(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 December 2017 (28.12.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/223018 A1

(51) International Patent Classification:
C08B 11/18 (2006.01) *C08L 1/30* (2006.01)

(21) International Application Number:
PCT/US2017/038218

(22) International Filing Date:
20 June 2017 (20.06.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/353,798 23 June 2016 (23.06.2016) US

(71) Applicant: **DOW GLOBAL TECHNOLOGIES LLC** [US/US]; 2040 Dow Center, Midland, MI 48674 (US).

(72) Inventor: **PETERMANN, Oliver**; August-Wolff-Strasse 13, 29699 Bomlitz (DE).

(74) Agent: **JOHNSON, Christopher**; The Dow Chemical Company, Intellectual Property, P.O. Box 1967, Midland, Michigan 48641-1967 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2017/223018 A1

(54) Title: ESTERIFIED CELLULOSE ETHERS COMPRISING TRIMELLITYL GROUPS

(57) Abstract: An esterified cellulose ether is provided wherein - the ester groups are (i) trimellityl groups or (ii) a combination of trimellityl groups and aliphatic monovalent acyl groups, - the degree of substitution of trimellityl groups is from 0.01 to 0.11, and - the degree of substitution of aliphatic monovalent acyl groups is from 0 to 0.40.

ESTERIFIED CELLULOSE ETHERS COMPRISING TRIMELLITYL GROUPS

FIELD

This invention concerns novel esterified cellulose ethers comprising trimellityl groups and their use for producing capsule shells or solid drug dispersions or for coating dosage forms.

INTRODUCTION

Various esterified cellulose ethers are useful in the pharmaceutical field, such as hydroxypropyl methylcellulose trimellitate (HPMCT).

US Patent No. 5,700,929 discloses a base for coating solid enteric pharmaceutical preparations which have a dissolution pH ranging from 3.5 to 4.5. The coating base essentially consists of hydroxypropyl methylcellulose trimellitate having 1.1 to 1.6 methoxy groups per glucose ring and 0.2 to 1.0 trimellitate groups per glucose ring.

International patent application WO 2006/082518 discloses compositions comprising hydroxypropyl methylcellulose alkanyl trimellitate having a degree of substitution of alkanyl groups, such as acetyl or propionyl, of at least 0.5, preferably at least 0.6, and a degree of substitution of trimellityl groups of at least 0.03, preferably at least 0.05. These polymers provide concentration enhancement of low-solubility drugs when used to formulate compositions of such drugs.

H. Kokubo et al. disclose "Development of Cellulose Derivatives as Novel Enteric Coating Agents Soluble at pH 3.5-4.5 and Higher" in *Chem. Pharm. Bull.* **45**(8) 1350 – 1353 (1997), Vol. 45, No. 8. Hydroxypropyl methyl cellulose (HPMC) was selected as base polymer to develop novel enteric coating agents for acid protection which can dissolve at pH around 4. HPMC was modified with trimellitic acid at degrees of substitution ranging from 0.28 – 0.65. Enteric polymers are those that are resistant to dissolution in the acidic environment of the stomach. 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. As disclosed in the article of H. Kokubo et al., enteric coating polymers having carboxyl groups in their undissociated form have very low solubility in water. The degree of neutralization defines the ratio of deprotonated carboxylic groups over the sum of deprotonated and protonated carboxylic groups; i.e., the lower the degree of neutralization,

the more carboxyl groups are present in their undissociated form. When the pH is raised by titration, the degree of neutralization of the carboxylic groups increases and water-solubility of the polymers increases. A HPMCT sample is insoluble in purified water and in 0.1 M aqueous NaCl solution when its degree of neutralization is less than 0.6 or less than 0.7, respectively.

Esterified cellulose ethers which comprise trimellityl groups of a low degree of neutralization are dissolved in organic solvents before use due their low solubility in water. However, the use of organic solvents for enteric coatings is considered disadvantageous, e.g., because of high production costs and potentially remaining amounts of organic solvents in the esterified cellulose ethers. Alternatively, aqueous dispersions of esterified cellulose ethers comprising trimellityl groups are prepared, but these preparation methods are quite time consuming. Therefore, it would be desirable to provide novel esterified cellulose ethers which comprise trimellityl groups and which are soluble in water even when the majority of the carboxylic groups are not neutralized.

Surprisingly, novel esterified cellulose ethers comprising trimellityl groups have been found which can be dissolved in water even when they comprise non-neutralized groups. The preferred embodiments of these esterified cellulose ethers display resistance to dissolution in the acidic environment of the stomach.

SUMMARY

One aspect of the present invention is an esterified cellulose ether wherein the ester groups are (i) trimellityl groups or (ii) a combination of trimellityl groups and aliphatic monovalent acyl groups, the degree of substitution of trimellityl groups is from 0.01 to 0.11, and the degree of substitution of aliphatic monovalent acyl groups is from 0 to 0.40.

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

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

Yet another aspect of the present invention is a process for coating a dosage form which comprises the step of contacting an above-mentioned liquid composition with the dosage form.

Yet another aspect of the present invention is a process for the manufacture of capsule shells which comprises the step of contacting the above-mentioned liquid composition with dipping pins.

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

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

Yet another aspect of the present invention is a capsule which comprises the above-mentioned capsule shell and further comprises a drug or a nutritional or food supplement or a combination thereof.

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.

DESCRIPTION OF EMBODIMENTS

Surprisingly, it has been found that the esterified cellulose ethers of the present invention have a solubility in water of at least 2.0 weight percent at 2 °C. Clear or turbid solutions with only a small portion of sediment or in the preferred embodiments even without sediment are obtained at a temperature of 2 °C or below. When the temperature of the prepared solution is increased to 15 °C or even to 20 °C, no precipitation occurs. Moreover, aqueous solutions of the preferred embodiments of the esterified cellulose ether of the present invention gel at slightly elevated temperature. This renders the esterified cellulose ether of the present invention very useful in a variety of application, e.g. for producing capsules or for coating dosage forms. The advantages of the esterified cellulose ether of the present invention will be described in more detail below.

