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(54) Title: NOVEL ESTERIFIED CELLULOSE ETHERS OF LOW VISCOSITY AND HIGH MOLECULAR WEIGHT

(57) Abstract: Esterified cellulose ethers which comprise (i) aliphatic monovalent acyl groups or (ii) groups of the formula -C(O) - R - COOA, wherein R is a divalent aliphatic or aromatic hydrocarbon group and A is hydrogen or a cation, or (iii) a combination of aliphatic monovalent acyl groups and groups of the formula -C(O) - R - COOA, which have a viscosity of up to 19 mPa·s, measured as a 10 wt% solution of the esterified cellulose ether in acetone at 20 °C, and which have a weight average molecular weight  $M_w$  of at least 90,000 Dalton, are useful for preparing solid dispersions comprising drugs.

NOVEL ESTERIFIED CELLULOSE ETHERS OF LOW VISCOSITY AND HIGH  
MOLECULAR WEIGHT

FIELD

5 This invention concerns novel esterified cellulose ethers, solid dispersions of an active ingredient in such esterified cellulose ether, as well as liquid compositions, coated dosage forms and capsules comprising such esterified cellulose ether.

INTRODUCTION

10 Esters of cellulose ethers, their uses and processes for preparing them are generally known in the art. Known methods of producing cellulose ether-esters include the reaction of a cellulose ether with an aliphatic monocarboxylic acid anhydride or a dicarboxylic acid anhydride or a combination thereof, for example as described in U.S Patent Nos. 4,226,981 and 4,365,060.

15 Various known esterified cellulose ethers are useful as enteric polymers for pharmaceutical dosage forms, such as methylcellulose phthalate, hydroxypropyl methylcellulose phthalate, methylcellulose succinate, or hydroxypropyl methylcellulose succinate. Dosage forms coated with such polymers protect the drug from inactivation or degradation in the acidic environment or prevent irritation of the stomach by the drug. US  
20 Patent No. 4,365,060 discloses enterosoluble capsules which are said to have excellent enterosolubility behavior.

US Patent Application Publication No. 2004/0152886 discloses the production of hydroxypropyl methylcellulose phthalate starting from hydroxypropyl methylcellulose having a viscosity of 3 to 20 cp, measured as a 2 wt.% aqueous solution.

25 International patent applications WO 2005/115330 and WO 2011/159626 disclose the preparation of hydroxypropyl methylcellulose acetate succinate (HPMCAS). HPMC having an apparent viscosity of 2.4 to 3.6 cp is recommended as a starting material. Alternatively, a HPMC starting material of 600 to 60,000 Daltons, preferably 3000 to 50,000 Daltons, more preferably 6,000 to 30,000 Daltons is recommended. According to Keary [Keary, C.M.;  
30 Carbohydrate Polymers 45 (2001) 293-303, Tables 7 and 8] HPMC having a weight average molecular weight of about 85-100 kDa has a viscosity of about 50 mPaxs, determined as a 2% by weight aqueous solution.

US Patent No. 5,776,501 teaches the usage of a water-soluble cellulose ether having a viscosity of 3 to 10 cp (mPa·s), determined as a 2% by weight aqueous solution. If the viscosity is less than 3 cp, the finally obtained coating film for solid enteric pharmaceutical preparations is insufficient in strength, while if it exceeds 10 cp, the viscosity observed  
5 when it is dissolved in a solvent to carry out a substitution reaction becomes extremely high.

European Patent Application EP-A- 0 219 426 discloses a method for preparing an enteric-soluble acidic dicarboxylic acid ester of a cellulose ether which is produced from a cellulose ether having a viscosity of at least 5 cp, measured as a 2% by weight aqueous solution at 20 °C. A HPMCAS produced from a HPMC of 6 cp viscosity had a higher  
10 molecular weight and a good resistance against a simulated gastric juice than a HPMCAS produced from a HPMC of 3 cp viscosity, which disintegrated in simulated gastric juice.

While esterified cellulose ethers of high molecular weight are very desirable for good resistance against a gastric juice, known esterified cellulose ethers of high molecular weight exhibit a high viscosity when they are dissolved at a high concentration in an organic  
15 solvent, such as a concentration of 7 – 10 weight percent, which reduces their efficiency in coating processes. In coating processes high concentrations of the esterified cellulose ether in an organic solvent are desired to minimize the amount of solvent that has to be subsequently removed. On the other hand, the viscosity of the solution should be low to facilitate spraying of the solution on the dosage forms, such as tablets, to be coated.

Moreover, a large number of presently known drugs have a low solubility in water, so  
20 that complex techniques are required to prepare a dosage form. One known method includes dissolving such drug together with a pharmaceutically acceptable water-soluble polymer, such as an esterified cellulose ether, in an organic solvent that is optionally blended with water, and to spray-dry the solution. The esterified cellulose ether is aimed at reducing the  
25 crystallinity of the drug, thereby minimizing the activation energy necessary for the dissolution of the drug, as well as establishing hydrophilic conditions around the drug molecules, thereby improving the solubility of the drug itself to increase its bioavailability, i.e., its *in vivo* absorption by an individual upon ingestion. Also in spray-drying processes high concentrations of the esterified cellulose ether in an organic solvent are desired to  
30 minimize the amount of solvent that has to be removed. However, when the viscosity of the organic solution comprising the esterified cellulose ether is high, the solution is difficult to be spray-dried and tends to clog the spray-drying device.

Accordingly, it would be highly desirable to find new esterified cellulose ethers which have a high molecular weight but which can still be efficiently used in spray-drying and coating processes.

## 5 SUMMARY

One aspect of the present invention is an esterified cellulose ether which comprises (i) aliphatic monovalent acyl groups or (ii) groups of the formula  $-C(O) - R - COOA$ , wherein R is a divalent aliphatic or aromatic hydrocarbon group and A is hydrogen or a cation, or (iii) a combination of aliphatic monovalent acyl groups and groups of the formula  
10  $-C(O) - R - COOA$ , which has a viscosity of up to 19 mPa•s, measured as a 10 wt% solution of the esterified cellulose ether in acetone at 20 °C, and which has a weight average molecular weight  $M_w$  of at least 90,000 Dalton.

Another aspect of the present invention is a composition which comprises a liquid diluent and at least one above-described esterified cellulose ether.

15 Yet another aspect of the present invention is a solid dispersion of at least one active ingredient in at least one above-described esterified cellulose ether.

Yet another aspect of the present invention is a dosage form which is coated with at least one above-described esterified cellulose ether.

20 Yet another aspect of the present invention is a capsule shell which comprises at least one above-described esterified cellulose ether.

Yet another aspect of the present invention is a process for producing the above-described esterified cellulose ether, wherein a cellulose ether which has a viscosity of from 1.20 to 2.33 mPa•s, measured as a 2 wt.-% solution in water at 20°C, is esterified with (i) an aliphatic monocarboxylic acid anhydride or (ii) a dicarboxylic acid anhydride or (iii) a  
25 combination of an aliphatic monocarboxylic acid anhydride and a dicarboxylic acid anhydride.

## DESCRIPTION OF EMBODIMENTS

The esterified cellulose ether has a cellulose backbone having  $\beta$ -1,4 glycosidically  
30 bound D-glucopyranose repeating units, designated as anhydroglucose units in the context of this invention. The esterified cellulose ether preferably is an esterified alkyl cellulose, hydroxyalkyl cellulose or hydroxyalkyl alkylcellulose. This means that in the esterified

cellulose ether of the present invention, at least a part of the hydroxyl groups of the anhydroglucose units are substituted by alkoxy groups or hydroxyalkoxy groups or a combination of alkoxy and hydroxyalkoxy groups. The hydroxyalkoxy groups are typically hydroxymethoxy, hydroxyethoxy and/or hydroxypropoxy groups.

5 Hydroxyethoxy and/or hydroxypropoxy groups are preferred. Typically one or two kinds of hydroxyalkoxy groups are present in the esterified cellulose ether. Preferably a single kind of hydroxyalkoxy group, more preferably hydroxypropoxy, is present. The alkoxy groups are typically methoxy, ethoxy and/or propoxy groups. Methoxy groups are preferred. Illustrative of the above-defined esterified cellulose ethers are esterified alkylcelluloses, 10 such as esterified methylcelluloses, ethylcelluloses, and propylcelluloses; esterified hydroxyalkylcelluloses, such as esterified hydroxyethylcelluloses, hydroxypropylcelluloses, and hydroxybutylcelluloses; and esterified hydroxyalkyl alkylcelluloses, such as esterified hydroxyethyl methylcelluloses, hydroxymethyl ethylcelluloses, ethyl hydroxyethylcelluloses, hydroxypropyl methylcelluloses, hydroxypropyl ethylcelluloses, 15 hydroxybutyl methylcelluloses, and hydroxybutyl ethylcelluloses; and those having two or more hydroxyalkyl groups, such as esterified hydroxyethylhydroxypropyl methylcelluloses. Most preferably, the esterified cellulose ether is an esterified hydroxyalkyl methylcellulose, such as hydroxypropyl methylcellulose.

