

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 75835 WO PCT	FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. PCTUS2015/027863	International filing date (<i>day/month/year</i>) 28.04.2015	Priority date (<i>day/month/year</i>) 20.05.2014	
International Patent Classification (IPC) or national classification and IPC INV. A61K9/48			
Applicant Dow Global Technologies LLC			
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>6</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ (<i>sent to the applicant and to the International Bureau</i>) a total of <u>5</u> sheets, as follows: ☒ sheets of the description, claims and/or drawings which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions). ☐ sheets containing rectifications, where the decision was made by this Authority not to take them into account because they were not authorized by or notified to this Authority at the time when this Authority began to draw up this report, and any accompanying letters (Rules 66.4bis, 70.2(e), 70.16 and 91.2). ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in the international application as filed, or the superseding sheets were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in item 4 of Box No. I and the Supplemental Box (see Rule 70.16(b)). b. ☐ (<i>sent to the International Bureau only</i>) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing, in the form of an Annex C/ST.25 text file, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 3ter of Annex C of the Administrative Instructions).			
4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ Box No. II Priority ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability ☐ Box No. IV Lack of unity of invention ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement ☐ Box No. VI Certain documents cited ☐ Box No. VII Certain defects in the international application ☐ Box No. VIII Certain observations on the international application			
Date of submission of the demand 03.12.2015		Date of completion of this report 20.04.2016	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465		Authorized officer Giménez Miralles, J Telephone No. +49 89 2399-8655	



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2015/027863

Box No. I Basis of the report

1. With regard to the **language**, this report is based on
- ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a) and (b))
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-26 as originally filed

Claims, Numbers

1-15 as originally filed

- ☐ a sequence listing - see Supplemental Box Relating to Sequence Listing.
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-bis)):
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
5. ☐ This report has been established:
- ☐ taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rules 66.1(d-bis) and 70.2(e)).
 - ☐ without taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91(Rules 66.4bis and 70.2(e)).

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2015/027863

6. ☒ With regard to top-up searches (Rules 66.1 *ter* and 70.2(f)):
- ☒ A top-up search was carried out by this Authority on 08.04.2016 (all discovered documents are listed in the Supplemental Box Relating to Top-up Search).
 - ☐ Additional relevant documents have been discovered during the top-up search.
 - ☐ No top-up search was carried out by this Authority because it would serve no useful purpose.
7. ☐ Supplementary international search report(s) from Authority(ies) has/have been received and taken into account in establishing this report (Rule 45bis.8(b) and (c)).

* If item 4 applies, some or all of those sheets may be marked "superseded".

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-15</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-15</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-15</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V

1. The relevant prior art documents are referred to as D1 to D4 as in the order of appearance in the International Search Report (ISR). Unless otherwise indicated, reference is made to the passages of said documents cited in the ISR.

2. Citations and explanations supporting the statement with regard to novelty (N), inventive step (IS) and industrial applicability (IA) (Rule 43*bis*.1(a)(i) and (b) PCT):

(N) The subject-matter of independent claims 1 and 10-15 is considered to be novel (Article 33(2) PCT).

The prior art does not anticipate an aqueous composition comprising at least 10 wt.% of a dispersed esterified cellulose ether (such as HPMCAS or HPMCP) at least partially neutralized with an ammonium salt of carbonic acid, formic acid or acetic acid, and having a particle size distribution wherein d₉₀ of the polymer particles is up to 10 microns.

(IS) The subject-matter of independent claims 1 and 10-15 is considered to involve an inventive step (Article 33(3) PCT) for the following reasons.

D1 or D2 can be seen as the closest prior art.

D1 discloses an aqueous dispersion comprising 15-25 wt.% partially neutralized HPMCAS, wherein partial neutralization is carried out by adding aqueous ammonium hydroxide; the aqueous dispersion is used as coating film for pharmaceutical dosage forms, and particularly for making enteric hard capsule shells by dip-moulding. In D1, it is explicitly disclosed that partial neutralization of HPMCAS renders an aqueous dispersion of colloidal size range having appropriate solid content, viscosity, and rheological properties for use in manufacturing capsule shells (paragraphs 10, 14 and 24).

