollen layer that has been formed by hydration of the HPMCAS on the outer surface of the dosage form. A strong swollen layer reduces the penetration of water into the sustained release dosage form, which delays the release of the active ingredient, particularly a water-soluble active ingredient, into an aqueous environment due to a reduced amount of water in the zone of the dosage form into which water diffuses and dissolves the active ingredient.

In the sustained release composition of the present invention the concentration of the HPMCAS is only from 0.1 to 20 wt.-%, preferably from 0.5 to 15 wt.-%, more preferably from 1 to 10 wt.-%, and most preferably from 4 to 8 wt.-% by weight of the active ingredient. The resulting sustained release unit dosage form that comprises or is produced from the sustained release, such as tablet or capsule, is smaller in size and therefore easier to ingest. It has furthermore been found that a satisfactory release rate may be obtained

without adding any other excipients to the dosage form though a surfactant may optionally be added during the manufacturing process as a defoaming agent.

The present composition may suitably be prepared by providing a solution of HPMCAS in an organic solvent such as ethanol, methanol, isopropanol or acetone or a
5 mixture thereof with water, optionally adding a surfactant to the solution as a processing aid. The HPMCAS is generally dissolved in organic solvent at a concentration of 2.0 – 30 weight percent, preferably 3.0 – 20 weight percent, more preferably 5.0 – 15 weight percent, based on the total weight of the HPMCAS and the solvent.

The active ingredient in powder or crystalline form and optionally one or more solid
10 excipients may then be mixed with the HPMCAS solution such that the weight of the HPMCAS is from 0.1 to 20 wt.-%, preferably from 0.5 to 15 wt.-%, more preferably from 1 to 10 wt.-%, and most preferably from 4 to 8 wt.-% by weight of the active ingredient. The sustained release composition of the present invention that comprises or consists of the mixture of active ingredient (and optionally one or more solid excipients) and the
15 HPMCAS solution generally comprises the solvent at a concentration of up to 200 %, preferably up to 150 %, more preferably up to 100 percent, and most preferably up to 70 percent by weight of the active ingredient. For forming a uniform mixture, the amount of the solvent is generally at least 10 %, preferably at least 20 %, more preferably at least 30%, and most preferably at least 50% by weight of the active ingredient.

20 Addition of a surfactant may help to distribute a low level of liquid diluent homogenously and produce a smooth highly viscous semi-solid paste, possibly due to defoaming and emulsification. The surfactant may be selected from conventional defoaming agents selected from the group consisting of anionic surfactants with anionic functional groups such as sulfates, sulfonates, phosphates and carboxylates such as alkyl sulfates, e.g.
25 ammonium lauryl sulfate, sodium lauryl sulfate (sodium dodecyl sulfate, SLS, or SDS), and alkyl-ether sulfates, such as sodium laureth sulfate (sodium lauryl ether sulfate or SLES), and sodium myreth sulfate; cationic surfactants with cationic functional groups such as cetrimonium bromide (CTAB), cetylpyridinium chloride (CPC), benzalkonium chloride (BAC), benzethonium chloride (BZT), dimethyldioctadecylammonium chloride,
30 dioctadecyldimethylammonium bromide (DODAB); zwitterionic surfactants such as cocamidopropyl betaine; and nonionic surfactants such as siloxane surfactants like modified

polydimethylsiloxane-based defoamer, ethoxylates, fatty acid esters of glycerol, sorbitol and sucrose. The concentration of surfactant is generally in the range of 0.01 to 1.0%, preferably from 0.05 to 0.5% by weight of the active ingredient.