The degree of the substitution of hydroxyl groups of the anhydroglucose units by 20 hydroxyalkoxy groups is expressed by the molar substitution of hydroxyalkoxy groups, the MS(hydroxyalkoxy). The MS(hydroxyalkoxy) is the average number of moles of hydroxyalkoxy groups per anhydroglucose unit in the esterified cellulose ether. It is to be understood that during the hydroxyalkylation reaction the hydroxyl group of a hydroxyalkoxy group bound to the cellulose backbone can be further etherified by an 25 alkylating agent, e.g. a methylating agent, and/or a hydroxyalkylating agent. Multiple subsequent hydroxyalkylation etherification reactions with respect to the same carbon atom position of an anhydroglucose unit yields a side chain, wherein multiple hydroxyalkoxy groups are covalently bound to each other by ether bonds, each side chain as a whole forming a hydroxyalkoxy substituent to the cellulose backbone.

30 The term "hydroxyalkoxy groups" thus has to be interpreted in the context of the MS(hydroxyalkoxy) as referring to the hydroxyalkoxy groups as the constituting units of hydroxyalkoxy substituents, which either comprise a single hydroxyalkoxy group or a side

chain as outlined above, wherein two or more hydroxyalkoxyl units are covalently bound to each other by ether bonding. Within this definition it is not important whether the terminal hydroxyl group of a hydroxyalkoxyl substituent is further alkylated or not; both alkylated and non-alkylated hydroxyalkoxyl substituents are included for the determination of  
 5 MS(hydroxyalkoxyl). The esterified cellulose ether of the invention generally has a molar substitution of hydroxyalkoxyl groups in the range 0.05 to 1.00, preferably 0.08 to 0.90, more preferably 0.12 to 0.70, most preferably 0.15 to 0.60, and particularly 0.21 to 0.50.

The average number of hydroxyl groups substituted by alkoxy groups, such as methoxyl groups, per anhydroglucose unit, is designated as the degree of substitution of  
 10 alkoxy groups, DS(alkoxyl). In the above-given definition of DS, the term "hydroxyl groups substituted by alkoxy groups" is to be construed within the present invention to include not only alkylated hydroxyl groups directly bound to the carbon atoms of the cellulose backbone, but also alkylated hydroxyl groups of hydroxyalkoxyl substituents bound to the cellulose backbone. The esterified cellulose ethers according to this invention  
 15 preferably have a DS(alkoxyl) in the range of 1.0 to 2.5, more preferably from 1.1 to 2.4, even more preferably from 1.2 to 2.2, most preferably from 1.6 to 2.05, and particularly from 1.7 to 2.05.

Most preferably the esterified cellulose ether is an esterified hydroxypropyl methylcellulose having a DS(methoxyl) within the ranges indicated above for DS(alkoxyl)  
 20 and an MS(hydroxypropoxyl) within the ranges indicated above for MS(hydroxyalkoxyl).

The esterified cellulose ether of the present invention has (i) aliphatic monovalent acyl groups or (ii) groups of the formula  $-C(O)-R-COOA$ , wherein R is a divalent aliphatic or aromatic hydrocarbon group and A is hydrogen or a cation, or (iii) a combination of aliphatic monovalent acyl groups and groups of the formula  $-C(O)-R-COOA$ .  
 25 The cation preferably is an ammonium cation, such as  $NH_4^+$  or an alkali metal ion, such as the sodium or potassium ion, more preferably the sodium ion. Most preferably, A is hydrogen.

The aliphatic monovalent acyl groups are preferably selected from the group consisting of acetyl, propionyl, and butyryl, such as n-butyryl or i-butyryl.

30 Preferred groups of the formula  $-C(O)-R-COOA$  are  $-C(O)-CH_2-CH_2-COOA$ , such as  $-C(O)-CH_2-CH_2-COOH$  or  $-C(O)-CH_2-CH_2-COO^-Na^+$ ,

– C(O) – CH = CH – COOA, such as – C(O) – CH = CH – COOH or – C(O) – CH = CH – COO<sup>-</sup>Na<sup>+</sup>, or

– C(O) – C<sub>6</sub>H<sub>4</sub> – COOA, such as – C(O) – C<sub>6</sub>H<sub>4</sub> – COOH or – C(O) – C<sub>6</sub>H<sub>4</sub> – COO<sup>-</sup>Na<sup>+</sup>.

In the groups of formula – C(O) – C<sub>6</sub>H<sub>4</sub> – COOA the carbonyl group and the  
5 carboxylic group are preferably arranged in ortho-positions.

Preferred esterified cellulose ethers are

i) HPMCXY, wherein HPMC is hydroxypropyl methyl cellulose, X is A (acetate), or  
X is B (butyrate) or X is Pr (propionate) and Y is S (succinate), or Y is P (phthalate) or Y is  
M (maleate), such as hydroxypropyl methyl cellulose acetate phthalate (HPMCAP),  
10 hydroxypropyl methyl cellulose acetate maleate (HPMCAM), or hydroxypropyl  
methylcellulose acetate succinate (HPMCAS), or

ii) hydroxypropyl methyl cellulose phthalate (HPMCP), hydroxypropyl cellulose  
acetate succinate (HPCAS), hydroxybutyl methyl cellulose propionate succinate  
(HBMCPPrS), hydroxyethyl hydroxypropyl cellulose propionate succinate (HEHPCPrS);  
15 and methyl cellulose acetate succinate (MCAS).

Hydroxypropyl methylcellulose acetate succinate (HPMCAS) is the most preferred  
esterified cellulose ether.

The esterified cellulose ethers generally have a degree of substitution of aliphatic  
monovalent acyl groups, such as acetyl, propionyl, or butyryl groups, of 0 to 1.75, preferably  
20 of 0.05 to 1.50, more preferably of 0.10 to 1.25, and most preferably of 0.20 to 1.00.

The esterified cellulose ethers generally have a degree of substitution of groups of  
formula –C(O) – R – COOA, such as succinoyl, of 0.05 to 1.6, preferably of 0.05 to 1.30,  
more preferably of 0.05 to 1.00, and most preferably of 0.10 to 0.70 or even 0.10 to 0.60.

The sum of i) the degree of substitution of aliphatic monovalent acyl groups and ii) the  
25 degree of substitution of groups of formula –C(O) – R – COOA is generally from 0.05 to  
2.0, preferably from 0.10 to 1.4, more preferably from 0.20 to 1.15, most preferably from  
0.30 to 1.10 and particularly from 0.40 to 1.00.

The content of the acetate and succinate ester groups is determined according to  
“Hypromellose Acetate Succinate”, United States Pharmacopeia and National Formulary,  
30 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 method may be used in

analogue manner to determine the content of propionyl, butyryl, phthalyl and other ester groups.

The content of ether groups in the esterified cellulose ether is determined in the same manner as described for “Hympromellose”, United States Pharmacopeia and National  
 5 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. The formulas may be used in analogue manner to determine the DS and MS of substituents of other cellulose ether esters.

10

*% cellulose backbone*

$$= 100 - \left( \%MeO * \frac{M(OCH_3) - M(OH)}{M(OCH_3)} \right) - \left( \%HPO * \frac{M(OCH_2CH(OH)CH_3) - M(OH)}{M(OCH_2CH(OH)CH_3)} \right) - \left( \%Acetyl * \frac{M(COCH_3) - M(H)}{M(COCH_3)} \right) - \left( \%Succinoyl * \frac{M(COC_2H_4COOH) - M(H)}{M(COC_2H_4COH)} \right)$$

$$DS(Me) = \frac{\frac{\%MeO}{M(OCH_3)}}{\frac{\%cellulose\ backbone}{M(AGU)}}$$

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

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

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

$$M(MeO) = M(OCH_3) = 31.03\ Da \quad M(HPO) = M(OCH_2CH(OH)CH_3) = 75.09\ Da \\ M(Acetyl) = M(COCH_3) = 43.04\ Da \quad M(Succinoyl) = M(COC_2H_4COOH) = 101.08\ Da \\ M(AGU) = 162.14\ Da \quad M(OH) = 17.008\ Da \quad M(H) = 1.008\ Da$$

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., -OCH<sub>3</sub>). The content of the hydroxyalkoxyl group is reported based on the mass of the hydroxyalkoxyl group (i.e., -O-alkylene-OH); such as hydroxypropoxyl (i.e., -O-CH<sub>2</sub>CH(CH<sub>3</sub>)-OH). The content of the aliphatic monovalent acyl groups is reported based on the mass of -C(O) - R<sub>1</sub> wherein R<sub>1</sub> is a monovalent aliphatic group, such as acetyl (-C(O)-CH<sub>3</sub>). The content of the group of

formula  $-C(O) - R - COOH$  is reported based on the mass of this group, such as the mass of succinoyl groups (i.e.,  $-C(O) - CH_2 - CH_2 - COOH$ ).