The esterified cellulose ether has a cellulose backbone having β-1,4 glycosidically 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, esterified hydroxyalkyl cellulose or hydroxyalkyl alkylcellulose, more preferably an esterified hydroxyalkyl methylcellulose. 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 alkoxyl groups or hydroxyalkoxyl groups or a combination of alkoxyl and hydroxyalkoxyl groups. The hydroxyalkoxyl groups are typically hydroxymethoxyl, hydroxyethoxyl and/or hydroxypropoxyl groups. Hydroxyethoxyl and/or hydroxypropoxyl

groups are preferred. Typically one or two kinds of hydroxyalkoxyl groups are present in the esterified cellulose ether. Preferably a single kind of hydroxyalkoxyl group, more preferably hydroxypropoxyl, is present. The alkoxyl groups are typically methoxyl, ethoxyl and/or propoxyl groups. Methoxyl groups are preferred. Illustrative of the above-defined esterified cellulose ethers are esterified alkylcelluloses, such as esterified methylcelluloses 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, 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 an esterified hydroxypropyl methylcellulose.

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

The term “hydroxyalkoxyl groups” thus has to be interpreted in the context of the MS(hydroxyalkoxyl) as referring to the hydroxyalkoxyl groups as the constituting units of hydroxyalkoxyl substituents, which either comprise a single hydroxyalkoxyl group or a side chain as outlined above, wherein two or more hydroxyalkoxy units are covalently bound to each other by ether bonding. Within this definition it is not important whether the terminal hydroxyl group of a hydroxyalkoxyl substituent is further alkylated, e.g. methylated, or not; both alkylated and non-alkylated hydroxyalkoxyl substituents are included for the determination of 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 0.70, 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 alkoxyl groups, such as methoxyl groups, per anhydroglucose unit, is designated as the degree of substitution of alkoxyl groups, DS(alkoxyl). In the above-given definition of DS, the term "hydroxyl groups substituted by alkoxyl 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 generally have a DS(alkoxyl) 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.

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

The ester groups in the esterified cellulose ether of the present invention are (i) trimellityl groups or (ii) a combination of trimellityl groups and aliphatic monovalent acyl groups, such as acetyl, propionyl, or butyryl, such as n-butyryl or i-butyryl. Specific examples of esterified cellulose ethers of the present invention are hydroxypropyl methyl cellulose acetate trimellitate (HPMCAT) and hydroxypropyl methyl cellulose trimellitate (HPMCT).

An essential feature of the esterified cellulose ethers of the present invention is their degree of substitution of trimellityl groups. The degree of substitution of trimellityl groups is at least 0.01 or at least 0.02, or at least 0.03, or at least 0.05, or in some embodiments at least 0.06. The degree of substitution of ester groups is not more than 0.11. In some embodiments of the invention the degree of substitution of trimellityl groups is up to 0.10 or up to 0.09. The esterified cellulose ethers of the present invention have been found to gel at elevated temperatures as described in the Examples section, depending on their concentration in water. Moreover, the esterified cellulose ethers of the present invention having a degree of substitution of trimellityl groups of from 0.06 to 0.11 have enteric properties, as shown in the Examples section.

The esterified cellulose ethers of the present invention have a degree of substitution of aliphatic monovalent acyl groups, such as acetyl, propionyl, or butyryl groups, of from 0 to

0.40. The presence of aliphatic monovalent acyl groups is optional but preferred. The esterified cellulose ethers of the present invention generally have a degree of substitution of aliphatic monovalent acyl groups, if present, of at least 0.02, preferably at least 0.05, more preferably at least 0.08, and most preferably at least 0.10. The esterified cellulose ethers generally have a degree of substitution of aliphatic monovalent acyl groups of up to 0.35, preferably up to 0.30, more preferably up to 0.25, and most preferably up to 0.20.

The content of the aliphatic monovalent acyl groups is determined in the same manner as described for "Hypromellose Acetate Succinate, United States Pharmacopia 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 trimellityl groups is determined as described for the phthalyl groups in Hypromellose Phthalate, United States Pharmacopia and National Formulary, NF 33, pp. 6701-6702.

The content of ether groups in the esterified cellulose ether 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. The formulas may be used in analogue manner to determine the DS and MS of substituents of other cellulose ether esters.

$$\%\ \text{cellulose backbone} = 100 - \left(\%\text{MeO} * \frac{\text{M}(\text{OCH}_3) - \text{M}(\text{OH})}{\text{M}(\text{OCH}_3)}\right) - \left(\%\text{HPO} * \frac{\text{M}(\text{OCH}_2\text{CH}(\text{OH})\text{CH}_3) - \text{M}(\text{OH})}{\text{M}(\text{OCH}_2\text{CH}(\text{OH})\text{CH}_3)}\right) - \left(\%\text{Acetyl} * \frac{\text{M}(\text{COCH}_3) - \text{M}(\text{H})}{\text{M}(\text{COCH}_3)}\right) - \left(\%\text{Trimellityl} * \frac{\text{M}(\text{COC}_6\text{H}_3(\text{COOH})_2) - \text{M}(\text{H})}{\text{M}(\text{COC}_6\text{H}_3(\text{COOH})_2)}\right)$$

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

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

$$M(MeO) = M(OCH_3) = 31.03\ Da \qquad M(HPO) = M(OCH_2CH(OH)CH_3) = 75.09\ Da$$
$$M(Acetyl) = M(COCH_3) = 43.04\ Da \qquad M(Trimellityl) = M(COC_6H_3(COOH)_2) = 193.14\ Da$$
$$M(AGU) = 162.14\ Da \qquad M(OH) = 17.008\ Da \qquad M(H) = 1.008\ Da$$

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_3). 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-$CH_2CH(CH_3)$-OH). The content of the aliphatic monovalent acyl group is reported based on the mass of –C(O) – R_1 wherein R_1 is a monovalent aliphatic group, such as acetyl (–C(O)-CH_3). The content of the trimellityl group is reported based on the mass of the trimellityl group (i.e., –C(O) – C_6H_3(–COOH)$_2$).