Incorporation of a plasticizer or viscosity modifier in the sustained release composition may also be useful. Suitable plasticizers include, for example, phthalic esters, such as dimethyl-, diethyl-, and diisopropyl-phthalate; citric esters, such as triethyl-, tributyl-, acetyltriethyl- and acetyltributyl-citrate; phosphoric esters, such as triethyl-, tricresyl, and triphenyl-phosphate; alkyl lactate; glycol esters; glycerol and glycerol esters, such as glycerol triacetate also known as triacetine; sucrose esters; oils and fatty acid esters; butyl stearate; dibutyl sebacate; dibutyl tartrate; diisobutyl adipate, tributyrin; propylene glycol; and mixtures thereof. In one embodiment, plasticizers or viscosity modifiers are cellulose ethers, such as carboxy methylcellulose, hydroxypropyl cellulose, ethyl cellulose, methylcellulose, hydroxypropylmethylcellulose (HPMC), e.g. HPMC types 2910, 2906 and/or 2208 as defined in USP30- NF25; gelatin, pullulan, non enteric starch derivatives, such as hydroxypropyl starch; polyvinyl acetate derivatives (PVAP); sorbitan monoesters; sorbitan polyoxyethylene esters; fatty acid esters; glycerol polyethylene, glycol ricinoleate; macrogolglycerides; triethyl citrate (TEC); acetyl trialkyl citrate; glycerol triacetate (triacetine); talc; and mixtures thereof. A preferred film forming aid is triethyl citrate (TEC). The amount of the plasticizer or viscosity modifier is generally in the range of 0.1 to 5, preferably 0.2 to 2 % by weight of the active ingredient.

In one embodiment of the invention, the sustained release composition comprising HPMCAS admixed with the active ingredient is in the form of a dry powder. The dry powder may be prepared by drying the mixture of the HPMCAS solution and active ingredient, preferably at a temperature of 40-100°C until the mixture has a moisture content of less than 10% by weight, preferably less than 5% by weight, more preferably less than 3% by weight, in particular less than 2% by weight, such as less than 1% by weight, followed by milling or grinding the mixture to granules of a desired particle size in a manner known in the art. The dry powder will typically contain granules comprising the active ingredient partially or completely encased by HPMCAS which facilitates sustained release of the active ingredient as discussed above.

In one embodiment, the invention relates to a unit dosage form comprising or produced from the sustained release composition of the present invention. The unit dosage form is preferably in the form of a capsule, tablet, pellet, pre-filled syringe or pouch. It is preferably intended for oral administration. The unit dosage form may, for example, be in the form of a tablet comprising compressed granules of the dried composition.

Alternatively, the unit dosage form may be in the form of a tablet or pellet prepared by extruding the semi-solid paste prepared as described above and cutting the extruded mass into pieces of an appropriate size followed by drying. The tablet may optionally comprise one or more other excipients, though preferably the HPMCAS is the only excipient included in the dosage form, except that a surfactant, plasticizer or viscosity modifier may optionally be included as indicated above. The unit dosage form may also be a capsule including the dried composition, preferably in the form of dry granules containing the mixture of HPMCAS and active ingredient. The unit dosage form may also be in the form of a syringe or pouch pre-filled with the wet mixture: this dosage form may more readily be administered to young children.

The sustained release composition comprises one or more active ingredients, typically one or more physiologically active ingredients as described further above. The dosage form has been found suitable for providing sustained release of active ingredients which are readily soluble in water at physiological pH. In this context, "readily soluble" is intended to mean a solubility in water of at least 1 mg/ml. The dosage form is believed to be particularly suited for administering highly dosed drugs, i.e. drugs administered in unit doses of 500 mg or more, as it is possible to provide a unit dose that includes the requisite amount of the active ingredient in a size that makes it easier to ingest. Examples of highly dosed drugs are metformin, metformin hydrochloride, acetaminophen (paracetamol) or acetylsalicylic acid. Thus, each unit dosage form may typically include 500-1000 mg of the active ingredient.

Some embodiments of the invention will now be described in detail in the following Examples.

EXAMPLES

Unless otherwise mentioned, all parts and percentages are by weight. In the Examples the following test procedures are used.

Content of ether and ester groups

5 The content of methoxyl and hydroxypropoxyl groups in the hydroxypropoxyl methylcellulose (HPMC) and hydroxypropoxyl methylcellulose acetate succinate (HPMCAS) is determined as described for “Hypromellose”, United States Pharmacopeia and National Formulary, USP 35, pp 3467-3469.

10 The ester substitutions with acetyl groups ($-\text{CO}-\text{CH}_3$) and with succinoyl groups ($-\text{CO}-\text{CH}_2-\text{CH}_2-\text{COOH}$) are determined according to Hypromellose Acetate Succinate, United States Pharmacopeia and National Formulary, NF 29, pp. 1548-1550”. Reported values for ester substitution are corrected for volatiles (determined as described in section “loss on drying” in the above HPMCAS monograph).