The esterified cellulose ethers of the present invention have a viscosity of only up to 19 mPa's, generally up to 17 mPa's, and in some embodiments of the invention even only up to 15 mPa's, more preferably up to 13 mPa's, and even more preferably up to 11 mPa's, measured as a 10 wt% solution of the esterified cellulose ether in acetone at 20 °C. In some embodiments of the present invention, esterified cellulose ethers can be produced that even have a viscosity of only up to 8.0 mPa's, preferably only up to 6.5 mPa's, more preferably only up to 5.0 mPa's, most preferably only up to 4.0 mPa's, and particularly only up to 3.0 mPa's, measured as a 10 wt% solution of the esterified cellulose ether in acetone at 20 °C. The esterified cellulose ethers of the present invention typically has a viscosity of 1.50 mPa's or more, more typically of 1.65 mPa's or more, and most typically of 1.80 mPa's or more, measured as a 10 wt% solution of the esterified cellulose ether in acetone at 20 °C. In some embodiments of the present invention, the esterified cellulose ethers have a viscosity of 5.0 mPa's or more, more typically 6.5 mPa's or more. The viscosity of the esterified cellulose ethers of the present, measured as a 10 wt% solution in acetone, is considerably lower than the viscosity of known esterified cellulose ethers in acetone. The low viscosity of the esterified cellulose ethers of the present invention is highly advantageous when a liquid composition comprising the esterified cellulose ether is subjected to spray-drying, for example for preparing solid dispersions comprising an active ingredient and an esterified cellulose ether. The 10 wt% solution of the esterified cellulose ether in acetone can be prepared as in described in the Examples further below.

The average molecular weights of the esterified cellulose ethers of the present invention depends on various factors, such as the viscosity of the cellulose ether, measured as a 2.0 wt% solution in water at 20 °C, which is used for preparing the esterified cellulose ethers of the present invention, and the weight ratios between the cellulose ether, diluent and catalyst that are used in the esterification reaction, as will be explained in more details below.

In one embodiment of the invention the esterified cellulose ethers have a viscosity of up to 2.33 mPa's, or up to 2.25 mPa's, preferably up to 2.10 mPa's, more preferably up to 1.95 mPa's, even preferably up to 1.80 mPa's, most preferably up to 1.70 mPa's, and particularly up to 1.55 mPa's, measured as a 2.0 wt% solution of the esterified cellulose

ether in 0.43 wt.-% aqueous NaOH at 20 °C. Generally the viscosity of the esterified cellulose ether is 1.20 mPa's or more, typically 1.30 mPa's or more, and more typically 1.40 mPa's or more, measured as a 2.0 wt% solution of the esterified cellulose ether in 0.43 wt% aqueous NaOH at 20 °C. The 2.0 % by weight solution of the esterified cellulose ether is  
5 prepared as described in "Hyromellose 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). It has been found that the viscosity of the esterified cellulose ether in 0.43 wt% aqueous NaOH is very similar to the viscosity of the cellulose ether which is useful as a starting material for producing the  
10 esterified cellulose ether.

The esterified cellulose ethers of the present invention have a weight average molecular weight  $M_w$  of at least 90,000 Dalton, preferably from 95,000 to 500,000 Dalton, more preferably from 100,000 to 350,000 Dalton, and particularly from 105,000 to 300,000 Dalton.

15 In one embodiment the esterified cellulose ethers of the present invention have a weight average molecular weight  $M_w$  of from 90,000 to 220,000 Dalton, typically from 100,000 to 200,000 Dalton, and more typically from 100,000 to 180,000 Dalton, and a viscosity of up to 17 mPa's, typically from 1.50 mPa's to 15 mPa's, more typically from 1.65 to 13 mPa's, and most typically from 1.80 mPa's to 11 mPa's, measured as a 10 wt% solution  
20 of the esterified cellulose ether in acetone at 20 °C. In another embodiment the esterified cellulose ethers of the present invention have a weight average molecular weight of from 220,000 to 500,000 Dalton, typically from 230,000 to 350,000 Dalton, and more typically from 250,000 to 300,000 Dalton, and a viscosity of up to 19 mPa's, typically from 5 to 18 mPa's, and more typically from 8 to 17 mPa's, measured as a 10 wt% solution of the  
25 esterified cellulose ether in acetone at 20 °C. When the weight average molecular weight of an esterified cellulose ether increases, this typically means that its viscosity in acetone also increases. Surprisingly, the esterified cellulose ethers of the present invention have the mentioned high weight average molecular weight in combination with the above-mentioned low viscosity in acetone.

30  $M_w$ ,  $M_n$  and  $M_z$  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  $\text{NaH}_2\text{PO}_4$  and 0.1 M  $\text{NaNO}_3$  as mobile

phase. The mobile phase is adjusted to a pH of 8.0. The measurement of  $M_w$ ,  $M_n$  and  $M_z$  is described in more details in the Examples.

The examples below describe how to prepare the esterified cellulose ethers of the present invention. Some aspects of the process for producing these esterified cellulose ethers  
5 will be described in more general terms below.

In a preferred method of producing the esterified cellulose ethers of the present invention a cellulose ether having a viscosity of from 1.20 to 2.33 mPa's, typically from 1.20 to 2.25 mPa's, preferably from 1.20 to 2.10 mPa's, more preferably from 1.20 to 1.95 mPa's, even more preferably from 1.20 to 1.80 mPa's, most preferably from 1.20 to 1.70 mPa's, and  
10 particularly from 1.20 to 1.55 mPa's, measured as a 2.0 wt% solution in water at 20 °C (+/- 0.1 °C), is esterified with (i) an aliphatic monocarboxylic acid anhydride or (ii) a dicarboxylic acid anhydride or (iii) a combination of an aliphatic monocarboxylic acid anhydride and a dicarboxylic acid anhydride. The process is described in more details below.

The 2.0 % by weight solution of a cellulose ether in water is prepared according to  
15 United States Pharmacopeia (USP 35, "Hypromellose", pages 3467-3469), followed by an Ubbelohde viscosity measurement according to DIN 51562-1:1999-01 (January 1999). A low viscosity cellulose ether used as a starting material allows for a good miscibility of the reaction mixture used for producing the esterified cellulose ethers resulting in a  
20 homogeneous reaction mixture. Preferably a cellulose ether is used which has the type of ether groups and the degree(s) of substitution of ether groups as described further above. The above-described cellulose ethers and their production are described in the international patent applications WO2009061821 and WO2009/061815.

The cellulose ether is reacted with (i) an aliphatic monocarboxylic acid anhydride or  
25 (ii) a dicarboxylic acid anhydride or (iii) a combination of an aliphatic monocarboxylic acid anhydride and a dicarboxylic acid anhydride. Preferred aliphatic monocarboxylic acid anhydrides are selected from the group consisting of acetic anhydride, butyric anhydride and propionic anhydride. Preferred dicarboxylic acid anhydrides are selected from the group consisting of succinic anhydride, maleic anhydride and phthalic anhydride. If a dicarboxylic  
30 acid anhydride and an aliphatic monocarboxylic acid anhydride are used in combination, the two anhydrides may be introduced into the reaction vessel at the same time or separately one after the other. The amount of each anhydride to be introduced into the reaction vessel is

determined depending on the desired degree of esterification to be obtained in the final product, usually being 1 to 10 times the stoichiometric amounts of the desired molar degree of substitution of the anhydroglucose units by esterification.

If an anhydride of a dicarboxylic acid is used, the molar ratio of [anhydride of  
5 dicarboxylic acid / anhydroglucose units of cellulose ether] generally is from 0.1 / 1 to 1.5/1, preferably from 0.13 / 1 to 1 / 1 for producing an esterified cellulose ether having a weight average molecular weight  $M_w$  of from 90,000 to 220,000 Dalton, typically from 100,000 to 200,000 Dalton, and more typically from 100,000 to 180,000 Dalton. If an anhydride of a  
10 dicarboxylic acid is used, the molar ratio of [anhydride of a dicarboxylic acid / anhydroglucose units of cellulose ether] generally is from 0.3 / 1 to 0.4 / 1, preferably from 0.33 / 1 to 0.35 / 1, for producing an esterified cellulose ether having an  $M_w$  of from 220,000 to 500,000 Dalton, typically from 230,000 to 350,000 Dalton, and more typically from 250,000 to 300,000 Dalton.