In the esterified cellulose ether of the present invention the degree of neutralization of the trimellityl groups generally is not more than 0.5, preferably not more than 0.4, more preferably not more than 0.3, even 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 carboxylic groups over the sum of deprotonated and protonated carboxylic groups, i.e., degree of neutralization =

[- C(O) – C_6H_3(–COOA) – COO^-] / [- C(O) – C_6H_3(–COOA) – COO^- +

- C(O) – C_6H_3(–COOA) – COOH], wherein COOA is COOH or COO^-.

The degree of neutralization can be evaluated by titration as described by H. Kokubo et al. in "Development of Cellulose Derivatives as Novel Enteric Coating Agents Soluble at pH 3.5-4.5 and Higher" in *Chem. Pharm. Bull.* **45**(8) 1350 – 1353 (1997), Vol. 45, No. 8, at page 1350. The formula above for the degree of neutralization is applied regardless whether COOA is COOH or COO^-; the degree of neutralization as defined herein relates to the degree of neutralization of the carboxylic group of stronger acidity, regardless of the degree of neutralization of the second carboxylic group. In neutralized trimellityl groups the

counter-cations preferably are ammonium cations, such as NH_4^+, or alkali metal ions, such as sodium or potassium ions, more preferably sodium ions.

Surprisingly, it has been found that the esterified cellulose ether of the present invention 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, and most preferably even at least 10.0 weight percent solution in water at 2 °C, even when the degree of neutralization of the trimellityl groups is not more than 0.5, or even less as defined above. Generally the esterified cellulose ether of the present invention 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 esterified cellulose ether is soluble in (100 – x) g of water at 2 °C.

When determining the water solubility as described in the Examples section, the esterified cellulose ether of the present invention preferably has solubility properties that at least 85 wt.%, typically at least 90 wt.%, more typically at least 95 wt.%, and in many cases at least 99 wt.% of the esterified cellulose ether is soluble in a mixture of 2.5 weight parts of the esterified cellulose ether and 97.5 weight parts of water at 2 °C. Typically this degree of solubility is also observed in a mixture of 5 or 10 weight parts of the esterified cellulose ether and 95 or 90 weight parts of water at 2 °C or even in a mixture of 20 weight parts of the esterified cellulose ether and 80 weight parts of water at 2 °C.

In more general terms, it has surprisingly been found that the esterified cellulose ether of the present invention is soluble in an aqueous liquid at a temperature of 2 °C, even when the esterified cellulose ether has a low degree of neutralization of trimellityl groups as described above and even when the esterified cellulose ether is blended with an aqueous liquid that does not increase the degree of neutralization of the esterified cellulose ether to more than 0.5 or a more preferred range listed above, e.g., when the esterified cellulose ether is blended with only water, such as deionized or distilled water. Clear or turbid solutions without sediment are obtained at 2 °C.

Moreover, it has been found that aqueous solutions of an esterified cellulose ether of the present invention gel at elevated temperature, typically at 30 to 80 °C, more typically at 40 to 70 °C. This renders the esterified cellulose ethers of the present invention very useful in a variety of application, e.g. for producing capsules and for coating dosage forms.

Gelling of aqueous solutions of these esterified cellulose ethers, such as hydroxypropyl methyl cellulose trimellitate (HPMCT) or hydroxypropyl methyl cellulose acetate trimellitate (HPMCAT), at elevated temperature is observed even when aqueous solutions of the cellulose ethers that are used as starting materials for producing the esterified cellulose ethers do not gel. E.g., the Examples of the present invention illustrate gelling HPMCAT and HPMCT of the present invention, although the corresponding hydroxypropyl methyl cellulose that is used as a starting material for preparing them does not gel to a significant degree. Gelation of the esterified cellulose ethers of the present invention typically occurs at concentrations of 2 to 30 weight percent, more typically at 5 to 20 weight percent, based on the total weight of esterified cellulose ether and aqueous liquid. The gelation is reversible, i.e. upon cooling to 20°C the gel transforms into a liquid aqueous solution.

The aqueous liquid in which the esterified cellulose ether of the present invention is soluble 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 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; 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 trimellityl groups of the esterified cellulose ether in the resulting blend of esterified cellulose ether and aqueous liquid should generally be not more than 0.5 or a preferred upper limit as described further above. 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 esterified cellulose ethers of the present invention generally have 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 esterified cellulose ether 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 esterified cellulose ether in 0.43 wt.-% aqueous NaOH at 20 °C.

Details of the production of the esterified cellulose ethers of the present invention are described in the examples. Some aspects of the production process are described below. The esterified cellulose ether of the present invention can be produced by esterifying a cellulose ether, such as an alkyl cellulose, hydroxyalkyl cellulose or hydroxyalkyl alkylcellulose described further above. The cellulose ethers preferably have a DS(alkoxyl) and/or an MS(hydroxyalkoxyl) as described further above. The cellulose ether used as a starting material for esterification generally has a viscosity of from 1.2 to 200 mPa·s, preferably from 1.8 to 100 mPa·s, more preferably from 2.4 to 50 mPa·s and in particular from 2.8 to 5.0 mPa·s, measured as a 2 weight-% aqueous solution at 20 °C according to ASTM D2363 – 79 (Reapproved 2006). Cellulose ethers of such viscosity can be obtained by subjecting a cellulose ether of higher viscosity to a partial depolymerization process. Partial depolymerization processes are well known in the art and described, for example, in European Patent Applications EP 1,141,029; EP 210,917; EP 1,423,433; and US Patent No. 4,316,982. Alternatively, partial depolymerization can be achieved during the production of the cellulose ethers, for example by the presence of oxygen or an oxidizing agent.