D2 discloses an aqueous dispersion comprising partially neutralized HPMCAS or HPMCP, wherein partial neutralization is carried out by adding aqueous ammonium hydroxide and emulsification; the aqueous dispersion is used for coating films and in manufacturing of enteric hard capsule shells by dip-moulding.

However, none of D1 or D2 discloses reduction of particle size of the polymer dispersion (by milling or by melting and emulsifying) simultaneously to neutralization to achieve a polymer dispersion having a particle size distribution wherein d90 of the polymer particles is up to 10 microns.

Starting from D1 or D2, present claims 1, 10 and 11 thus differ in that the partial neutralization is carried out with an ammonium salt of carbonic acid, formic acid, or acetic acid; and in that the aqueous dispersion of polymer is submitted to particle size reduction (by milling or by melting and emulsifying) simultaneously to neutralization to achieve a polymer dispersion having a particle size distribution wherein d90 of the polymer particles is up to 10 microns.

The effect shown in the application is the provision of an aqueous polymer dispersion of a partially neutralized esterified cellulose ether for forming enteric films for capsule shells having improved storage stability, whereby film formation by dip-molding results in films which are less milky than customary HPMCAS or HPMCP films.

The solution claimed in claims 1, 10 and 11 using an ammonium salt of carbonic acid, formic acid, or acetic acid for partial neutralization, in combination with particle size reduction ($d_{90} < 10$ microns) simultaneously to neutralization is non-obvious. The applicant has submitted additional comparative data showing that neutralization with ammonium bicarbonate, as compared to ammonium hydroxide, in combination with particle size reduction, results in better long-term storage stability of the aqueous dispersion in terms of dispersion homogeneity and avoidance of particle aggregation (re-dispersibility upon storage).

Use of an ammonium salt of carbonic acid, formic acid, or acetic acid instead of ammonium hydroxide for neutralization of acidic polymers such as HMPCAS or HPMCP, in combination with particle size reduction ($d_{90} < 10$ microns) simultaneously to neutralization, would not have been a trivial option in the light of the prior art in the expectation of avoiding aggregation of colloidal particles.

In D2, it is disclosed that the compositions of examples 6-7 result in films which are less milky or hazy.

D3 discloses an aqueous dispersion of an acidic polymer such as HPMCAS or HPMCP, among a list of polymers, partially neutralized with ammonium bicarbonate. The ammonium salt of the polymer enhances polymer solubility for the preparation of film coating for nanoparticles.

However, none of D2 or D3 teaches or suggests particle size reduction during neutralization, and none of them is concerned with the question of particle size stability (avoidance of particle aggregation) and homogeneity (re-dispersibility upon storage) of the colloidal dispersion.

Thus, in view of D2 and D3 it would not have been obvious for the skilled person to use ammonium bicarbonate instead of ammonium hydroxide for partial neutralization of aqueous dispersions of esterified cellulose ether (such as HPMCAS or HPMCP), in combination with particle size reduction ($d_{90} < 10$ microns) simultaneously to neutralization, with an expectation of being able to improve dispersion homogeneity and particle size stability of the aqueous dispersions disclosed in D1.

Independent claims 12-15 (capsule shell, dosage form comprising said capsule shell, and process for manufacturing the capsule shell by dip-molding) are also non-obvious for analogous reasons.

(IA) The subject-matter of claims 1-15 is considered to be industrially applicable (Article 33(4) PCT). The possibility of industrial application is beyond any doubt.



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IN THE EUROPEAN PATENT OFFICE INTERNATIONAL PRELIMINARY
EXAMINING AUTHORITY (IPEA/EP)

Applicant(s): DOW GLOBAL TECHNOLOGIES LLC

International Application No.: PCT/US2015/027863

International filing date: 28 April 2015

DOW REFERENCE: 75835-WO-PCT

Demand for International Preliminary Examination

Dear Sir/Madam:

In response to the International Search Report and Written Opinion mailed on 6 July 2015, please find below Applicant's comments to patentability and additional comparative data supporting the comments. A Demand for International Preliminary Examination is being filed concurrently herewith.

