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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 April 2013 (04.04.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/045961 A1

(51) **International Patent Classification**:
A61K 9/28 (2006.01)

(21) **International Application Number**:
PCT/HU2011/000095

(22) **International Filing Date**:
29 September 2011 (29.09.2011)

(25) **Filing Language**: Hungarian

(26) **Publication Language**: English

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(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, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, 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, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, 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, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2013/045961 A1

(54) **Title**: COATING COMPOSITION

(57) **Abstract**: The present invention relates to a coating comprisition comprising polyvinyl-alcohol film-forming polymer and montmorillonit for decrease of moisture regain of tablets containing active pharmaceutical ingredients, nutrition agents or supplements.

Coating composition

SUBJECT OF THE INVENTION

The present invention relates to a coating composition comprising a polyvinyl-alcohol film-forming polymer and montmorillonit decreasing the moisture absorption of tablets containing active pharmaceutical ingredients, nutrition agents or supplements.

TECHNICAL BACKGROUND OF THE INVENTION

During storage a considerable amount of solid compositions, e.g. tablets, pellets or granules containing pharmaceutical active ingredients, nutrition agents or supplements undergo a degradation or disintegration due to the humidity. Humidity may cause disintegration of the active ingredients on the one hand, and the change of the pharmaceutically important properties of the tablets, e.g. the disintegration properties on the other. Owing to the moisture the binding and the filling agents get frequently cemented, thus the tablets can not disintegrate at an appropriate rate, consequently the absorbtion rates of the pharmaceutical ingredients completely change depending on the shelf life. An appropriate packaging of the solid compositions may slow the degradation processes, but in case of an opened package only a moisture barrier coating may ensure appropriate protection. The traditional moisture barrier coatings are prepared from water-insoluble polymers. This method has two disadvantages: on the one hand the process for the preparation of the coating requires in many cases the use of organic solvents, on the other hand the low solubility of the coating makes the disintegration of the tablets longer, therefore the dissolution of the active ingredient is delayed, resulting in a delayed or decreased effect of the active ingredient. In most cases the film-forming polymers used for moisture barrier coatings are water-insoluble cellulose-acetate-phthalate or methylcellulose acetate phthalate polymers containing carboxyl groups [Baudoux, M., Dechesne, J.P. and Delattre, L., 1990. Pharm. Tech. Int. 12, 18-26], or methacrylic acid copolymers [Gutierrez-Rocca, JC. and McGinity, W.C., 1993. Drug Dev. Ind. Pharm. 19, 315-332,

Thomaa, K and Bechtoldb, K, 1999. Eur. J. Pharm. Biopharm. 47, 39-50.]. Pharmaceutical compositions coated with such coatings pass through the stomach in an unchanged form and are disintegrated only at the higher pH level of the intestinal fluid. Although methacrylic acid copolymers containing basic amino (dimethylaminoethyl) groups dissolve in the stomach, the process for the preparation of such coating needs the use of organic solvents [Bauer, K. H., Lehmann, K., Osterald, H. P., Rothgang, G. Überzogene Arzneiformen, page 73 (WVG, Stuttgart, 1988.)]. The best moisture protection coating is provided by Eudragyt L, which is insoluble in water and in acidic media, but this coating is not suitable for the preparation of immediate release tablets because it does not dissolve in the stomach but only at a higher level of pH (above pH 5.5) in the intestinal tract. Therefore, it is not suitable as a coating of immediate release compositions because the dissolution of the active ingredient begins 2-3 hours after the administration. Recently, for these reasons water-soluble polymers are more and more used for the preparation of so called „moisture barrier" film coatings. In order to impove the moisture impermeability hydrophobic compounds or special polymers are added to the film-forming polymers. In case of use of water-insoluble polymers containing inert groups such as ethylcellulose [Yang, T.S.and Ghebre-Sellassie, I.,1990. Int. J. Pharm. 60, 109-124, Ozturk, AG., Ozturk, S.S., Palsson, B.O., Wheatley, T.A. gand Dressman, J.B., 1990. J. Controll. Rel. 14, 203-213] and polyacrylate copolymers [Ghebre-Sellassie, I., Gordon, RH., Nesbitt, RU. and Fawzi, M.B., 1987. Int. J. Pharm. 37, 211-218, Petereit, H-U. and Weisbrod, W., 1999. Eur. J. Pharm. Biopharm. 47, 15-25] water-soluble accessory agents have to be added to the coating to help the disintegration of the tablets, but these accessory agents decrease the moisture impermeability of the coatings.