The cellulose ether is reacted with trimellitic anhydride and optionally with an aliphatic monocarboxylic acid anhydride, such as acetic anhydride, butyric anhydride and propionic anhydride. The molar ratio between the trimellitic anhydride and the anhydroglucose units of cellulose ether generally is at least 0.02 : 1, preferably at least 0.05 : 1, more preferably at least 0.1 : 1, and even more preferably at least 0.12 : 1. In some embodiments of the invention, the molar ratio between the trimellitic anhydride and the anhydroglucose units of cellulose ether is 0.15 : 1 or more or even 0.20 : 1 or more. The molar ratio between the trimellitic anhydride and the anhydroglucose units of cellulose ether

generally is not more than 0.47 : 1, typically not more than 0.46 : 1. If the cellulose ether is additionally reacted with an aliphatic monocarboxylic acid anhydride, The molar ratio between the anhydride of an aliphatic monocarboxylic acid and the anhydroglucose units of the cellulose ether generally is at least 0.04 : 1, preferably at least 0.05 : 1, and more preferably at least 0.08 : 1. In preferred embodiments of the invention the molar ratio between the anhydride of an aliphatic monocarboxylic acid is at least 0.10 : 1. The molar ratio between the anhydride of an aliphatic monocarboxylic acid and the anhydroglucose units of the cellulose ether generally is up to 0.45 : 1, preferably up to 0.40 : 1, and more preferably up to 0.35 : 1. The molar number of anhydroglucose units of the cellulose ether utilized in the process 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 conducted in an aliphatic 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 tetrahydrofurane; or halogenated C_1-C_3 derivatives, like dichloro methane or dichloro methyl ether, but the amount of the aliphatic carboxylic acid should generally be more than 50 percent, preferably at least 75 percent, and more preferably at least 90 percent, based on the total weight of the reaction diluent. Most preferably the reaction diluent consists of an aliphatic carboxylic acid, more preferably acetic acid. The molar ratio [aliphatic carboxylic acid / anhydroglucose units of cellulose ether] generally is from 5 : 1 to 11 : 1.

The esterification reaction is 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 [2.0 / 1.0] to [3.0 / 1.0], and preferably from [2.3 / 1.0] to [2.6 / 1.0].

The reaction temperature for the esterification is generally from 85° C to 100 ° C, preferably from 90 ° C to 98° C. The esterification reaction is typically completed within 2.5 to 4 hours. After completion of the esterification reaction, the esterified cellulose ether can be precipitated from the reaction mixture in a known manner, for example as described in U.S. Patent No. 4,226,981, International Patent Application WO 2005/115330, European

Patent Application EP 0 219 426 or International Patent Application WO2013/148154. The precipitated esterified cellulose ether is typically washed with an aqueous liquid at a temperature of from 70 to 100 °C. Suitable aqueous liquids are described further above.

Another aspect of the present invention is an aqueous composition comprising one or more of the above described esterified cellulose ethers of the present invention dissolved in an aqueous liquid. The aqueous liquid is a described further above. The esterified cellulose ether of the present invention can be brought into aqueous solution by cooling the aqueous composition to a temperature of - 2 °C to less than 10 °C, preferably of 0 °C to less than 8 °C, more preferably of 0.5 °C to less than 5 °C, and most preferably of 0.5 °C to 3 °C. The aqueous composition preferably comprises at least 5 wt.-%, more preferably at least 10 wt.-%, and preferably up to 30 wt.-%, more preferably up to 20 wt.-% of the esterified cellulose ether of the present invention, based on the total weight of the aqueous composition.

The aqueous composition comprising one or more of the above described esterified cellulose ethers of the present invention dissolved in an aqueous liquid is useful in the manufacture of capsules which comprises the step of contacting the liquid composition with dipping pins. Typically an aqueous composition having a temperature of less than 20 °C, more typically less than 15 °C or in some embodiments less than 10 °C is contacted with dipping pins having a higher temperature than the aqueous composition and that have a temperature of at least 21 °C, more typically at least 25 °C, and up to 95 °C, preferably up to 80 °C.

The aqueous composition comprising one or more of the above described esterified cellulose ethers dissolved in an aqueous liquid is also useful for coating dosage forms, such as tablets, granules, pellets, caplets, lozenges, suppositories, pessaries or implantable dosage forms.

Another aspect of the present invention is a liquid composition comprising an organic diluent and one or more of the above described esterified cellulose ethers of the present invention. The organic diluent may be present in the liquid composition alone or mixed with water. Preferred organic diluents are described further above. The liquid composition preferably comprises at least 5 wt.-%, more preferably at least 10 wt.-%, and preferably up to 30 wt.-%, more preferably up to 20 wt.-% of the esterified cellulose ether of the present invention, based on the total weight of the liquid composition.

The composition of the present invention comprising an aqueous liquid or an organic diluent as described above and one or more of the above described esterified cellulose

ethers is also 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 or 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. In another aspect of the invention the composition of the present invention is used for producing a solid dispersion comprising at least one active ingredient, such as a drug, at least one esterified cellulose ether as described above and optionally one or more adjuvants. A preferred method of producing a solid dispersion is by spray-drying. Spray-drying processes and spray-drying equipment are described generally in Perry's Chemical Engineers' Handbook, pages 20-54 to 20-57 (Sixth Edition 1984). 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 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 a) from 20 to 99.9 percent, more preferably from 30 to 98 percent, and most preferably from 60 to 95 percent of an esterified cellulose ether as described above, and b) 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 adjuvants c) as described below. Once the solid dispersion comprising at least one active ingredient in at least one esterified cellulose ether has been formed, several processing operations can be used, such as drying, granulation, and milling, to facilitate incorporation of the dispersion into a 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.

The aqueous composition, the liquid composition comprising an organic diluent and the solid dispersion of the present invention may further comprise optional adjuvants, such as coloring agents, pigments, opacifiers, flavor and taste improvers, antioxidants, and any combination thereof.

EXAMPLES

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

Content of ether and ester groups of hydroxypropyl methylcellulose trimellitate (HPMCT) or hydroxypropyl methylcellulose acetate trimellitate (HPMCAT)

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

The content of the acetyl groups, if present, is determined as described for the acetyl groups in Hypromellose Acetate Succinate, United States Pharmacopia 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).