If an anhydride of a monocarboxylic acid is used, the molar ratio [anhydride of an  
15 aliphatic monocarboxylic acid / anhydroglucose units of cellulose ether] generally is at least 0.9 / 1, preferably at least 1.0 / 1, and generally up to 8 / 1, preferably up to 6 / 1, and more preferably up to 4 / 1, for producing an esterified cellulose ether having a weight average molecular weight  $M_w$  of from 90,000 to 220,000 Dalton, typically from 100,000 to 200,000 Dalton, and more typically from 100,000 to 180,000 Dalton. If an anhydride of a  
20 monocarboxylic acid is used, the molar ratio [anhydride of an aliphatic monocarboxylic acid / anhydroglucose units of cellulose ether] generally is from 1.2 / 1 to 1.4 / 1, preferably from 1.25 / 1 to 1.32 / 1, for producing an esterified cellulose ether having an  $M_w$  of from 220,000 to 500,000 Dalton, typically from 230,000 to 350,000 Dalton, and more typically from 250,000 to 300,000 Dalton.

25 The molar number of anhydroglucose units of the cellulose ether utilized in the process of the present invention can be determined from the weight of the cellulose ether used as a starting material, by calculating the average molecular weight of the substituted anhydroglucose units from the DS(alkoxyl) and MS(hydroxyalkoxyl).

The esterification of the cellulose ether is preferably conducted in an aliphatic  
30 carboxylic acid as a reaction diluent, such as acetic acid, propionic acid, or butyric acid. The reaction diluent can comprise minor amounts of other solvents or diluents which are liquid at room temperature and do not react with the cellulose ether, such as aromatic or aliphatic

solvents like benzene, toluene, 1,4-dioxane, or tetrahydrofuran; or halogenated C<sub>1</sub>-C<sub>3</sub> derivatives, like dichloro methane or dichloro methyl ether, but the amount of the aliphatic carboxylic acid is preferably more than 50 percent, more preferably at least 75 percent, and even more preferably at least 90 percent, based on the total weight of the reaction diluent.

5 Most preferably the reaction diluent consists of an aliphatic carboxylic acid.

Therefore, the esterification process is described below with reference to the use of an aliphatic carboxylic acid as reaction diluent although the process is not limited to it.

It has been found that the viscosity of an esterified cellulose ether, measured as a 10 wt% solution in acetone at 20 °C, can be influenced by three major parameters of the esterification reaction: 1. the viscosity of the cellulose ether used as a starting material; 2. 10 the molar ratio [aliphatic carboxylic acid / anhydroglucose units of cellulose ether]; and 3. the molar ratio [esterification catalyst / anhydroglucose units of cellulose ether]. Based on the general teaching herein and the more specific teaching in the Examples, the skilled artisan knows how to choose these three major parameters of the esterification reaction to arrive at the esterified cellulose ethers of the present invention. 15

Surprisingly, it has been found that an esterified cellulose ether with a considerably lower viscosity, measured as a 10 wt% solution in acetone, is obtained, when a cellulose ether is used as a starting material which has a viscosity of from 1.20 to 2.33 mPa's, measured as a 2.0 wt% solution in water at 20 °C, than when a cellulose ether of a viscosity 20 of 3 mPa's or more is used as disclosed in the prior art, while keeping the other reaction parameters constant.

The appropriate molar ratio [aliphatic carboxylic acid / anhydroglucose units of cellulose ether] depends on the viscosity of the cellulose ether used as a starting material. When the viscosity of the cellulose ether used as a starting material is from 1.9 – 2.33 25 mPa's, measured as a 2.0 wt% solution in water at 20 °C, the molar ratio [aliphatic carboxylic acid / anhydroglucose units of cellulose ether] is generally 2.8 / 1.0 or more, preferably 3.0 / 1.0 or more, and more preferably 3.5 / 1.0 or more,. When the viscosity of the cellulose ether used as a starting material is only 1.2 – 1.8 mPa's, measured as a 2.0 wt% solution in water at 20 °C, the molar ratio [aliphatic carboxylic acid / anhydroglucose units 30 of cellulose ether] can be even lower, such as 0.5 / 1 or more, typically 1.0 / 1 or more, more typically 1.5 / 1 or more, and most typically 1.7 / 1 or more, while still preparing esterified

cellulose ethers which have the above-described low viscosity, measured as a 10 wt% solution of the esterified cellulose ether in acetone at 20 °C.

If an esterified cellulose ether is obtained which has a too high viscosity, measured as a 10 wt% solution in acetone, the molar ratio [aliphatic carboxylic acid / anhydroglucose units of cellulose ether] should be increased and/or the viscosity of the cellulose ether used as a starting material, measured as a 2.0 wt% solution in water at 20 °C, should be decreased in line with the present teaching.

To achieve a weight average molecular weight  $M_w$  of at least 90,000 Dalton, preferably at least 95,000 Dalton, more preferably at least 100,000 Dalton, and most preferably at least 105,000 Dalton, the molar ratio [aliphatic carboxylic acid / anhydroglucose units of cellulose ether] typically is up to 8.0 / 1.0, more typically up to 6.0 / 1.0, even more typically up to 5.0 / 1.0, and most typically up to 4.4 / 1.0, depending on the viscosity of the cellulose ether used as a starting material. The higher the molar ratio [aliphatic carboxylic acid / anhydroglucose units of cellulose ether] is, the lower is generally the weight average molecular weight of the esterified cellulose ethers, if the other reaction parameters are kept constant. If an esterified cellulose ether is obtained which has a too low molecular weight, the molar ratio [aliphatic carboxylic acid / anhydroglucose units of cellulose ether] should be decreased and/or the cellulose ether used as a starting material, measured as a 2.0 wt% solution in water at 20 °C, should be slightly increased in line with the teaching of the present invention. Choosing a cellulose ether of significantly higher viscosity as a starting material would however increase the acetone viscosity of the esterified cellulose ether in an unpredictable way.

When the weight average molecular weight of an esterified cellulose ether increases, this typically means that its viscosity in acetone also increases. However, it has very surprisingly been found that when cellulose ethers are used as a starting material which have a viscosity of only 1.20 to 2.0 mPa's, more preferably from 1.20 to 1.80 mPa's, and most preferably from 1.20 to 1.60 mPa's, measured as a 2.0 wt% solution in water at 20 °C, esterified cellulose ethers can be produced which have a high weight average molecular weight but an extremely low viscosity, in acetone, measured as 10 wt.% solution at 20 °C.

The esterification reaction is generally conducted in the presence of an esterification catalyst, preferably in the presence of an alkali metal carboxylate, such as sodium acetate or potassium acetate. The molar ratio [alkali metal carboxylate / anhydroglucose units of

cellulose ether] is generally from [0.4 / 1.0] to [3.8 / 1.0], preferably from [0.6 / 1.0] to [2.7 / 1.0], and more preferably from [0.8 / 1.0] to [1.6 / 1.0]. The higher the molar ratio [alkali metal carboxylate / anhydroglucose units of cellulose ether] is, the higher is generally the weight average molecular weight of the esterified cellulose ethers, if the other reaction  
5 parameters are kept constant in the defined ranges. If an esterified cellulose ether is obtained which has a too high viscosity, measured as a 10 wt% solution in acetone, the molar ratio [alkali metal carboxylate / anhydroglucose units of cellulose ether] should be decreased and/or the molar ratio [aliphatic carboxylic acid / anhydroglucose units of cellulose ether] should be increased and/or the viscosity of the cellulose ether used as a starting material,  
10 measured as a 2.0 wt% solution in water at 20 °C, should be decreased in line with the present teaching.

The reaction mixture is generally heated at 60 °C to 110 °C, preferably at 70 to 100 °C, for a period of time sufficient to complete the reaction, that is, typically from 2 to 25 hours, more typically from 2 to 8 hours. The reaction mixture should be thoroughly mixed  
15 to provide a homogeneous reaction mixture. After completion of the esterification reaction, the reaction product can be precipitated from the reaction mixture in a known manner, for example by contacting it with a large volume of water, such as described in U.S. Patent No. 4,226,981, International Patent Application WO 2005/115330 or European Patent Application EP 0 219 426. In a preferred embodiment of the invention the reaction product  
20 is precipitated from the reaction mixture as described in US Provisional Application 61/616207, filed 27 March 2012 or in its corresponding International Patent Application PCT/US13/030394, published as WO 2013/148154.

Another aspect of the present invention is a composition comprising a liquid diluent and one or more of the above described esterified cellulose ethers. The term “liquid diluent”  
25 as used herein means a diluent that is liquid at 25 °C and atmospheric pressure. The diluent can be water or an organic liquid diluent or a mixture of water and an organic liquid diluent. Preferably the amount of the liquid diluent is sufficient to provide sufficient fluidity and processability to the composition for the desired usage, such as spray-drying or for coating purposes.

30 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.

