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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, DS^{Ac}#191 + DS^S#191 of from 0.10 to 0.70, wherein the concentration of hydroxypropyl methylcellulose acetate succinate is from 0.1 to 20 % by weight of the active ingredient. 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 cellulose derivative.

INTRODUCTION

10 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 time. Sustained release pharmaceutical dosage forms are desirable because they provide a
15 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 form a gel layer. A fast formation of the gel layer is important to prevent wetting of the
20 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.

A commonly used cellulose ether for providing sustained release of an active
25 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 providing sustained release of a drug usually at a concentration of 30% to 60% by weight of
30 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
5 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, preferably an 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.

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SUMMARY

It has surprisingly been found that when a 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
15 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
20 intestine. US Patent No. 4,365,060 discloses enterosoluble capsules.

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 from 0.10 to 0.70, wherein the concentration
25 of hydroxypropyl methylcellulose acetate succinate is from 0.1 to 20 % by weight of the active ingredient.

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
30 methylcellulose acetate succinate having a total degree of substitution of acetyl and succinoyl groups, DS_{Ac} + DS_S, of from 0.10 to 0.70 as an excipient of a polymeric matrix

providing sustained release of an active ingredient from a solid dosage form, preferably from an oral solid dosage form.

BRIEF DESCRIPTION OF DRAWINGS

5 Fig. 1 is a graph showing the release over time of acetaminophen (APAP) from a composition of the invention when a gelatin capsule containing the composition is immersed in 900 ml of 0.1 N HCl pH 1.1.

DESCRIPTION OF EMBODIMENTS

10 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.

HPMCAS polymers which are suitable for use in the sustained release composition of
15 this invention are described in International Patent Application Publication No. WO2016/148977. WO2016/148977 mentions the use of these HPMCAS polymers in dosage form, such as strands, pellets, granules, pills, tablets, caplets, microparticles, fillings of capsules or injection molded capsules or in the form of a powder, film, paste, cream, suspension or slurry. However these dosage forms contain 20 to 99.9 percent, most
20 preferably from 60 to 95 percent of an esterified cellulose ether, such as HPMCAS, and only 0.1 to 80 percent, most preferably from 5 to 40 percent of an active ingredient. Moreover, WO2016/148977 does not suggest anywhere sustained release compositions.

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
25 invention. At least a part of the hydroxyl groups of the anhydroglucose units are substituted by a combination of methoxyl and hydroxypropoxyl groups.

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
30 hydroxypropoxyl groups per anhydroglucose unit in the HPMCAS. 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 hydroxypropoxyl 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 0.10, preferably at least 0.15, more preferably at least 0.20, and most preferably at least 0.25. The total degree of substitution of acetyl and succinoyl groups, $DS_{Ac} + DS_S$, is not more than 0.70, generally not more than 0.67, preferably up to 0.65, more preferably up to 0.60, and most preferably up to 0.55 or up to 0.50. In one aspect of the present invention a HPMCAS

having a $DS_{Ac} + DS_S$ of from 0.10 to 0.65 and particularly from 0.20 to 0.60 is preferred. In another aspect of the present invention a HPMCAS having a $DS_{Ac} + DS_S$ of from 0.20 to 0.50 and particularly from 0.25 to 0.44 is preferred.

The HPMCAS utilized in the sustained release composition of this invention has a
5 degree of substitution of acetyl groups of generally at least 0.05, preferably at least 0.10, more preferably at least 0.15, most preferably at least 0.20, and particularly at least 0.25 or at least 0.30. The HPMCAS generally has a degree of substitution of acetyl groups of up to 0.69, preferably up to 0.60, more preferably up to 0.55, most preferably up to 0.50, and particularly up to 0.45 or even only up to 0.40. In one embodiment of the invention the
10 HPMCAS has a degree of substitution of acetyl groups of from 0.25 to 0.69 or from 0.25 to 0.65. In another embodiment of the invention the HPMCAS has a degree of substitution of acetyl groups of from 0.10 to 0.38.