15 Determination of M_w and M_n

M_w and M_n were measured according to Journal of Pharmaceutical and Biomedical Analysis 56 (2011) 743 unless stated otherwise. The mobile phase was a mixture of 40 parts by volume of acetonitrile and 60 parts by volume of aqueous buffer containing 50 mM NaH_2PO_4 and 0.1 M NaNO_3 . The mobile phase was adjusted to a pH of 8.0. Solutions of the HPMCAS were filtered into a HPLC vial through a syringe filter of 0.45 μm pore size. The exact details of measuring M_w , M_n and M_z are disclosed in the International Patent Application No. WO 2014/137777 in the section “Examples” under the title “Determination of M_w , M_n and M_z ”. The recovery rate was at least 97 %.

25 HPMCAS used for preparing solid dosage forms containing acetaminophen

 HPMCAS was used that had a DS(Me) of 1.91, an MS(HP) of 0.25, a DS(Ac) of 0.55, a DS(Suc) of 0.28, a M_w of 151 kDa and a viscosity of 2.9 mPa.s when measured as a 2% by weight solution of the HPMCAS in 0.43% by weight aqueous NaOH. The HPMCAS was prepared as follows: glacial acetic acid, acetic anhydride, a hydroxypropyl methylcellulose (HPMC), succinic anhydride and sodium acetate (water free) were

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introduced in the amounts listed in Table 1 of EP 2888293 B1 into a reaction vessel under thorough stirring.

The HPMC had a methoxyl and hydroxypropoxyl substitution as listed in Table 2 of EP 2888293 B1 and a viscosity of about 3 mPa·s, measured as a 2 % solution in water at 20 °C according to ASTM D2363 – 79 (Reapproved 2006). The HPMC is commercially available from DuPont as Methocel E3 LV Premium cellulose ether.

The mixture was heated at 85° C with agitation for 3 or 3.5 hours, as listed in Table 1 of EP 2888293 B1, to effect esterification. x L of water was added to the reactor under stirring to precipitate the HPMCAS. The precipitated product was removed from the reactor and washed with y L of water by applying high shear mixing using an Ultra-Turrax stirrer S50-G45 running at 5200 rpm. The numbers of water x and y are listed in Table 1 of EP 2888293 B1. The product was isolated by filtration and dried at 50°C. The product was then thoroughly washed by repeatedly slurrying the product in excess water using the Ultra-Turrax stirrer S50-G45 and isolating the product by filtration. The washed product was dried again at 50°C.

Example 1: Release of Acetaminophen (APAP) from dried HPMC capsules containing HPMCAS

A 10% by weight solution of HPMCAS prepared as described above in ethanol:water 80:20 was prepared.

7.0 g of finely ground acetaminophen (abbreviated herein to APAP) was intimately mixed with 3.0 g of the HPMCAS solution until a white homogenous and highly viscous paste was obtained. The paste was filled into a syringe and injected into HPMC capsule shells (size 00) which were subsequently closed and sealed. The filled capsules were then dried carefully overnight at 60 °C.

The dried capsules were placed in 900 ml of 0.1N HCl pH 1.1 at 37°C and drug release was measured in a USP II dissolution apparatus at 37°C, 100 rpm, for 22 hours at a wavelength of 243 nm and a path length of 0.1 mm. The release of APAP from the capsules is shown as -▲- in Fig. 1 from which it appears that about 80% of the drug was released after 22 hours.

Example 2: Release of Acetaminophen (APAP) from dried HPMC capsules containing HPMCAS

A 20% by weight solution of HPMCAS prepared as described above in ethanol:water 80:20 was prepared.

5 7.0 g of finely ground acetaminophen (abbreviated herein to APAP) was intimately mixed with 3.0 g of the HPMCAS solution until a white homogenous and highly viscous paste was obtained. The paste was filled into a syringe and injected into HPMC capsule shells (size 00) which were subsequently closed and sealed. The filled capsules were then dried carefully overnight at 60 °C.