In one embodiment the composition of the present invention comprises as liquid diluent an organic diluent alone or mixed with a minor amount of water. In this embodiment the composition of the present invention preferably comprises more than 50, more preferably at least 65, and most preferably at least 75 weight percent of an organic liquid diluent and preferably less than 50, more preferably up to 35, and most preferably up to 25 weight percent of water, based on the total weight of the organic liquid diluent and water. This embodiment of the invention is of particularly useful if the present invention comprises an active ingredient of poor water solubility.

In another embodiment the composition of the present invention comprises as liquid diluent water alone or mixed with a minor amount of an organic liquid diluent as described above. In this embodiment the composition of the present invention preferably comprises at least 50, more preferably at least 65, and most preferably at least 75 weight percent of water and preferably up to 50, more preferably up to 35, and most preferably up to 25 weight percent of an organic liquid diluent, based on the total weight of the organic liquid diluent and water. This embodiment of the invention is particularly useful for providing coatings or capsules from aqueous compositions comprising the esterified cellulose ether of the present invention. When preparing an aqueous solution, it is preferred that at least a portion of the groups of formula  $-C(O)-R-COOA$  are in their salt form.

The composition of the present invention comprising a liquid diluent and one or more of the above described esterified cellulose ethers is useful as an excipient system for active ingredients and particularly useful as an intermediate for preparing an excipient system for active ingredients, such as fertilizers, herbicides or pesticides, or biologically active ingredients, such as vitamins, herbals and mineral supplements and drugs. Accordingly, the composition of the present invention preferably comprises one or more active ingredients, most preferably one or more drugs. The term "drug" is conventional, denoting a compound having beneficial prophylactic and/or therapeutic properties when administered to an animal, especially humans. Preferably, the drug is a "low-solubility drug", meaning that the

drug has an aqueous solubility at physiologically relevant pH (e.g., pH 1-8) of about 0.5 mg/mL or less. The invention finds greater utility as the aqueous solubility of the drug decreases. Thus, compositions of the present invention are preferred for low-solubility drugs having an aqueous solubility of less than 0.1 mg/mL or less than 0.05 mg/mL or less than 5 0.02 mg/mL, or even less than 0.01 mg/mL where the aqueous solubility (mg/mL) is the minimum value observed in any physiologically relevant aqueous solution (e.g., those with pH values between 1 and 8) including USP simulated gastric and intestinal buffers. The active ingredient does not need to be a low-solubility active ingredient in order to benefit from this invention, although low-solubility active ingredients represent a preferred class for 10 use with the invention. An active ingredient that exhibits appreciable aqueous solubility in the desired environment of use may have an aqueous solubility up to 1 to 2 mg/mL, or even as high as 20 to 40 mg/mL. Useful low-solubility drugs are listed in the International Patent Application WO 2005/115330, pages 17 – 22.

The liquid composition of the present invention preferably comprises from 1 to 40 15 percent, more preferably from 5 to 35 percent, even more preferably from 7 to 30 percent, and most preferably from 10 to 25 percent of at least one esterified cellulose ether as described above, from 40 to 99 percent, more preferably from 50 to 94.9 percent, even more preferably from 65 to 92.5 percent and most preferably from 70 to 89 percent of a liquid diluent described further above, and from 0 to 40 percent, more preferably from 0.1 to 20 40 percent, even more preferably from 0.5 to 25 percent, and most preferably from 1 to 15 percent of an active ingredient, based on the total weight of the composition. The low viscosity of the esterified cellulose ether, measured as a 10 wt% solution in acetone at 20 °C, allows the incorporation of a high concentration of the esterified cellulose ether, i.e., a high ratio of esterified cellulose ether to liquid diluent, while still providing a liquid 25 composition of reasonably low viscosity. This can be utilized in two ways to produce solid dispersions of an active ingredient in an esterified cellulose ether: 1. Either the ratio of esterified cellulose ether/active ingredient is kept the same as in known, more dilute compositions. In this case a higher concentration of the esterified cellulose ether also leads to a higher concentration of the active ingredient in the liquid composition, and, accordingly 30 to an increased throughput of the active ingredient in the production of solid dispersions while maintaining the same stability of the active ingredient. 2. Alternatively, only the concentration of the esterified cellulose ether in the liquid composition is increased, but not

the concentration of the active ingredient. This leads to a higher ratio of esterified cellulose ether/active ingredient, which leads to an improved stabilization of the active ingredient in the matrix of the esterified cellulose ether upon removal of the liquid diluent without decreasing the throughput of the active ingredient. This means that formulators can operate  
5 at a higher content of the esterified cellulose ether in the liquid formulation – without the need to reduce the content of the active ingredient - in order to achieve enhanced stabilization of the amorphous state of an active ingredient in a solid dosage form. The esterified cellulose ethers of the present invention allow a high loading of the active ingredient in the liquid composition while still achieving a reasonably high throughput in  
10 preparing a solid dispersion. The production of semi-ordered instead of amorphous dispersions to achieve a higher active ingredient throughput as proposed in WO2004/014342, page 13, last paragraph, is not necessary.

In one aspect of the invention the composition comprising at least one esterified cellulose ether as described above, one or more active ingredients and optionally one or  
15 more adjuvants can be used in liquid form, for example in the form of a suspension, a slurry, a sprayable composition, or a syrup. The liquid composition is useful, e.g., for oral, ocular, topical, rectal or nasal applications. The liquid diluent should generally be pharmaceutically acceptable, such as ethanol or glycerol, optionally mixed with water as described above. The low viscosity of the esterified cellulose ether in acetone or another organic solvent  
20 significantly improves the handling of the liquid composition, such as its ability of being poured or pumped.

In another aspect of the invention the liquid composition of the present invention is used for producing a solid dispersion comprising at least one active ingredient, such as a drug described further above, at least one esterified cellulose ether as described above and  
25 optionally one or more adjuvants. The solid dispersion is produced by removing the liquid diluent from the composition. The low viscosity of the esterified cellulose ether in acetone or another organic solvent allows the incorporation of a high concentration of the esterified cellulose ether, and accordingly a high concentration of a drug, into the composition while still maintaining a reasonably low viscosity of the liquid composition. This is highly  
30 advantageous for achieving a high throughput when the liquid composition is used for coating purposes or when the comprising the esterified cellulose ether is subjected to spray-drying, for example for preparing solid dispersions comprising an active ingredient and an

esterified cellulose ether. Moreover, liquid formulations using a high ratio of esterified cellulose ether to active ingredient, as described above, can be formulated with spray drying. A high ratio of esterified cellulose ether to active ingredient is desired in maintaining supersaturation of poorly soluble active ingredients and for increasing its bioavailability.

5 One method of removing the liquid diluent from the liquid composition is by casting the liquid composition into a film or a capsule or by applying the liquid composition onto a solid carrier that in turn may comprise an active ingredient. The use of the liquid composition of the present invention for coating purposes is a preferred aspect of the present invention.

10 A preferred method of producing a solid dispersion is by spray-drying. The term "spray-drying" refers to processes involving breaking up liquid mixtures into small droplets (atomization) and rapidly removing solvent from the mixture in a spray-drying apparatus where there is a strong driving force for evaporation of solvent from the droplets. Spray-drying processes and spray-drying equipment are described generally in Perry's Chemical  
15 Engineers' Handbook, pages 20-54 to 20-57 (Sixth Edition 1984). More details on spray-drying processes and equipment are reviewed by Marshall, "Atomization and Spray-Drying," 50 Chem. Eng. Prog. Monogr. Series 2 (1954), and Masters, Spray Drying Handbook (Fourth Edition 1985). A useful spray-drying process is described in the International Patent Application WO 2005/115330, page 34, line 7 – page 35, line 25.

20 Alternatively, the solid dispersion of the present invention may be prepared by i) blending a) at least one esterified cellulose ether defined above, b) one or more active ingredients and c) one or more optional additives, and ii) subjecting the blend to extrusion. The term "extrusion" as used herein includes processes known as injection molding, melt casting and compression molding. Techniques for extruding, preferably melt-extruding compositions  
25 comprising an active ingredient such as a drug are known and described by Joerg Breitenbach, Melt extrusion: from process to drug delivery technology, *European Journal of Pharmaceutics and Biopharmaceutics* 54 (2002) 107–117 or in European Patent Application EP 0 872 233. The solid dispersion of the present invention preferably comprises from 20 to 99.9 percent, more preferably from 30 to 98 percent, and most  
30 preferably from 60 to 95 percent of an esterified cellulose ether a) as described above, and preferably from 0.1 to 80 percent, more preferably from 2 to 70 percent, and most preferably from 5 to 40 percent of an active ingredient b), based on the total weight of the esterified

cellulose ether a) and the active ingredient b). The combined amount of the esterified cellulose ether a) and the active ingredient b) is preferably at least 70 percent, more preferably at least 80 percent, and most preferably at least 90 percent, based on the total weight of the solid dispersion. The remaining amount, if any, consists of one or more of the  
5    adjuncts c) as described below. The solid dispersion can comprise one or more of the esterified cellulose ethers a), one or more of the active ingredients b), and optionally one or more of the adjuncts c), however their total amount is generally within the above-mentioned ranges.