The content of the trimellityl groups is determined as described for the phthalyl groups in Hypromellose Phthalate, United States Pharmacopia and National Formulary, NF 33, pp. 6701-6702.

Water-Solubility

Quantitative determination: 2.5 weight parts of HPMCT or HPMCAT, based on its dry weight, were added to 97.5 weight parts of deionized water having a temperature of 2 °C followed by stirring for 6 hours at 2°C and storing for 16 h at 2°C. A weighed amount of this mixture was transferred to a weighed centrifuge vial; the transferred weight of the mixture was noted as M1 in g. The transferred weight of HPMCT or HPMCAT [M2] was calculated as (transferred weight of mixture in g/100 g x 2.5g). The mixture was centrifuged for 60 min at 5000 rpm (2823 xg, Biofuge Stratos centrifuge from Thermo Scientific) at

2 °C. After centrifugation an aliquot was removed from the liquid phase and transferred to a dried weighed vial. The weight of the transferred aliquot was recorded as M3 in g. The aliquot was dried at 105°C for 12 h. The remaining g of HPMCT or HPMCAT was weighed after drying and recorded as M4 in g.

The term "% water soluble at 2.5 %" in Tables 3 and 4 below expresses the percentage of HPMCT or HPMCAT that is actually dissolved in the mixture of 2.5 weight parts of HPMCT or HPMCAT and 97.5 weight parts of deionized water. It is calculated as (M4 / M2) x (M1 / M3) x 100, which corresponds to (g HPMCT or HPMCAT in liquid aliquot / g HPMCT or HPMCAT transferred to centrifuge vial) x (g mixture transferred to centrifuge vial / g liquid aliquot after centrifugation) x 100. In the formulas above " x " stands for the multiplication operator.

Qualitative determination: A 2 wt. percent mixture of HPMCT or HPMCAT and water was prepared by mixing 2.0 g HPMCT or HPMCAT, based on its dry weight, with 98.0 g water under vigorous stirring at 0.5°C for 16 hours. The temperature of the mixture of HPMCT or HPMCAT and water was then increased to 4°C in a refrigerator. HPMCT or HPMCAT that is soluble at 4°C is also soluble at 2°C; at 2°C the solubility is at least as high as at 4°C. The water solubility of the HPMCT or HPMCAT was determined by visual inspection. The determination whether the HPMCT or HPMCAT was water-soluble at 2% at 2 °C or not was done as follows. "Water soluble at 2% - yes" means that a solution without sediment was obtained according to the procedure above. "Water soluble at 2% - no" means that at least a significant portion of the HPMCT or HPMCAT remained undissolved and formed sediment when mixing 2.0 g HPMCT or HPMCAT, based on its dry weight, with 98.0 g water according to the procedure above.

Viscosity of HPMCT or HPMCAT

The 2.0 % by weight solution of HPMCT or HPMCAT in 0.43 wt.% aqueous NaOH was prepared as described in"Hypromellose Acetate Succinate, United States Pharmacopia and National Formulary, NF 29, pp. 1548-1550". An Ubbelohde viscosity measurement according to DIN 51562-1:1999-01 (January 1999) was carried out. The measurement was done at 20 °C. The 2.0 % by weight solution of the HPMCT or HPMCAT in 0.43 wt.% aqueous NaOH is listed in Table 2 below as "2.0 % viscosity in 0.43 % NaOH".

Production of HPMCAT of Examples 1 – 5 and Comparative Examples A and B

500 g of acetic acid was filled in a reactor and stirred. Then 230 g of sodium acetate (water free) and 230 g HPMC (water free) were added. The HPMC had a methoxyl substitution (DS_M) of 1.98, a hydroxypropoxyl substitution (MS_{HP}) of 0.25 and a viscosity of 3.0 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 is commercially available from The Dow Chemical Company as Methocel E3 LV Premium cellulose ether. Inertisation with nitrogen was carried out. The mixture was heated to 97°C under stirring. After reaching the temperature of 97°C the reaction mixture was allowed to stir for 10 min. Then trimellitic anhydride and acetic anhydride were added as listed in Table 1 below, and the reaction mixture was allowed to react for 3.5 hours. After the esterification reaction the mixture was quenched with an aqueous sodium chloride solution. The aqueous sodium chloride solution contained 21.88 wt.-% of sodium chloride, based on the total weight of the aqueous sodium chloride solution, and had a temperature of 70°C. Then 2 L of the aqueous sodium chloride solution (temperature 70°C) was added into the reactor under stirring to precipitate the HPMCAT. The precipitated HPMCAT was removed from the reactor by filtration. After filtration the filter cake was washed several times with hot water (temperature about 95°). The washed HPMCAT was isolated by vacuum-filtration and dried at 55°C overnight.

Table 1

(Comparative) Example	HPMC*		Glacial acetic acid		Trimellitic anhydride		Acetic anhydride		Sodium acetate	
	g	Mol	g	mol/mol HPMC	g	mol/mol HPMC	g	mol/mol HPMC	g	mol/mol HPMC
1	230	1.14	500	7.3	15.0	0.06	5.0	0.044	230	2.46
2	230	1.14	500	7.3	30	0.13	10.0	0.088	230	2.46
3	230	1.14	500	7.3	45	0.19	20.0	0.18	230	2.46
4	230	1.14	500	7.3	610	0.25	30.0	0.26	230	2.46
5	230	1.14	500	7.3	45	0.19	40.0	0.35	230	2.46
A	230	1.14	500	7.3	45	0.19	60.0	0.53	230	2.46
B	230	1.14	500	7.3	45	0.19	100	1.10	230	2.46