The HPMCAS utilized in the sustained release composition of this invention has a degree of substitution of succinoyl groups of generally at least 0.01, preferably at least 0.02,
15 more preferably at least 0.05, and most preferably at least 0.10. The HPMCAS generally has a degree of substitution of succinoyl groups of up to 0.65, 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 invention the HPMCAS has a degree of substitution of succinoyl groups of 0.05 to 0.45. In another embodiment of the invention the HPMCAS has a degree of substitution of
20 succinoyl groups of 0.02 to 0.14.

Moreover, the sum of i) the degree of substitution of acetyl groups and ii) the degree of substitution of succinoyl groups and iii) the degree of substitution of methoxyl groups, $DS(\text{methoxyl})$, generally is not more than 2.60, preferably not more than 2.55, more preferably not more than 2.50, and most preferably not more than 2.45. In one aspect of the
25 invention the sum of degrees of substitution of i) acetyl groups and ii) succinoyl groups and iii) methoxyl groups is not more than 2.40. A HPMCAS having such sum of degrees of substitution generally forms clear solutions in water at a concentration of 2 wt.-%. The HPMCAS generally has a sum of degrees of substitution of i) acetyl groups and ii) succinoyl groups and iii) methoxyl groups of at least 1.7, preferably at least 1.9, and most
30 preferably at least 2.1.

The content of the acetate and succinate ester groups is determined according to "Hypromellose Acetate Succinate, United States Pharmacopeia and National Formulary, NF

29, pp. 1548-1550". Reported values are corrected for volatiles (determined as described in 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 "Hypromellose", 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.

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

$$\begin{aligned}
 \text{DS}(\text{Me}) &= \frac{\frac{\% \text{MeO}}{M(\text{OCH}_3)}}{\frac{\% \text{cellulose backbone}}{M(\text{AGU})}} & \text{MS}(\text{HP}) &= \frac{\frac{\% \text{HPO}}{M(\text{HPO})}}{\frac{\% \text{cellulose backbone}}{M(\text{AGU})}} \\
 \text{DS}(\text{Acetyl}) &= \frac{\frac{\% \text{Acetyl}}{M(\text{Acetyl})}}{\frac{\% \text{cellulose backbone}}{M(\text{AGU})}} & \text{DS}(\text{Succinoyl}) &= \frac{\frac{\% \text{Succinoyl}}{M(\text{Succinoyl})}}{\frac{\% \text{cellulose backbone}}{M(\text{AGU})}}
 \end{aligned}$$

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

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
 5 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
 10 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
 15 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 degree of neutralization of the succinoyl groups of not more than 0.4, preferably not
 20 more than 0.3, more preferably not more than 0.2, most preferably not more than 0.1, and particularly not more than 0.05 or even not more than 0.01. The degree of neutralization can even be essentially zero or only slightly above it, e.g. up to 10^{-3} or even only up to 10^{-4} .

The term “degree of neutralization” as used herein defines the ratio of deprotonated succinoyl groups over the sum of deprotonated and protonated succinoyl groups, i.e., degree
 25 of neutralization =

$$[-\text{C}(\text{O}) - \text{CH}_2 - \text{CH}_2 - \text{COO}^-] / [-\text{C}(\text{O}) - \text{CH}_2 - \text{CH}_2 - \text{COO}^- + -\text{C}(\text{O}) - \text{CH}_2 - \text{CH}_2 - \text{COOH}].$$

The HPMCAS generally has a solubility in water of at least 2.0 weight percent at 2 °C, i.e., it can be dissolved as an at least 2.0 weight percent solution, preferably at least 3.0 weight percent solution, more preferably at least 5.0 weight percent solution or even at
 30 least 10.0 weight solution in water at 2 °C. Generally the HPMCAS can be dissolved as up to 20 weight percent solution or in the most preferred embodiments even as up to 30 weight percent solution in water at a temperature of 2 °C. The term “an x weight percent solution in

water at 2 °C” as used herein means that x g of the HPMCAS is soluble in (100 – x) g of water at 2 °C.

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, and most preferably up to 5.0 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 International Patent Application Publication No. WO2016/148977 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.

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.