Once the solid dispersion comprising at least one active ingredient in at least one  
10    esterified cellulose ether has been formed, several processing operations can be used to facilitate incorporation of the dispersion into a dosage form. These processing operations include drying, granulation, and milling. The inclusion of optional adjuncts in the solid dispersion may be useful in order to formulate the composition into dosage forms. The solid dispersion of the present invention may be in various forms, such as in the form of strands,  
15    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.

The amount of the active ingredient in the dosage form is generally is at least 0.1 percent, preferably at least 1 percent, more preferably at least 3 percent, most preferably at least 5 percent and generally up to 70 percent, preferably up to 50 percent, more preferably  
20    up to 30 percent, most preferably up to 25 percent, based on the total weight of the dosage form.

In another aspect of the invention the composition of the present invention comprising a liquid diluent and one or more of the above described esterified cellulose ethers may be used for coating dosage forms, such as tablets, granules, pellets, caplets,  
25    lozenges, suppositories, pessaries or implantable dosage forms, to form a coated composition. If the composition of the present invention comprises an active ingredient, such as a drug, drug layering can be achieved, i.e., the dosage form and the coating may comprise different active ingredients for different end-uses and/or having different release kinetics.

In yet another aspect of the invention the composition of the present invention comprising a liquid diluent and one or more of the above described esterified cellulose

ethers may be used for the manufacture of capsules in a process which comprises the step of contacting the liquid composition with dipping pins.

The liquid composition and the solid dispersion of the present invention may further comprise optional additives, such as coloring agents, pigments, opacifiers, flavor and taste improvers, antioxidants, and any combination thereof. Optional additives are preferably pharmaceutically acceptable. Useful amounts and types of one or more optional adjuvants  
5 are generally known in the art and depend on the intended end-use of the liquid composition or the solid dispersion of the present invention.

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

## 10 EXAMPLES

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

### Viscosity of Hydroxypropyl Methyl Cellulose (HPMC) samples

15 The viscosity of the HPMC samples was measured as a 2.0 % by weight solution in water at  $20^{\circ}\text{C} \pm 0.1^{\circ}\text{C}$ . The 2.0 % by weight HPMC solution in water was prepared according to United States Pharmacopeia (USP 35, "Hyromellose", pages 3467-3469), followed by an Ubbelohde viscosity measurement according to DIN 51562-1:1999-01 (January 1999).

20

### Viscosity of Hydroxypropyl Methyl Cellulose Acetate Succinate (HPMCAS)

The 2.0 % by weight solution of the HPMCAS in 0.43 wt% aqueous NaOH was prepared as described in "Hyromellose Acetate Succinate, United States Pharmacopia and National Formulary, NF 29, pp. 1548-1550", followed by an Ubbelohde viscosity  
25 measurement at  $20^{\circ}\text{C}$  according to DIN 51562-1:1999-01 (January 1999).

The 10 wt% solution of the esterified cellulose ether in acetone was prepared by first determining the loss on drying of the HPMCAS according "Hyromellose Acetate Succinate, United States Pharmacopia and National Formulary, NF 29, pp. 1548-1550". Subsequently 10.00 g HPMCAS, based on its dry weight, was mixed with 100 g of acetone  
30 under vigorous stirring at room temperature. The mixture was rolled on a roller mixer for

about 24 hours. The solution was centrifuged at 2000 rpm for 3 minutes using a Megafuge 1.0 centrifuge, commercially available from Heraeus Holding GmbH, Germany, followed by an Ubbelohde viscosity measurement at 20 °C according to DIN 51562-1:1999-01 (January 1999).

5

#### Content of ether and ester groups of HPMCAS

The content of ether groups in the esterified cellulose ether was determined in the same manner as described for “Hydromellose”, United States Pharmacopeia and National Formulary, USP 35, pp 3467-3469.

10

The ester substitution with acetyl groups (-CO-CH<sub>3</sub>) and the ester substitution with succinoyl groups (-CO-CH<sub>2</sub>-CH<sub>2</sub>-COOH) were determined according to Hydromellose Acetate Succinate, United States Pharmacopeia and National Formulary, NF 29, pp. 1548-1550”. Reported values for ester substitution were corrected for volatiles (determined as described in section “loss on drying” in the above HPMCAS monograph).

15

#### Determination of M<sub>w</sub>, M<sub>n</sub> and M<sub>z</sub> of HPMCAS

M<sub>w</sub>, M<sub>n</sub> and M<sub>z</sub> 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<sub>2</sub>PO<sub>4</sub> and 0.1 M NaNO<sub>3</sub>. The mobile phase was adjusted to a pH of 8.0. Solutions of the cellulose ether esters were filtered into a HPLC vial through a syringe filter of 0.45 μm pore size.

20

More specifically, the utilized Chemicals and solvents were:  
Polyethylene oxide standard materials (abbreviated as PEOX 20 K and PEOX 30 K) were purchased from Agilent Technologies, Inc. Palo Alto, CA, catalog number PL2083-1005 and PL2083-2005.

25

Acetonitrile (HPLC grade ≥ 99.9 %, CHROMASOL plus), catalog number 34998, sodium hydroxide (semiconductor grade, 99.99 %, trace metal base), catalog number 306576, water (HPLC grade, CHROMASOLV Plus) catalog number 34877 and sodium nitrate (99,995 %, trace metal base) catalog number 229938 were purchased from Sigma-Aldrich, Switzerland.

30

Sodium dihydrogen phosphate ( $\geq 99.999\%$  TraceSelect) catalog number 71492 was purchased from FLUKA, Switzerland.

The normalization solution of PEOX20 K at 5 mg/mL, the standard solution of PEOX30 K at 2 mg/mL, and the sample solution of HPMCAS at 2 mg/mL were prepared by adding a weighed amount of polymer into a vial and dissolving it with a measured volume of mobile phase. All solutions were allowed to dissolve at room temperature in the capped vial for 24 h with stirring using a PTFE-coated magnetic stirring bar.

The normalization solution (PEOX 20k, single preparation, N) and the standard solution (PEOX30 K, double preparation, S1 and S2) were filtered into a HPLC vial through a syringe filter of 0.02  $\mu\text{m}$  pore size and 25 mm diameter (Whatman Anatotop 25, catalog number 6809-2002), Whatman.

The test sample solution (HPMCAS, prepared in duplicate, T1, T2) and a laboratory standard (HPMCAS, single preparation, LS) were filtered into a HPLC vial through a syringe filter of 0.45  $\mu\text{m}$  pore size (Nylon, e.g. Acrodisc 13 mm VWR catalog number 514-4010).

Chromatographic condition and run sequence were conducted as described by Chen, R. et al.; Journal of Pharmaceutical and Biomedical Analysis 56 (2011) 743–748). The SEC-MALLS instrument set-up included a HP1100 HPLC system from Agilent Technologies, Inc. Palo Alto, CA; a DAWN Heleos II 18 angle laser light scattering detector and a OPTILAB rex refractive index detector, both from Wyatt Technologies, Inc. Santa Barbara, CA. The analytical size exclusion column (TSK-GEL® GMPWXL, 300  $\times$  7.8 mm) was purchased from Tosoh Bioscience. Both the OPTILAB and the DAWN were operated at 35 °C. The analytical SEC column was operated at room temperature ( $24 \pm 5$  °C). The mobile phase was a mixture of 40 volume parts of acetonitrile and 60 volume parts of aqueous buffer containing 50 mM NaH<sub>2</sub>PO<sub>4</sub> and 0.1 M NaNO<sub>3</sub> prepared as follows:

Aqueous buffer: 7.20 g of sodium dihydrogen phosphate and 10.2 g of sodium nitrate were added to 1.2 L purified water in a clean 2 L glass bottle under stirring until dissolution.

Mobile phase: 800 mL of acetonitrile were added to 1.2 L of the aqueous buffer prepared above, and stirred until a good mixture was achieved and the temperature equilibrated to ambient temperature.

The mobile phase was pH adjusted to 8.0 with 10M NaOH and filtered through a 0.2 m nylon membrane filter. The flow rate was 0.5 mL/min with in-line degassing. The injection volume was 100  $\mu$ L and the analysis time was 35 min.