10 The dried capsules were placed in 900 ml of 0.1N HCl pH 1.1 at 37°C and drug release was measured in a USP II dissolution apparatus at 37°C, 100 rpm, for 22 hours at a wavelength of 243 nm and a path length of 0.1 mm. The release of APAP from the capsules is shown as -■- in Fig. 1 from which it appears that about 63% of the drug was released after 22 hours.

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Example 3: Release of Acetaminophen (APAP) from dried HPMC capsules containing HPMCAS

A 25% by weight solution of HPMCAS prepared as described above in ethanol:water 80:20 was prepared.

20 7.0 g of finely ground acetaminophen (abbreviated herein to APAP) was intimately mixed with 3.0 g of the HPMCAS solution until a white homogenous and highly viscous paste was obtained. The paste was filled into a syringe and injected into HPMC capsule shells (size 00) which were subsequently closed and sealed. The filled capsules were then dried carefully overnight at 60 °C.

25 The dried capsules were placed in 900 ml of 0.1N HCl pH 1.1 at 37°C and drug release was measured in a USP II dissolution apparatus at 37°C, 100 rpm, for 22 hours at a wavelength of 243 nm and a path length of 0.1 mm. The release of APAP from the capsules is shown as -●- in Fig. 1 from which it appears that about 88% of the drug was released after 22 hours.

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Example 4: Release of Acetaminophen (APAP) from dried HPMC capsules containing HPMCAS

A 30% by weight solution of HPMCAS prepared as described above in ethanol:water 80:20 was prepared.

5 7.0 g of finely ground acetaminophen (abbreviated herein to APAP) was intimately mixed with 3.0 g of the HPMCAS solution until a white homogenous and highly viscous paste was obtained. The paste was filled into a syringe and injected into HPMC capsule shells (size 00) which were subsequently closed and sealed. The filled capsules were then dried carefully overnight at 60 °C.

10 The dried capsules were placed in 900 ml of 0.1N HCl pH 1.1 at 37°C and drug release was measured in a USP II dissolution apparatus at 37°C, 100 rpm, for 22 hours at a wavelength of 243 nm and a path length of 0.1 mm. The release of APAP from the capsules is shown as – in Fig. 1 from which it appears that about 68% of the drug was released after 22 hours.

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Claims

1. A sustained release composition comprising an active ingredient mixed with a hydroxypropyl methylcellulose acetate succinate having a total degree of substitution of acetyl and succinoyl groups, DS_{Ac} + DS_S, of at least 0.75, wherein the concentration of hydroxypropyl methylcellulose acetate succinate is from 0.1 to 20 % by weight of the active ingredient and wherein the active ingredient has a solubility in water of at least 1 mg/ml.

2. The composition of claim 1, wherein the concentration of hydroxypropyl methylcellulose acetate succinate is from 0.5 to 15 % by weight of the active ingredient.

3. The composition of claim 2, wherein the concentration of hydroxypropyl methylcellulose acetate succinate is from 1 to 10 % by weight of the active ingredient.

4. The composition of any one of claims 1 to 3 wherein the HPMCAS has a viscosity of between 1.2 mPa.s and 200 mPa.s, measured as a 2.0 wt.-% solution of the HPMCAS in 0.43 wt.-% aqueous NaOH at 20 °C.

5. The composition of any one of claims 1 to 4 wherein the total degree of substitution of acetyl and succinoyl groups, DS_{Ac} + DS_S, is from 0.80 to 0.95.

6. The composition of any one of claims 1 to 5 in the form of a dry powder.

7. The composition of any one of claims 1 to 6 further comprising a surfactant.

8. The composition of any one of claims 1 to 7 further comprising a plasticizer or viscosity modifier.

9. A unit dosage form comprising or produced from a composition according to any one of claims 1 to 8.

10. The unit dosage form of claim 9 which is a capsule, tablet, pellet, pre-filled syringe or pouch.

11. A unit dosage form of claim 9 or 10 comprising from 500 to 1000 mg of the
5 active ingredient.

12. A unit dosage form according to any one of claim 9 to 11, wherein the active ingredient is selected from the group consisting of metformin, metformin hydrochloride, acetaminophen and acetylsalicylic acid.