The sustained release composition may comprise optional adjuvants, such as coloring agents, pigments, opacifiers, flavor and taste improvers, antioxidants, surfactants, film-forming aids and any combination thereof. Preferred surfactants and film-forming aids 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 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 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 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 in the polymeric matrix, they may be selected from cellulose ethers such as hydroxypropyl methylcellulose, hydroxyethyl methylcellulose, methylcellulose, hydroxypropyl cellulose or carboxymethyl cellulose, or they may be selected from other polysaccharides such as sodium alginate or calcium alginate. It is, however, generally preferred that the HPMCAS constitutes 100% by weight of the polymeric matrix.

The HPMCAS may be included in sustained release dosage forms, in particular 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 also reduces the penetration of water into the sustained release dosage form, which further 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 aqueous diluent, optionally adding a surfactant to the solution as a processing aid. The HPMCAS is generally dissolved in an aqueous liquid 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 aqueous diluent. Dissolution preferably is conducted at a temperature of up to 5 °C, such as at 2 °C.

The aqueous liquid in which the HPMCAS is dissolved may additionally comprise a minor amount of an organic liquid diluent; however, the aqueous liquid should generally comprise at least 80, preferably at least 85, more preferably at least 90, and particularly at least 95 weight percent of water, based on the total weight of the aqueous liquid. The term “organic liquid diluent” as used herein means an organic solvent or a mixture of two or more organic solvents. Preferred organic liquid diluents are polar organic solvents having one or more heteroatoms, such as oxygen, nitrogen or halogen like chlorine. More preferred organic liquid diluents are alcohols, for example multifunctional alcohols, such as glycerol, or preferably monofunctional alcohols, such as methanol, ethanol, isopropanol or n-propanol; ethers, such as tetrahydrofuran, ketones, such as acetone, methyl ethyl ketone, or methyl isobutyl ketone; acetates, such as ethyl acetate; halogenated hydrocarbons, such as methylene chloride; or nitriles, such as acetonitrile. More preferably the organic liquid diluents have 1 to 6, most preferably 1 to 4 carbon atoms. The aqueous liquid may comprise a basic compound, but the degree of neutralization of the succinoyl groups in the resulting blend of HPMCAS and aqueous liquid should generally be not more than 0.4, preferably not more than 0.3 or 0.2 or 0.1, more preferably not more than 0.05 or 0.01, and most preferably not more than 10^{-3} or even not more than 10^{-4} . Preferably the aqueous liquid does not comprise a substantial amount of a basic compound. More preferably, the aqueous diluent does not contain a basic compound. Even more preferably, the aqueous liquid comprises from 80 to 100 percent, preferably 85 to 100 percent, more preferably 90 to 100 percent and most preferably 95 to 100 percent of water, and from 0 to 20 percent, preferably 0 to 15 percent, more preferably 0 to 10 percent, and most preferably 0 to 5 percent of an organic liquid diluent, based on the total weight of the aqueous liquid. Most preferably the aqueous liquid consists of water, e.g., deionized or distilled water.

The active ingredient in powder or crystalline form 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 consist of the mixture of active ingredient and the HPMCAS solution generally comprises the aqueous diluent 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 aqueous diluent 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.

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. 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, 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 water 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 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.

5

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

EXAMPLES

10 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

15 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.

20 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).

Determination of M_w and M_n

25 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
30 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 %.

Example**Production of hydroxypropyl methylcellulose acetate succinate (HPMCAS)**

65.0 g of hydroxypropyl methyl cellulose (HPMC, water free), 171 g of glacial acetic acid (8.88 mol / mol HPMC) and 13.8 g of sodium acetate (water free, 0.53 mol / mol HPMC) were introduced into a reaction vessel. The amount of HPMC was calculated on a dried basis. The HPMC had a methoxyl substitution (DS_M) of 1.94 and hydroxypropoxyl substitution (MS_{HP}) of 0.24 and a viscosity of 3.3 mPa's, measured as a 2 % solution in water at 20 °C according to ASTM D2363 – 79 (Reapproved 2006). The weight average molecular weight of the HPMC was about 20,000 Dalton. The HPMC was commercially available from DuPont as Methocel E3 LV Premium cellulose ether.