No amendment to the claims is suggested. Please conduct an International Preliminary Examination based on the original claims.

A) Novelty

Novelty of all claims has been confirmed.

C) Inventive Step

D1 (US 2013/295188)

D1 relates to an aqueous dispersion of a hydroxypropyl methyl cellulose acetate succinate (HPMCAS) wherein the dispersed polymer is partially neutralized with at least one alkaline material, such as ammonia, sodium hydroxide, calcium hydroxide, potassium hydroxide, cationic polymers and mixtures thereof (*Claims 1*

and 5). For example, ammonia is added in the form of aqueous ammonium hydroxide (paragraph 0022).

The present invention differs from D1 in that at least a part of the groups $-C(O) - R - COOH$ are neutralized with an ammonium salt of carbonic acid, formic acid or acetic acid instead of a neutralizing agent disclosed in D1.

The use of an ammonium salt of carbonic acid, formic acid or acetic acid, such as NH_4HCO_3 , provides significant advantages over the use of other neutralizing agents.

The advantage of using NH_4HCO_3 as a neutralizing agent instead of sodium hydroxide (NaOH) is shown in Comparative Example A and Example 1 at pages 24 and 25 of the present patent application. The dispersion of Example 1 formed a film that was more transparent and less milky than the film according to Comparative Example A (page 25, lines 26 – 32 of the present patent application).

The advantage of using an ammonium salt of carbonic acid, formic acid or acetic acid, such as NH_4HCO_3 , as a neutralizing agent instead of ammonia, e.g. in the form of ammonium hydroxide, is shown by the additional comparative data in the attached Annex A. The dispersion of Example 2 (neutralization agent NH_4HCO_3) could easily be re-dispersed even after storage at room temperature for 22 days. The dispersion of Comparative Example B (neutralization with ammonium hydroxide) resulted in an unstable dispersion. Severe aggregation of solid particles and a hard crust were observed after 22 days of storage at room temperature.

D2 (EP 2 476 439)

D2 relates to aqueous compositions for enteric hard capsules. D2 discloses an enteric base material, such as HPMCAS in water and a neutralization agent to solubilize the enteric base material (paragraphs [0031] and [0035]). Ammonia is added in the form of ammonium hydroxide (Table 1). D2 does not disclose a dispersion but an aqueous HPMCAS solution. The amount of neutralizing agent is chosen to solubilize the enteric base material, such as HPMCAS in the aqueous composition.

Hence, D2 does not disclose an aqueous composition comprising a dispersed esterified cellulose ether wherein d90 of the dispersed esterified cellulose ether particles is up to 10 micrometers. D2 is further remote from the present invention than D1.

Moreover, the advantage of using an ammonium salt of carbonic acid, formic acid or acetic acid, such as NH_4HCO_3 , as a neutralizing agent instead of ammonia, e.g. in the form of ammonium hydroxide, is shown by the additional comparative data in the attached Annex A and is discussed above in the discussion of D1.

D3 (US 2009/297565)

D3 relates to coated nanoparticles. An aqueous polymer solution is used as dispersion medium during the production of nanocrystals and for coating nanoparticles, specifically nanocrystals (*paragraph [0064]*). In the case of acidic polymers, such as HPMCAS, a sufficient amount of volatile bases, such as ammonium bicarbonate, is added to shift the pH into a range in which the polymer is soluble (*paragraph [0068]*).

Combination of D1 or D2 with D3

As explained above, D1 is considered to be the closest prior art. Starting from D1 as the closest prior art, the skilled artisan would not combine D1 with D3 with a reasonable expectation of success in obtaining an aqueous dispersion of an esterified cellulose ether having improved re-dispersibility upon storage. Neither D1 nor D3 address the storage problem of a dispersion of an esterified cellulose. D3 does not even relate to a dispersion of an esterified cellulose ether but to a solution thereof.

A combination of D2 with D3 would not lead to the present invention. D2 and D3 do not even relate to a dispersion of an esterified cellulose ether but to a solution thereof.