Production of HPMCT of Examples 6 - 10 and Comparative Examples C – H

The amount of acetic acid as listed in Table 2 below was filled in a reactor and stirred. Then the amount of sodium acetate (water free) and the amount of HPMC (water free) as listed in Table 2 below were added. The HPMC had a methoxyl substitution (DS_M) of 1.98, a hydroxypropoxyl substitution (MS_{HP}) of 0.24 and a viscosity of 3.0 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 is commercially available from The Dow Chemical Company as Methocel E3 LV Premium cellulose ether. Inertisation with nitrogen was carried out. The mixture was heated to 97°C under stirring. After reaching the temperature of 97°C the reaction mixture was allowed to stir for 10 min. Then trimellitic anhydride was added as listed in Table 2 below, and the reaction mixture was allowed to react for 3.5 hours. After the esterification reaction the mixture was quenched with an aqueous sodium chloride solution. The aqueous sodium chloride solution contained 21.88 wt.-% of sodium chloride, based on the total weight of the aqueous sodium chloride solution, and had a temperature of 70°C. Then 2 L of the aqueous sodium chloride solution (temperature 70°C) was added into the reactor under stirring to precipitate the HPMCT. The precipitated HPMCT was removed from the reactor by filtration. After filtration the filter cake was washed several times with hot water (temperature about 95°). The washed HPMCT was isolated by vacuum-filtration and dried at 55°C overnight.

Table 2

	HPMC*		**Glacial acetic acid**		**Trimellitic anhydride**		**Sodium acetate**	
(Comp.) Example	g	Mol	g	mol/mol HPMC	g	mol/mol HPMC	g	mol/mol HPMC
6	230	1.14	700	10.3	30	0.13	230	2.47
7	230	1.14	500	7.3	60	0.25	230	2.47
8	230	1.14	500	7.3	75	0.31	230	2.47
9	230	1.14	500	7.3	95	0.4	230	2.47
10	230	1.14	500	7.3	110	0.46	230	2.47

	HPMC*		**Glacial acetic acid**		**Trimellitic anhydride**		**Sodium acetate**	
(Comp.) Example	g	Mol	g	mol/mol HPMC	g	mol/mol HPMC	g	mol/mol HPMC
C	230	1.14	500	7.3	130	0.54	230	2.47
D	230	1.14	500	7.3	150	0.63	230	2.47
E	198	0.98	418	7.1	150	0.73	192.5	2.4
F	230	1.14	500	7.3	115	0.48	230	2.47
G	230	1.14	500	7.3	120	0.50	230	2.47
H	230	1.14	500	7.3	125	0.52	230	2.47

The properties of the HPMCAT of Examples 1 - 5 and Comparative Examples A and B and of the HPMCT of Examples 6 - 10 and Comparative Examples C – H are listed in Table 3 below. In Tables 3 and 4 the abbreviations have the following meanings:

DS_M = DS(methoxyl): degree of substitution of methoxyl groups;

MS_{HP} = MS(hydroxypropoxyl): molar substitution of hydroxypropoxyl groups;

DS_{ac} = degree of substitution of acetyl groups;

DS_T = degree of substitution of trimellityl groups.

The results in Tables 3 and 4 below illustrate that the esterified cellulose ethers of Examples 1 –10 are soluble in water at 2 °C, but those of Comparative Examples A – G are not or insufficiently soluble in water.

Warming up of Aqueous Solutions of HPMCT or HPMCAT

Aqueous solutions of 2 wt.% HPMCT or HPMCAT were prepared as described above in the paragraph "Water-Solubility", Qualitative determination". Subsequently the mixtures were gradually warmed up by storing them at 40 ° C for 1 hour, then at 50 ° C for 1 hour, then at 60 ° C for 1 hour, then at 70 ° C for 1 hour, and then at 80 ° C for 1 hour . The effect of the temperature increase on the solutions was visually inspected. The results are listed in Table 5 below.

Table 3

(Comp.) Example	Methoxyl (%)	Hydroxy-propoxyl (%)	Acetyl (%)	trimellityl (%)	DS_{ac}	DS_T	% water - soluble at 2.5 % (quantitative)	Water-soluble at 2% (qualitative)	2% viscosity in 0.43 % NaOH [mPa·s]
1	29.4	8.4	1.40	1.3	0.07	0.01	99 %	Yes [1)]	4.0
2	28.7	8.2	1.60	2.7	0.08	0.03	99 %	Yes [1)]	3.8
3	28.2	8.2	1.90	4.9	0.10	0.06	99 %	Yes [1)]	3.6
4	26.9	8.0	2.20	8.6	0.12	0.10	94 %	Yes [2)]	3.4
5	27	8.0	2.80	7.4	0.15	0.09	97 %	Yes [2)]	3.4
A	25.6	7.6	3.80	10.9	0.21	0.13	41 %	No [3)]	3.2
B	23.1	7.2	8.30	12.8	0.50	0.17	7 %	No [3)]	3.0

[1)] clear solution [2)] slightly turbid [3)] sediment formed

-20-

Table 4

(Comparative) Example	Methoxyl (%)	Hydroxy-propoxyl (%)	Acetyl (%)	trimellityl (%)	DS_{ac}	DS_T	% water - soluble at 2.5 % (quantitative)	Water-soluble at 2% (qualitative)	2% viscosity in 0.43 % NaOH [mPa·s]
6	29.8	8.8	--	0.8	--	0.01	100 %	Yes [1)]	4.1
7	29.6	8.4	--	3.2	--	0.03	98 %	Yes [1)]	4.5
8	29.3	8.3	--	4.3	--	0.05	99 %	Yes [1)]	4.3
9	28.2	8.4	--	6.1	--	0.07	99 %	Yes [1)]	3.7
10	27.5	8.2	--	8.3	--	0.10	99 %	Yes [2)]	3.6
C	26.3	7.8	--	18.0	--	0.18	31 %	No [3)]	n.m.
D	25.2	7.3	--	23.8	--	0.23	14 %	No [3)]	n.m.
E	23.6	6.8	--	13.2	--	0.33	0 %	No [3)]	n.m.
F	26.7	7.6	--	12.7	--	0.16	43 %	No [3)]	n.m.
G	26.4	7.8	--	13.9	--	0.15	48 %	No [3)]	n.m.
H	26.2	7.7	--	18.0	--	0.17	37 %	No [3)]	n.m.