The MALLS data were collected and processed by Wyatt ASTRA software (version 5.3.4.20) using dn/dc value (refractive index increment) of 0.120 mL/g for HPMCAS. The light scattering signals of detector Nos. 1–4, 17, and 18) were not used in the molecular weight calculation. A representative chromatographic run sequence is given below: B, N, LS, S1 (5x), S2, T1 (2x), T2 (2x), T3 (2x), T4 (2x), S2, T5(2x), etc., S2, LS, W, where, B represents blank injection of mobile phase, N1 represents normalization solution; LS represents a laboratory standard HPMCAS; S1 and S2 represent standard solutions one and two, respectively; T1, T2, T3, T4, and T5 represent test sample solutions and W represents water injection. (2x) and (5x) denote the number of injections of the same solution.

Both the OPTILAB and the DAWN were calibrated periodically according to the manufacturer's recommended procedures and frequency. A 100  $\mu$ L injection of a 5 mg/mL polyethylene oxide standard (PEOX20 K) was employed for normalizing all angle light scattering detectors relative to 90° detector for each run sequence.

Use of this mono-dispersed polymer standard also enabled the volume delay between the OPTILAB and the DAWN to be determined, permitting proper alignment of the light scattering signals to the refractive index signal. This is necessary for the calculation of the weight-averaged molecular weight ( $M_w$ ) for each data slice.

#### Production of Hydroxypropyl Methyl Cellulose Acetate Succinate (HPMCAS) of Examples 1 – 4

Glacial acetic acid, acetic anhydride, a hydroxypropyl methylcellulose (HPMC), succinic anhydride and sodium acetate (water free) were introduced in the amounts listed in Table 1 below into a reaction vessel under thorough stirring to produce a homogeneous reaction mixture. The HPMC had a methoxyl and hydroxypropoxyl substitution and a viscosity, measured as a 2 % solution in water at 20 °C, as listed in Table 2 below.

The mixture was heated at 85° C with agitation for 3 or 3.5 hours, as listed in Table 1 below, 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 washing was conducted in several portions with intermediate filtration steps to obtain HPMCAS of very high purity. The HPMCAS products should be washed and filtrated until their viscosity is substantially constant (10 wt.% in acetone). The numbers of L of water x and y are listed in Table 1 below. After the last filtration step the product was dried at 50°C overnight.

Example 4 was repeated. The average of two experiments leading to substantially the same results are listed in Table 2 below.

#### Production of HPMCAS of Comparative Examples A and B

The production of HPMCAS according to Comparative Examples A and B was carried out as in Examples 1 to 4, except that the type of HPMC and the weight ratios of glacial acetic acid, acetic anhydride, HPMC, succinic anhydride and sodium acetate (water free) were used as disclosed in Example 2 of European Patent Application EP 0219 426 A2. The used amounts are listed in Table 1 below.

The HPMC used in Comparative Example A had a viscosity of 6.0 mPa's, measured as a 2 % solution in water at 20 °C, 28.2 % by weight of hydroxypropoxyl groups and 9.0 % by weight of methoxyl groups. This HPMC is commercially available from The Dow Chemical Company as Methocel E6 LV Premium cellulose ether. The HPMC used in Comparative Example B had a viscosity of 3.1 mPa's, measured as a 2 % solution in water at 20 °C, 9.3 % by weight of hydroxypropoxyl groups and 28.2 % by weight of methoxyl groups. This HPMC is commercially available from The Dow Chemical Company as Methocel E3 LV Premium cellulose ether.

The mixture was heated at 85° C with agitation for 3.5 hours 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 below. The product was isolated by filtration and dried at 55°C for 12 h.

The obtained ester substitutions % acetyl and % succinoyl in Comparative Examples A and B were significantly different from those disclosed in Example 2 of European Patent Application EP 0219 426 A2. Therefore, Comparative Examples A and B were repeated. The obtained ester substitutions % acetyl and % succinoyl in the repeated Examples A and

B were substantially the same as in the first set of Comparative Examples A and B. The results in Tables 2 show the average of the two runs of Comparative Examples A and B.

Production of HPMCAS of Comparative Examples C and D

5 The production of HPMCAS according to Comparative Examples C and D was carried out as in Examples 1 to 4, except that the weight ratios of glacial acetic acid, acetic anhydride, HPMC, succinic anhydride and sodium acetate (water free) were used as disclosed International Patent Application WO 2005/115330, pages 51 and 52, polymers 1 and 3. The product was obtained, separated and washed as described in International Patent  
10 Application WO 2005/115330. The reaction mixture was quenched into 2.4L of water, precipitating the polymer. An additional 1L of water was used to complete the precipitation for example C only. The polymer was then isolated and washed with 3x 300 mL of water. Then the polymer was dissolved in 600 mL of acetone and again precipitated in 2.4L of water. To complete precipitation another 1L of water was added.

15

Comparative Examples E to G

As disclosed in International Patent Application WO 2011/159626 on pages 1 and 2, HPMCAS is currently commercially available from Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan), known by the trade name "AQOAT". Shin-Etsu manufactures three grades of  
20 AQOAT polymers that have different combinations of substituent levels to provide enteric protection at various pH levels, AS-L, AS-M, and AS-H, typically followed by the designation "F" for fine or "G", such as AS-LF or AS-LG. Their sales specifications are listed below.

Properties of AQOAT polymers as listed in WO 2011/159626

Designation of analyzed commercial samples: Comparative Example	E	F	G
Substituent content	Published Composition of AQOAT polymers (wt %)		
	L-Grade	M-Grade	H-Grade
Methoxyl	20.0 – 24.0	21.0 – 25.0	22.0 – 26.0
Hydroxypropoxyl	5.0 – 9.0	5.0 – 9.0	6.0 – 10.0
Acetyl	5.0 – 9.0	7.0 – 11.0	10.0 – 14.0
Succinoyl	14.0 – 18.0	10 – 14	4.0 – 8.0

Samples of the commercially available materials were analyzed as described further above.

5           Comparative Examples H, I-1, I-2, J-1 and J-2

HPMCAS samples were produced as described on pages 34 and 35 of WO 2011/159626. In Comparative Example H the recipe for HPMCAS-K(1) was exactly repeated. In Comparative Examples I-1 and I-2 the recipe for HPMCAS-K(2) and in Comparative Examples J-1 and J-2 the recipe for HPMCAS-K(3) were exactly repeated.

10          Comparative Examples I and J were each conducted twice and reported as I-1, I-2, J-1 and J-2 respectively since the results in Comparative Examples I-1 and J-1 for  $DOS_{Ac}$  and  $DOS_s$  deviated from the results reported in WO 2011/159626 for HPMCAS-K(2) and HPMCAS-K(3).

15           The properties of the HPMCAS produced according to Examples 1 – 4 and comparative Examples A – D, H, I-1, I-2, J-1 and J-2 and the properties of the commercially available Comparative Examples E to G are listed in Table 2 below.

In Table 2 below the abbreviations have the following meanings:

- $DS_M$  = DS(methoxyl): degree of substitution with methoxyl groups;
- 20           $MS_{HP}$  = MS(hydroxypropoxyl): molar subst. with hydroxypropoxyl groups;
- $DOS_{Ac}$ : degree of substitution of acetyl groups;
- $DOS_s$ : degree of substitution of succinoyl groups.

Table 1

Table 1 (Comp.) Example	HPMC*		HPMC, 2% viscosity in water (mPa-s)	acetic acid		Succinic anhydride		Acetic anhydride		Sodium acetate		Heating at 85 °C	x L of water	y L of water
	g	Mol		G	mol/mol HPMC	g	mol/mol HPMC	g	mol/mol HPMC	g	mol/mol HPMC			
1	60	0.3	1.39	30	1.7	10.1	0.34	37.2	1.28	17.4	0.72	3.5	0.8	29
2	100	0.49	2.0	117	4.0	16.9	0.34	62	1.28	41.4	1.02	3.5	1.33	6.8
3	100	0.49	2.0	126	4.3	16.9	0.34	62	1.28	41.4	1.02	3.5	1.33	6.3
4	230	1.14	2.1	253	3.7	38.8	0.34	143	1.28	95.2	1.02	3.5	3	11
A	100	0.49	6.0	300	10.1	25.0	0.51	38	0.78	80	1.97	3.5	1.2	12
B	200	0.96	3.1	600	10.2	50.0	0.51	76	0.78	160	1.97	3.5	2.4	11
C	80	0.40	3.1	420	17.7	18.9	0.48	640.2	16.53	40.43	1.25	21.75	See Comp. Examples C and D above	
D	80	0.40	3.1	420	17.7	13.2	0.33	432.8	11.17	40.43	1.25	21.75		