D4 (GB 2 325 623)

D4 discloses dissolution of HPMCAS with ammonia, preferably in the form of aqueous ammonium hydroxide. D4 further remote from the present invention than D2 because D4 does not relate to a dispersion of an esterified cellulose ether.

Accordingly, the subject matter of all claims is not only novel but also inventive over the prior art cited by the Authorized Officer.

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Example 2

To produce an aqueous HPMCAS dispersion, water was loaded first and recirculated through a Drais DCP-12 media mill (1.0 mm Ytterum Stabilized Zirconia media, 0.5 mm screen size). During the milling process HPMCAS solids were loaded gradually to water having a temperature of 16-20 °C and recirculating through the mill at a mill speed of 1000 rev/min. Addition of HPMCAS was continued until a total solids loading of about 20 % was achieved, based on the total amount of the composition. At this point, 20 wt.% NH_4HCO_3 was added to the mill to adjust the pH to 4.7. Milling continued until the final median particle size, d_{50} , of 1.1 μm was obtained.

The resultant degree of neutralization of succinoyl groups was 28 mole percent, i.e., 28 mole percent of the groups - $\text{CO}-\text{CH}_2-\text{CH}_2-\text{COOH}$ of the HPMCAS comprised in the aqueous dispersion were neutralized and present as - $\text{CO}-\text{CH}_2-\text{CH}_2-\text{COO}^- \text{NH}_4^+$ groups. The resultant dispersion had a solids content of 20.2 weight percent and a pH of 4.7. The HPMCAS particles had a median particle size, d_{50} , of 1.1 μm , a mean particle size of 1.6 μm and a particle size d_{90} of 3.4 μm .

The freshly prepared HPMCAS dispersion had a good fluidity. The HPMCAS dispersion gradually lost some of its fluidity upon standing during aging at room temperature for a time period of 22 days, but the HPMCAS particles could easily be re-dispersed in the aqueous diluent by simple, low intensity stirring.

Comparative Example B

The procedure in Example 2 was repeated, except that ammonium hydroxide was added as a 15 wt. % ammonium hydroxide solution to the mill to adjust the pH to 4.8.

The resultant degree of neutralization of succinoyl groups was 33 mol percent, i.e., 33 mole percent of the groups - $\text{CO}-\text{CH}_2-\text{CH}_2-\text{COOH}$ of the HPMCAS comprised in the aqueous dispersion were neutralized and present as - $\text{CO}-\text{CH}_2-\text{CH}_2-\text{COO}^- \text{NH}_4^+$ groups. The resultant dispersion had a solids content of 20.2 weight percent and a pH of 4.8. The HPMCAS particles had a median particle size, d_{50} , of 1.6 μm , a mean particle size of 2.0 μm and a particle size d_{90} of 4.0 μm .

The freshly prepared HPMCAS dispersion had a reasonably good fluidity, although it had a higher viscosity over the temperature range of 2 to 72 °C than the freshly prepared HPMCAS dispersion of Example 2. The HPMCAS dispersion gradually lost its fluidity during aging at room temperature for a time period of 22 days. Severe aggregation of solid particles and a hard crust were observed after 22 days. A meaningful viscosity measurement was not possible after 22 days. After an effort to re-disperse the HPMCAS particles, still some aggregated particles of increased density were visible that could not be re-dispersed into an apparently homogeneous dispersion.

For assessing the storage stability of the dispersions, the particle size distributions in diluted dispersions of Example 2 and Comparative Example B were re-measured after their preparation as listed in the table below by laser diffraction particle size analysis as described in the paragraph “HPMCAS particle size measurement in the aqueous dispersion” at page 22 of the patent application. The results are listed in the Table below.

(Comp.) Example	Days after preparation	Mean (μm)	d50 (μm)	d90 (μm)
2	31	8	2	29
2	55	13	3	30
B	24	6	2	20
B	48	37	6	140

The results in the Table above illustrate that the HPMCAS of Example 2, which is partially neutralized with NH_4HCO_3 , has much better storage stability than the HPMCAS of Comparative Example B which is partially neutralized with ammonium hydroxide.