Most of the water-soluble polymers used for film-coating are cellulose ethers, such as HPMC (hydroxypropylmethycellulose) and polyvinyl derivatives, such as PVA (polyvinyl alcohol) or PVP-PVAc copolymer (polyvinylpyrrolidone-polyvinylacetate copolymer). The compositions coated with water-soluble coating quickly disintegrate in the stomach and such coatings do not change the dissolution rate of the active ingredient.

Hydroxypropylmethylcellulose (HPMC) is a cellulose derivative, in which the hydroxyl groups are substituted with methyl and hydroxypropyl groups. HPMC has numerous features that are expected from the coating polymers. It provides a clear, tough, flexible film which protects the fragile tablets and covers the unpleasant taste of drugs, improve their appearance. HPMC is stable against heat, light, air and the indoor moisture but slightly hygroscopic [www.greatvistachemicals.com].

Polyvinyl alcohol is a water-soluble polymer having excellent film-forming properties. Films formed from it have an excellent tearing strength and flexibility. Its main properties are determined by the degree of polymerisation, the rate of hydrolysation and the configuration of the hydroxyl groups.

The viscosity of 4% solutions of polyvinyl alcohols having different polymerisation degrees was measured at 20°C and it was found that the viscosity depends on the polymerisation degree. To degrees of polymerisation of 500, 1700 and 2000 viscosities of 5cP, 20-30cP and 40-50 cP were measured, respectively. [www.nexant.com]

The most frequently used film-coating compositions are shown in Table 1 as follows:

Table 1

CHEMICAL NAME	BRAND NAME	FEATURE OF THE COATING
Ethylcellulose	Ethocel	water-insoluble
	Aquacoat® ECD	
	Surelease	
Polyvinylacetate	Kollicoat ® SR	water-insoluble
Methacrylate copolymers	Eudragit® NE, RL, RS	water-insoluble
	Kollicoat ®EMM	
	Eudragit® L,S, FS	enteric
	Kollicoat ® MAE	
	Eudragit E	stomach-soluble
Cellulose half esters	Aquacoat® CPD	enteric

Hydroxypropylmethylcellulose	Pharmacoat 606	water-soluble
	Sepifilm 752	
	Opadry I.	
Polyvinylalcohol (PVA)	Opadry II Clear	water-soluble
	Opadry II White	

Some recently used water-soluble film-coatings having a so-called „moisture protection" feature contain hydrofobic components (glycerides, stearinic acid) for achieving the moisture impermeability. Such water-soluble and mositure protection coating polymer compositions are Sepifilm LP770 and Aqua Polish containing HPMC as film-coating agent. Another possibility is the use of special, less hygroscopic film-forming polymers, omitting the use of water-soluble plasticizers (polyethyleneglycol). Such a film-coating composition is Opadry AMB. The disadvantage of the use of Opadry AMD is that during the coating process it has a strong adhesion tendency.

The composition of cited moisture resistant coating systems is summarized in Table 2 as follows:

Table 2

Brand name	Main components
Sepifilm LP770	HPMC, TiO_2, Staerinic acid
Aqua Polish	HPMC, TiO_2, C_8-C_{12} fatty acid triglyceride
Opadry AMB (Aqueous Moisture Barrier)	PVA, TiO_2, xanthan gum, talc, lecithin

The moisture impermeability of the above-mentioned coating compositions can be examined if test tablets are coated with them. Tablets containing zink-aspartate, magnesium-aspartate, potassium dihydrogen phosphate, dipotassium hydrogen phosphate, povidon, crospovidon, colloidal silica and magnesium stearate can be used as test tablets. The test tablets are coated with an amount of 4% of coating composition based on the weight of the tablet, then the tablets are conditioned in

place having 33% of relative humidity at room temperature, and then put to a place having 75% relative humidity where the weight gain of the tablets is measured. The rate of weight gain in percent, as tables and figures show, is calculated as follows:

m/m%= (tablet weight/ weight of conditioned tablet)*100

The humidity absorptions of the tablets having different film-coatings are compared in Figure 1.