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13. Use of a hydroxypropyl methylcellulose acetate succinate having a total degree of substitution of acetyl and succinoyl groups, $DS_{Ac} + DS_S$, of at least 0.75 as an excipient of a polymeric matrix providing sustained release of an active ingredient from a solid dosage form.

14. The use of claim 13, wherein the hydroxypropyl methylcellulose acetate succinate constitutes at least 50%, preferably 60-100%, by weight of the polymeric matrix.

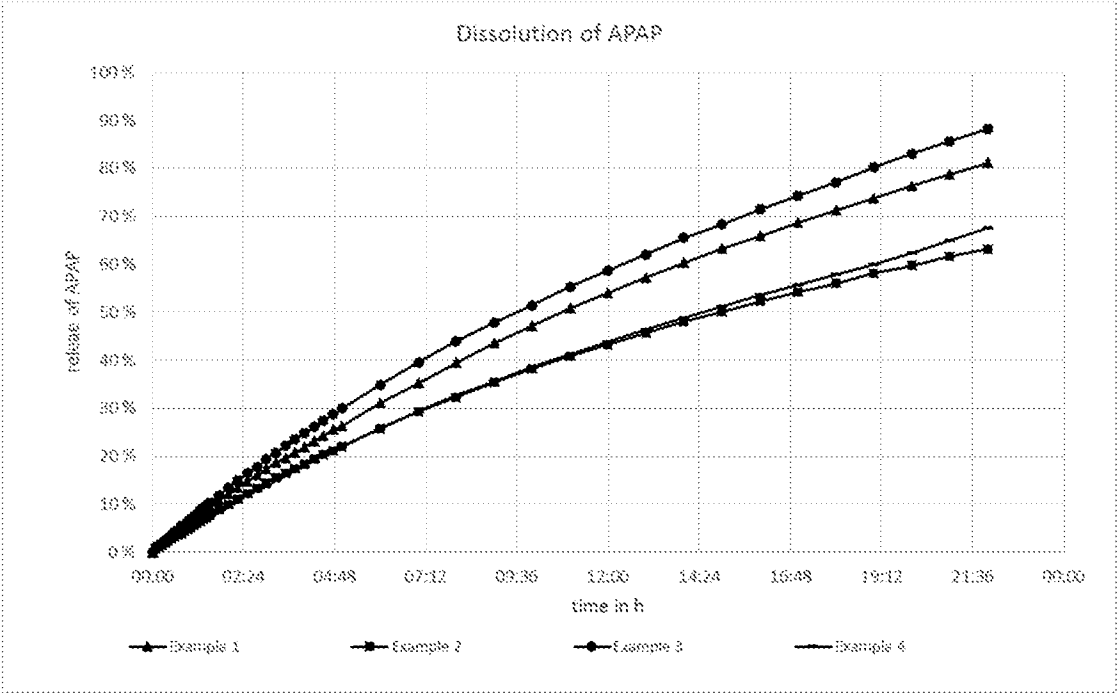


Fig. 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/066737

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K47/38 A61K9/16 C08B11/20
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C08B C09J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2005/115330 A2 (PFIZER PROD INC [US]; BABCOCK WALTER CHRISTIAN [US] ET AL.) 8 December 2005 (2005-12-08)	1-11,13
A	page 3, line 30 - line 32; claims; table 15 ----- -/--	12,14



Further documents are listed in the continuation of Box C.



See patent family annex.

* 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 application or patent but published on or after the international filing date

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"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 when the document is taken alone

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

"&" document member of the same patent family

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2019/066737

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HILTON A K ET AL: "Use of hydroxypropyl methylcellulose acetate succinate in an enteric polymer matrix to design controlled-release tablets of amoxicillin trihydrate", JOURNAL OF PHARMACEUTICAL SCIENCES, AMERICAN PHARMACEUTICAL ASSOCIATION, US, vol. 82, no. 7, 1 July 1993 (1993-07-01), pages 737-743, XP002156064, ISSN: 0022-3549, DOI: 10.1002/JPS.2600820713	1-11,13
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A	WO 2016/148977 A1 (DOW GLOBAL TECHNOLOGIES LLC [US]) 22 September 2016 (2016-09-22) paragraph [0052]; claims -----	1-14

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International application No

PCT/US2019/066737

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