The mixture of HPMC, glacial acetic acid and sodium acetate was heated to 80 °C. 30.4 g of acetic anhydride (0.97 mol / mol HPMC) and 3.8 g of succinic anhydride (0.12 mol / mol HPMC) were added under stirring. The reaction mixture was allowed to react at 80 °C for 30 minutes. Then 41.3 g of sodium acetate (water free, 1.57 mol / mol HPMC) were added under stirring and the reaction mixture was allowed to react at 80 °C for three hours.

Then the crude product was precipitated by adding excess water having a temperature of 60 °C. Subsequently the precipitated product was separated from the mixture by filtration and washed several times with water having a temperature of 60 °C. Then the product was isolated by filtration and dried at 55°C overnight.

The produced HPMCAS had the following properties: 25.4 wt.-% methoxyl groups, 7.8 wt.-% hydroxypropoxyl groups, 9.0 wt.-% acetyl groups and 4.8 wt.-% succinoyl groups. This corresponds to a $DS(\text{methoxyl})$, i.e., a degree of substitution with methoxyl groups, DS_M , of 1.92; a $MS(\text{hydroxypropoxyl})$, i.e., a molar substitution with hydroxypropoxyl groups, MS_{HP} of 0.24; a degree of substitution of acetyl groups, DS_{Ac} , of 0.49, and a degree of substitution of succinoyl groups, DS_s , of 0.11.

M_n : 21,000 Dalton;

M_w : 51,000 Dalton;

M_w/M_n : 2.43; and

M_z : 569,000 Dalton.

Release of Acetaminophen (APAP) from dried gelatin capsules containing the HPMCAS

10 g of HPMCAS that had been produced as described above, 2 g of triethyl citrate (TEC) and 0.1 g of a defoamer were dissolved in 87.9 g water at a temperature of 2 °C to
5 produce a 10% by weight aqueous HPMCAS solution. The defoamer was a non-ionic mixture of modified alcohols and a polysiloxane adduct. It is commercially available from BASF under the tradename Dehydran® 1620.

61.9 g of acetaminophen (abbreviated herein to APAP) was intimately mixed with 38.1 g of the HPMCAS solution until a white homogenous and highly viscous paste was
10 obtained. Gelatin capsule shells (size 000) were filled with about 1.4 g of the paste and subsequently closed. The filled capsules were then dried carefully overnight at 60 °C. Each capsule contained 889 mg of APAP and 55 mg of HPMCAS in dried form.

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
15 wavelength of 243 nm and a path length of 0.1 mm. The gelatin capsule shells dissolved within about 10 min. leaving the capsule content exposed to 0.1N HCl. The capsule content was a HPMCAS hydrogel loaded with the APAP in the shape of capsules. The release of APAP from these capsules is shown in Fig. 1 from which it appears that 78% of the drug was released after 24 hours.

20 Visual inspection showed that even after 22 hours of immersion in 0.1N HCl pH 1.1 a white body comprising HPMCAS and APAP was still clearly visible.

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 from 0.10 to 0.70, wherein the concentration of hydroxypropyl methylcellulose acetate succinate is from 0.1 to 20 % by weight of the active ingredient.

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 total weight of the active ingredient and the hydroxypropyl methylcellulose acetate succinate is at least 50 percent, based on the total dry weight of the composition.

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 0.20 to 0.60.

6. The composition of any one of claims 1 to 5 wherein the degree of neutralization of the succinoyl groups is not more than 0.4.

7. The composition of any one of claims 1 to 6 further comprising an aqueous diluent at a concentration of up to 200 % by weight of the active ingredient.

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

9. The composition of any one of claims 1 to 8 further comprising a surfactant.

10. The composition of any one of claims 1 to 9 further comprising a plasticizer or viscosity modifier.

11. A unit dosage form comprising or produced from a composition according to any one of claims 1 to 10.

5 12. The unit dosage form of claim 11 which is a capsule, tablet, pellet, pre-filled syringe or pouch.