We found that using the best moisture impermeable coating (OPADRY AMB) the weight gain of the tablet was 0.65% during 24 hours. Consequently, a tablet coated with Opadry AMB absorbs an amount of 34% of the absorption of an uncoated tablet in a place having 75% relative humidity. A part of the active ingredients used as pharmaceuticals, nutrition agents or supplements is sensitive for humidity, therefore the solid compositions containing these have to be coated with such coatings which enable the immediate release in aqueous media, but protect the active ingredients from the humidity as well as possible. Using a coating with a better moisture resistance broadens the selection of the usable accessory agents, since some of them, which are generally excluded as being incompatible in the presence of humidity, may be used in this case. Such a coating improves the physical and chemical stability of the composition. It reduces the change of the dissolution rates of active ingredients during the shelf life. A less moisture impermeable composition can be used in broader geographical territories.

Our aim was to develop a mositure protective but water-soluble coating composition, for which it is not required to use organic solvents in the course of coating process, which is water-soluble, but has an appropriate moisture impermeability, preventing both the damage of active ingredient or ingredients of the solid composition and the change of the dissolution properties of the composition during the shelf life.

ESSENCE OF THE INVENTION

The present invention relates to a coating composition comprising a polyvinyl-alcohol film-forming polymer and montmorillonit (hereinafter referred to as MMT)

decreasing the moisture absorption of tablets containing active pharmaceutical ingredients, nutrition agents or supplements.

Furthermore, the present invention refers to a coating composition, which comprises a polyvinyl-alcohol film-forming polymer and montmorillonit.

A further aspect of the present invention relates to solid compositions, which are coated with a coating comprising a polyvinyl-alcohol film-forming polymer and montmorillonit.

The present invention further refers to a process for the preparation of a composition comprising a polyvinyl-alcohol film-forming polymer and montmorillonit, which can be prepared by mixing polyvinyl-alcohol with montmorillonit alone or with further accessory agents in the form of powder and the obtained mixture is granulated, if necessary. It can be prepared also by mixing the polyvinyl alcohol or an aqueous solvent thereof to the aqueous suspension of MMT. Moreover, the present invention refers to a process for the coating of solid compositions comprising pharmaceutical, nutrition active ingredients or supplements with a coating comprising a polyvinyl-alcohol film-forming polymer and montmorillonit, in which the solid compositions are coated with a coating composition comprising a polyvinyl-alcohol film-forming polymer and montmorillonit in the form of an aqueous suspension in a known manner.

DETAILED DESCRIPTION OF THE INVENTION

In the course of our experiments we found that in case montmorillonit is mixed into the film-forming polymers comprising polyvinyl alcohol, the moisture impermeability of the polyvinyl alcohol coating is considerably increased.

We found surprisingly that the montmorillonit integrated into polyvinyl alcohol strongly inhibits the water permeability of the formed polymer film, meanwhile this effect is negligible in the case of use of films containing other polymers, e.g. HPMC.

The polyvinyl alcohol (PVA) montmorillonit nanocomposite is a mixture of an organic (polymer) and an inorganic (silicate) compound. The particles of montmorillonit consist of platelets having a size of 100 nm*100 nm*1 nm as it is

shown in Figure 5. The structure of the platelets is octahedral, which consists of two tetrahedral silica oxide layers and easily hydratable metal ions between them, which are usually alkali metal or alkali earth metal ions. These cations make the layers strongly hydrophilic because of their partial positive charge. Montmorilonnit has considerable hydratation energy. The structure of montmorillonit is shown in Figure 6.

The water molecules are adsorbed on the surface of the montmorillonit and thus are capable to neutralize these partial charges on the surface with ion-dipol interaction. The hydration of monovalent cations is responsible for swelling. When the layers are hydrated, the layers divide and the corners having slightly positive charge magnetize the layer surfaces having lightly negative charge. The result is a three dimensional structure which looks like a house of cards resulting in a quick increase of viscosity. In the course of time it is increasingly difficult to find appropriate partners for the particles and therefore the viscosity much less increases.