[1)] clear solution [2)] slightly turbid [3)] sediment formed

-21-

Table 5

(Comp.) Example	After 1 hour at 40 °C	After 1 hour at 50 °C	After 1 hour at 60 °C	After 1 hour at 70 °C	After 1 hour at 80 °C
1	Clear solution	Slightly milky solution	Milky, turbid; soft, flowing gel	Milky, turbid; soft, flowing gel	Milky, turbid; soft, flowing gel
2	Clear solution	Slightly milky turbid solution	Milky turbid; very soft, flowing gel	Milky turbid; very soft, flowing gel	Large, soft agglomerates
3	Slightly turbid solution	Milky turbid; very soft, flowing gel	Soft, milky, turbid gel	White, soft gel	White, soft gel
4	Milky, turbid solution	milky turbid solution	milky turbid solution	Turbid, dissolved, some flakes	Turbid, dissolved, some flakes
5	Milky, turbid solution	Milky turbid; very soft, flowing gel	White, soft gel	White gel	White gel
A	Not assessed because of insufficient water solubility and formation of sediment				
B	Not assessed because of insufficient water solubility and formation of sediment				
6	Clear solution	Clear solution	Milky; very soft, flowing gel	Milky, white soft gel, flows as lumps	Soft, milky gel, gel flows
7	Clear solution	Milky solution	Milky; very soft, flowing gel	Milky, white soft gel, flows as lumps	Soft gel, falls apart to big lumps when flowing

-22-

(Comp.) Example	After 1 hour at 40 °C	After 1 hour at 50 °C	After 1 hour at 60 °C	After 1 hour at 70 °C	After 1 hour at 80 °C
8	Slightly milky, turbid solution	Milky, increased viscosity, still flowing	Milky; soft, flowing gel	Milky, white soft gel, flows as lumps	Soft gel, falls apart to big lumps when flowing
9	Milky solution	Milky solution	Milky, slight gelation, starts to flocculate	flocky	White gel, big lumps
10	Very milky solution	Very milky solution	milky solution	milky solution	milky solution
C	Not assessed because of insufficient water solubility and formation of sediment				
D	Not assessed because of insufficient water solubility and formation of sediment				
E	Not assessed because of insufficient water solubility and formation of sediment				
F	Not assessed because of insufficient water solubility and formation of sediment				
G	Not assessed because of insufficient water solubility and formation of sediment				
H	Not assessed because of insufficient water solubility and formation of sediment				

-23-

Gelation

Some aqueous solutions of the HPMCT or HPMCAT of the present invention gel at elevated temperature, typically at 30 to 80 °C, more typically at 40 to 70 °C. Preferred embodiments of the HPMCT or HPMCAT of the present invention even gel at a concentration as low as 2 wt.-%. It is very surprising that the esterified hydroxyalkyl alkyl celluloses gel in spite of their very low total degree of ester substitution. The HPMC that is used as starting material for preparing the HPMCT or HPMCAT does not gel at a concentration of 2 wt.-%. A 2 wt.-% solution of Methocel E3 LV Premium cellulose ether in water after heating to 65 °C does not form a gel but only flocculates.

Rheology measurements were carried out to measure the gelation temperatures and gel strength according to the storage modulus G' at 65 °C of 2 wt.-%, 5 wt.-%, 10 wt.-% and/or 20 wt.-% solutions of the HPMCT or HPMCAT of Examples 2, 3, 7, 9, 10 and 11 in water as described further above. The results are listed in Table 7 below.

Table 7

Example	Wt.-% HPMCT or HPMCAT in water	Gelation Temperature, °C	*Gel Strength G'* at 65 °C, Pa
2	2	55	21
2	5	49	767
2	10	45	5916
2	20	35	27220
3	2	52	26
3	5	41	1627
3	10	37	7770
3	20	32	16440
6	2	59	18
6	5	54	353
6	10	47	2262
6	20	37	16920
7	2	54	13
7	5	47	910
7	10	42	8014

Example	Wt.-% HPMCT or HPMCAT in water	Gelation Temperature, °C	*Gel Strength G'* at 65 °C, Pa
7	20	36	37390
8	2	56	6
8	5	45	1056
8	10	41	7582
8	20	37	26700
9	2	Not measurable	Not measurable -
9	5	42	903
9	10	39	3706
9	20	35	10480
Methocel E3 LV Premium cellulose ether	2	55	0.6 *
	5	63	2
	10	58	73
	20	50	911

* No significant gelling, only flocculation

Enteric Properties of the HPMCAT or HPMCT

To test the solubility of the HPMCAT or HPMCT in the stomach, HPMCAT or HPMCT in powder form at a concentration of 1 wt. % was stirred in 0.1 N HCl for 2 hours at a temperature of 37 °C to simulate the stomach fluid.

To test the solubility of the HPMCAT or HPMCT in the intestine or colon, HPMCAT or HPMCT in powder form at a concentration of 1 wt.% was stirred in McIlvaine's buffer solutions (containing disodium monophosphate and citric acid) that had a temperature of 37 °C and a pH of 3.0; 4.0; 4.5; 5.0; 5.5; 6.0 or 6.8, respectively.

The results are listed in Table 8 below.