13. A unit dosage form of claim 11 or 12 comprising from 500 to 1000 mg of the active ingredient.

10

14. A unit dosage form according to any one of claim 10 to 13, wherein the active ingredient is selected from the group consisting of metformin, metformin hydrochloride, acetaminophen and acetylsalicylic acid.

15. Use of a hydroxypropyl methylcellulose acetate succinate having a total degree of substitution of acetyl and succinoyl groups, $DS_{Ac} + DS_S$, of from 0.10 to 0.70 as an excipient of a polymeric matrix providing sustained release of an active ingredient from a solid dosage form.

15

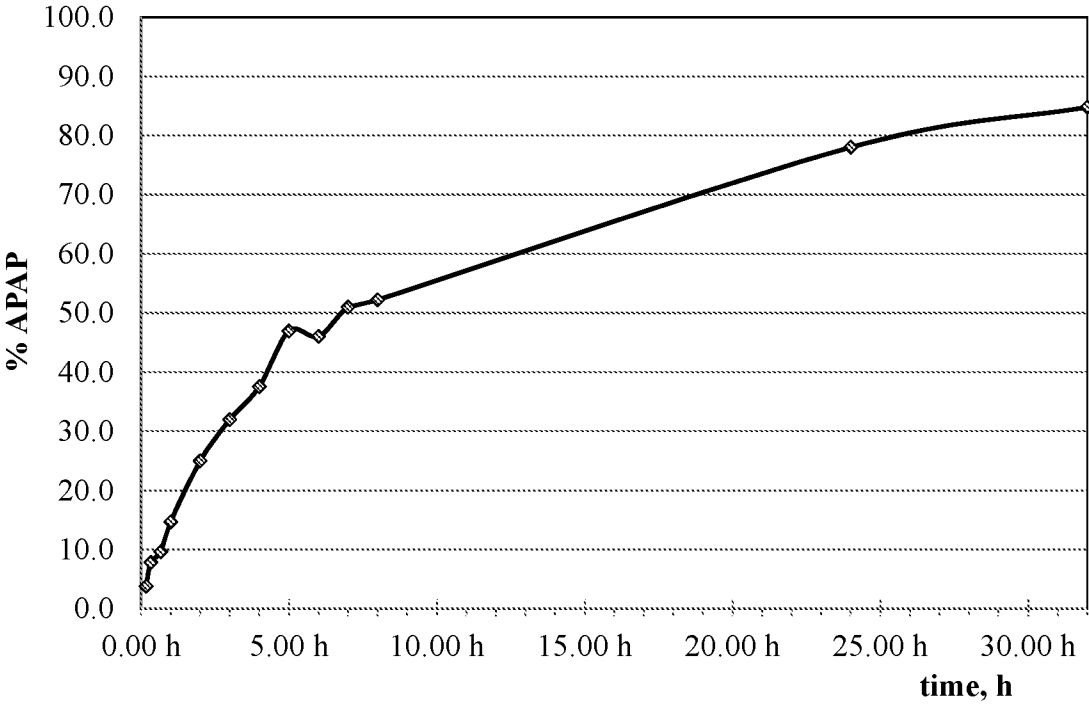


Fig. 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/066713

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K47/38 A61K9/16 C08B11/20 A61K9/48 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 <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>Y</td> <td>WO 2016/148977 A1 (DOW GLOBAL TECHNOLOGIES LLC [US]) 22 September 2016 (2016-09-22) cited in the application page 17, line 2 - line 16; claims -----</td> <td>1-15</td> </tr> <tr> <td>Y</td> <td>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 page 740, column second; figure 6 ----- -/--</td> <td>1-15</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	Y	WO 2016/148977 A1 (DOW GLOBAL TECHNOLOGIES LLC [US]) 22 September 2016 (2016-09-22) cited in the application page 17, line 2 - line 16; claims -----	1-15	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 page 740, column second; figure 6 ----- -/--	1-15
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☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.											
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Date of the actual completion of the international search		Date of mailing of the international search report									
7 February 2020		18/02/2020									
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Couckuyt, Philippe									

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2019/066713

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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