\* calculated on the dried basis

Table 2

Table 2 (Comp.) Example	Molecular weight (kDA)			10% viscosity in acetone (mPa·s)	2% viscosity in NaOH* (mPa·s)	Ether Substitution		Ester substitution		Ether Substitution		Ester substitution	
	Mn	Mw	Mz			Methoxyl (%)	Hydroxy- Propoxyl, %	Acetyl (%)	Succinoyl (%)	DS <sub>M</sub>	MS <sub>HP</sub>	DOS <sub>Ac</sub>	DOS <sub>s</sub>
1	12	112	863	2.41	1.49	22.7	7.7	10.2	11.6	1.90	0.27	0.62	0.30
2	28	158	950	10.4	2.0	23.1	7.9	9.3	11.4	1.91	0.27	0.56	0.29
3	20	105	649	8.5	2.0	23.3	7.8	9.4	11.7	1.94	0.27	0.56	0.30
4**	51	280	1694	15.9	1.96	23.3	7.6	9.7	12.0	1.96	0.26	0.57	0.31
A	87	270	1060	638	4.58	21.9	7.2	5.6	16.8	1.83	0.25	0.34	0.43
B	26	65	329	16.6	2.89	22.9	7.3	5.7	16.0	1.91	0.25	0.34	0.41
C	23	51	462	12.8	2.86	22.3	7.4	11.7	11.7	1.90	0.26	0.72	0.31
D	22	54	1158	13.5	2.86	22.6	7.1	12.6	9.1	1.87	0.24	0.75	0.23
E	33	153	889	27.7	3.00	22.5	7.0	8.1	14.7	1.90	0.24	0.49	0.38
F	27	114	654	22.9	2.94	23.1	7.3	9.3	10.6	1.88	0.24	0.54	0.26
G	29	137	821	29.8	2.89	23.6	7.2	11.6	7.9	1.90	0.24	0.67	0.19
H	94	427	2592	insoluble	2.06	15.7	6.2	12.1	20.8	1.47	0.24	0.82	0.60
I-1	recovery rate only 71%			partially insoluble	2.05	16.2	6.3	14.3	16.6	1.47	0.24	0.94	0.46
I-2	recovery rate only 71%			partially insoluble	1.97	15.8	6.0	14.8	17.1	1.45	0.23	0.98	0.48

Table 2 (Comp.) Example	Molecular weight (kDA)			10% viscosity in acetone (mPa·s)	2% viscosity in NaOH* (mPa·s)	Ether Substitution		Ester substitution		Ether Substitution		Ester substitution	
	Mn	Mw	Mz			Methoxyl (%)	Hydroxy- Propoxyl, %	Acetyl (%)	Succinoyl (%)	DS <sub>M</sub>	MS <sub>HP</sub>	DOS <sub>Ac</sub>	DOS <sub>s</sub>
J-1	39	234	2701	partially insoluble	1.92	17.2	6.6	19.1	8.2	1.49	0.24	1.19	0.22
J-2	25	143	2280	partially insoluble	1.81	16.9	6.4	19.0	8.7	1.47	0.23	1.19	0.23

\*viscosity measured as a 2.0 wt% solution of the esterified cellulose ether in 0.43 wt% aqueous NaOH at 20 °C

\*\* average of two separate production experiments

European Patent Application EP 0 219 426 discloses that the HPMCAS of Comparative Example A is useful as an enterosoluble film-coating material on tablets which has resistance against a simulated gastric juice, whereas tablets coated with HPMCAS of Comparative Example B disintegrate in simulated gastric juice. The HPMCAS of Comparative Example A has a higher weight average molecular weight than Comparative Example B. HPMCAS of a high weight average molecular weight is evidently very desirable, however the HPMCAS of Comparative Example A has a much higher viscosity, measured as a 10 wt.% solution in acetone, and can be less efficiently processed in spray-drying or coating processes.

The comparison between Examples 1 – 4 on one hand and Comparative Examples E – G on the other hand illustrates that the HPMCAS of Examples 1 – 4 have weight average molecular weights in the same range as or even higher than the HPMCAS of Comparative Examples E – G but a much lower viscosity, measured as a 10 wt.% solution in acetone.

The comparison between Examples 1 - 3 on one hand and Comparative Examples B – D on the other hand illustrates that the HPMCAS of Examples 1 – 4 have a higher weight average molecular weight than the HPMCAS of Comparative Examples B – D, and the HPMCAS of Examples 1 – 4 exhibit a 10 % viscosity in acetone that is comparable to or even significantly lower than the 10 % viscosity in acetone of Comparative Examples B – D.

The HPMCAS of Comparative Examples H, I-1, I-2, J-1 and J-2 were not or only partially soluble in acetone at a concentration of 10 wt-%. In Comparative Examples I-1 and I-2 the recovery rate in the utilized HPLC method was too low to make a reasonably reliable  $M_w$ ,  $M_n$  and  $M_z$  determination. Recovery rate = [weight of HPMCAS recovered from HPLC column / weight of HPMCAS introduced into HPLC column] x 100.

### Claims

1. An esterified cellulose ether comprising (i) aliphatic monovalent acyl groups or (ii) groups of the formula  $-C(O)-R-COOA$ , wherein R is a divalent aliphatic or aromatic hydrocarbon group and A is hydrogen or a cation, or (iii) a combination of aliphatic monovalent acyl groups and groups of the formula  $-C(O)-R-COOA$ , having a viscosity of up to 19 mPa•s, measured as a 10 wt% solution of the esterified cellulose ether in acetone at 20 °C, and having a weight average molecular weight  $M_w$  of at least 90,000 Dalton.
2. The esterified cellulose ether of claim 1 additionally having a viscosity of up to 2.33 mPa•s, measured as a 2.0 wt% solution of the esterified cellulose ether in 0.43 wt% aqueous NaOH at 20 °C.
3. The esterified cellulose ether of claim 1 or 2 having a weight average molecular weight  $M_w$  of from 90,000 to 220,000 Dalton and a viscosity of from 1.50 mPa•s to 15 mPa•s, measured as a 10 wt% solution of the esterified cellulose ether in acetone at 20 °C.
4. The esterified cellulose ether of claim 1 or 2 having a weight average molecular weight  $M_w$  of from 220,000 to 350,000 Dalton and a viscosity of from 5 to 18 mPa•s, measured as a 10 wt% solution of the esterified cellulose ether in acetone at 20 °C.
5. The esterified cellulose ether of any one of claims 1 to 4 wherein the aliphatic monovalent acyl groups are acetyl, propionyl or butyryl groups and the groups of the formula  $-C(O)-R-COOA$  are  $-C(O)-CH_2-CH_2-COOA$ ,  $-C(O)-CH=CH-COOA$ , or  $-C(O)-C_6H_4-COOA$  groups.
6. The esterified cellulose ether of any one of claims 1 to 5 being an esterified hydroxyalkyl methyl cellulose.

7. The esterified cellulose ether of any one of claims 1 to 6 being hydroxypropyl methyl cellulose acetate succinate.
8. A composition comprising a liquid diluent and at least one esterified cellulose ether of any one of claims 1 to 7.
9. The composition of claim 8 additionally comprising at least one active ingredient and optionally one or more adjuvants.
10. The composition of claim 8 or 9 comprising from 10 to 25 percent of at least one esterified cellulose ether, from 70 to 89 percent of a liquid diluent, and from 1 to 15 percent of an active ingredient, based on the total weight of the composition.
11. A solid dispersion comprising at least one active ingredient and at least one esterified cellulose ether of any one of claims 1 to 7.
12. The solid dispersion of claim 11 wherein the solid dispersion has been formulated into tablets, pills, granules, pellets, caplets, microparticles, fillings of capsules, or into a paste, cream, suspension or slurry.
13. A dosage form being coated with at least one esterified cellulose ether of any one of claims 1 to 7.
14. A capsule shell comprising at least one esterified cellulose ether of any one of claims 1 to 7.
15. A process for producing the esterified cellulose ether of any one of claims 1 to 7, wherein a cellulose ether having a viscosity of from 1.20 to 2.33 mPa•s, measured as a 2 wt.-% solution in water at 20°C, is esterified with (i) an aliphatic monocarboxylic acid anhydride or (ii) a dicarboxylic acid anhydride or (iii) a combination of an aliphatic monocarboxylic acid anhydride and a dicarboxylic acid anhydride.

INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2014/019328

A. CLASSIFICATION OF SUBJECT MATTER  
INV. C08B13/00 A61K9/28  
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)  
C08B A61K

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, BIOSIS, EMBASE, MEDLINE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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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
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

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

Date of the actual completion of the international search  30 April 2014	Date of mailing of the international search report  09/05/2014
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  Friedrich, Christof

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2014/019328

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TANNO FUMIÉ ET AL: "Evaluation of hypromellose acetate succinate (HPMCAS) as a carrier in solid dispersions", DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, NEW YORK, NY, US, vol. 30, no. 1, 1 January 2004 (2004-01-01), pages 9-17, XP009124621, ISSN: 0363-9045, DOI: 10.1081/DDC-120027506 table 2	1-15
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Information on patent family members

International application No

PCT/US2014/019328

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