Table 8

(Comp.) Ex.	0.1 M HCl	McIlvaine's buffer					
		pH 6.8	pH 6.0	pH 5.5	pH 5.0	pH 4.0	pH 3.0
1	-	o	o	o	o	o	o
2	o	-	-	-	-	-	o
3	x	-	-	-	-	o	o
4	x	-	-	-	-	x	x
5	x	-	-	-	-	x	x
A	x	-	-	-	-	x	x
B	x	-	-	-	o	o	x
6	o	o	o	o	o	o	o
7	o	-	-	-	-	-	o
8	o	-	-	-	-	o	o
9	x	-	-	-	-	o	o
10	x	-	-	-	-	o	x
C	o	-	-	-	-	o	o
D	x	-	-	-	-	o	x
E	x	-	-	-	-	o	x
F	slightly o	-	-	-	-	o	x
H	x	-	-	-	-	o	x

o : swollen, will disintegrated when in form of coating or capsule shell

x : insoluble

- : dissolved

The results in Table 8 above illustrate that the preferred embodiments of the esterified cellulose ethers of the present invention display enteric properties (see Examples 3 – 5, 9 and 10) and are also water-soluble. The esterified cellulose ethers of Comparative Examples A, B, D, E and H also display enteric properties, but they are not water-soluble.

Claims

1. An esterified cellulose ether wherein
- the ester groups are (i) trimellityl groups or (ii) a combination of trimellityl groups and aliphatic monovalent acyl groups,
- the degree of substitution of trimellityl groups is from 0.01 to 0.11, and
- the degree of substitution of aliphatic monovalent acyl groups is from 0 to 0.40.

2. The esterified cellulose ether of claim 1 wherein the degree of neutralization of the trimellityl groups is not more than 0.5 and the esterified cellulose ether has a solubility in water of at least 2.0 weight percent at 2 °C.

3. The esterified cellulose ether of claim 1 or claim 2 wherein the degree of substitution of aliphatic monovalent acyl groups is from 0.02 to 0.35.

4. The esterified cellulose ether of any one of claims 1 to 3 wherein at least 85 wt.% of the esterified cellulose ether is soluble in a mixture of 2.5 weight parts of the esterified cellulose ether and 97.5 weight parts of water at 2 °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.

6. The esterified cellulose ether of any one of claims 1 to 5 being an esterified hydroxyalkyl alkylcellulose.

7. The esterified cellulose ether of any one of claims 1 to 6 being a hydroxypropyl methylcellulose acetate trimellitate or hydroxypropyl methylcellulose trimellitate.

8. A liquid composition comprising an esterified cellulose ether of any one of claims 1 to 7 dissolved in an aqueous liquid.

9. A liquid composition comprising at least one esterified cellulose ether of any one of claims 1 to 7 and an organic diluent.

10. A process for coating a dosage form comprising the step of contacting the composition of claim 8 or 9 with the dosage form.

11. A process for the manufacture of capsule shells comprising the step of contacting the composition of claim 8 or 9 with dipping pins.

12. A coated dosage form wherein the coating comprises at least one esterified cellulose ether of any one of claims 1 to 7.

13. A polymeric capsule shell comprising at least one esterified cellulose ether of any one of claims 1 to 7.

14. A capsule comprising a capsule shell of claim 13 and further comprising a drug or a nutritional or food supplement or a combination thereof.

15. A solid dispersion of at least one active ingredient in at least one esterified cellulose ether of any one of claims 1 to 7.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/038218

A. CLASSIFICATION OF SUBJECT MATTER
INV. C08B11/18 C08L1/30
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 C08L

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, CHEM ABS Data, COMPENDEX, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007/148124 A1 (LABIB MOHAMED E [US] ET AL) 28 June 2007 (2007-06-28) the whole document in particular: abstract; [0057]-[0113] and [0229]-[0241]; claims 1-59; figures 1-13; examples	1-15
X	WO 2006/082518 A1 (PFIZER PROD INC [US]; BABCOCK WALTER CHRISTIAN [US]; FRIESEN DWAYNE TH) 10 August 2006 (2006-08-10) cited in the application the whole document in particular: abstract; page 1, line 35 - page 3, line 2; page 8, line 25 - page 15, line 1; claims 1-15; figures 1-4; examples	1-15

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 November 2017	27/11/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Ferreira, Roger

4

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/041973 A1 (DOW GLOBAL TECHNOLOGIES LLC [US]) 26 March 2015 (2015-03-26) the whole document in particular: abstract; page 4, line 1 - page 7, line 4; claims 1-15; examples	1-15
X	WO 2013/148154 A1 (DOW GLOBAL TECHNOLOGIES LLC [US]) 3 October 2013 (2013-10-03) cited in the application the whole document in particular: abstract; page 3, line 25 - page 4, line 16; page 6, line 13 - page 8, line 4; claims 1-14; figures 1-7; examples	1-15
A	US 2007/141141 A1 (BATEMAN NICOLA F [GB] ET AL) 21 June 2007 (2007-06-21) the whole document	1-15

4

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2017/038218

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2007148124 A1	28-06-2007	AU 2005243219 A1	24-11-2005
		BR PI0510628 A	13-11-2007
		CA 2565551 A1	24-11-2005
		EP 1749041 A2	07-02-2007
		JP 2007536237 A	13-12-2007
		US 2005244365 A1	03-11-2005
		US 2007148124 A1	28-06-2007
		WO 2005111112 A2	24-11-2005
WO 2006082518 A1	10-08-2006	EP 1844078 A1	17-10-2007
		EP 2548894 A1	23-01-2013
		US 2008064763 A1	13-03-2008
		US 2014171441 A1	19-06-2014
		WO 2006082518 A1	10-08-2006
WO 2015041973 A1	26-03-2015	CN 105829352 A	03-08-2016
		EP 3049446 A1	03-08-2016
		JP 6073526 B2	01-02-2017
		JP 2016532725 A	20-10-2016
		KR 20160044586 A	25-04-2016
		US 2016222133 A1	04-08-2016
		WO 2015041973 A1	26-03-2015
WO 2013148154 A1	03-10-2013	CN 104245741 A	24-12-2014
		EP 2831121 A1	04-02-2015
		JP 2015512456 A	27-04-2015
		KR 20140141681 A	10-12-2014
		US 2015031873 A1	29-01-2015
		WO 2013148154 A1	03-10-2013
US 2007141141 A1	21-06-2007	EP 1651233 A2	03-05-2006
		JP 2007500176 A	11-01-2007
		US 2007141141 A1	21-06-2007
		WO 2005011647 A2	10-02-2005