The used time period, the intensity of the mixing and the used temperature are important from the point of view of hydration, which define the obtained structure and the properties of the suspension.

A longer period under higher revolution per minute and at a higher temperature results in a more stable structure and higher viscosity. The adjustment of parameters is a routine task for the person skilled in the art.

Montmorillonit has been used as an auxiliary agent in the pharmaceutical industry for a long time. It is used primarily in liquid compositions as stabilizer of suspensions or emulsions and as an agent regulating the dissolution of the active ingredient in ointments and suppositories. In solid compositions it is used traditionally as a binding or disintegrating agent in case of wet granulation, and in a micronized form it is used in direct compression processes. The use of montmorillonit in solid pharmaceutical compositions increases, because its physico-chemical properties allow the formation of special interactions between the active ingredients and accessory agents.

Montmorillonit suitable for pharmaceutical use is marketed under the brand name Veegum HS by Vanderbilt company, the quality of the product corresponds to the requirements of the USP (United State Pharmacopeia) as purified bentonite. For measuring the water permeability of the film-coatings comprising PVA montmorrillonit nanocomposite test tablets were coated with this coating. The weight of the coating was 4% based on the weight of the tablets in all cases. Tablets containing zinc-aspartate, magnesium-aspartate, potassium dihydrogen phosphate, dipotassium hydrogen phosphate, povidon, crospovidon, colloidal silica and magnesium stearate were used as test tablets. Both the coated tablets and the uncoated ones were conditioned in a place having 33% of relative humidity at room temperature for 48 hours, then the tablets were put to a place having 75% relative humidity and the weight gain of the tablets was measured at specified time periods. Moreover it was tested how the weight changes if the tablets are put cyclically to places having 33% relative humidity and 75% relative humidity.

The moisture absorption profiles of tablets coated with the Opadry Clear film-coating system comprising polyvinyl alcohol and modified with montmorrilonit nanoparticles under 75 % relative humidity are shown in Figure 2. The changes are summarized in the following table:

Table 3

	Uncoated tablet	Opadry Clear coating	Opadry Clear + 5 % MMT coating	Opadry Clear + 10 % MMT coating	Opadry Clear + 20 % MMT coating
T (h)	m/m [%]	m/m [%]	m/m [%]	m/m [%]	m/m [%]
0	0	0	0	0	0
2.5	0.37	0.05	0.04	0.03	0.02
5	0.70	0.16	0.14	0.09	0.08
24	1.91	1.08	0.86	0.71	0.58

The results clearly show that the moisture permeability of the coatings comprising 5, 10, 20% of montmorrilonit decreases monotonously with the increase of the amount of montmorillonit. The weight gain of the compositions coated with

Opadry Clear and with modified coatings is compared to the uncoated tablets and to tablets without montmorillonit and is summarised in the following table:

Table 4

T =24 h	Uncoated tablet	Opadry Clear coating	Opadry Clear + 5 % MMT coating	Opadry Clear + 10 % MMT coating	Opadry Clear + 20 % MMT coating
m/m [%]	1.91%	1.08%	0.86%	0.71%	0.58%
Coated tablet m/m [%] / uncoated tablet m/m [%]	100%	57%	45%	37%	30%
Tablets coated with Modified Opadry Clear m/m [%] / Tablets coated with Opadry Clear m/m [%]	-	100%	80%	66%	54%

As the table shows the water absorption of the tablets coated with a coating comprising montmorillont can be reduced to 30% compared to uncoated tablets, and the montmorillonit can double the moisture impermeability of the coating.

In Figure 3 and in Table 5 below it is shown that the weight gain of the tablets coated with the Opadry Clear film-forming polymer modified with 10% of montmorrilonit is less then that of the tablets coated with Opadry AMB coating, which has the best moisture impermeability among the commercially available coating systems. In a place where the relative humidity was cyclically changed, the samples were stored alternately under 33% and 75% of relative humidity, the results are as follows:

Table 5

	Uncoated	Opadry II Clear + 10% MMT	Opadry II AMB
t/h	m/m [%]	m/m [%]	m/m [%]
0	0	0	0
46	2.57	1.15	1.48
70	3.3	1.68	2.27
144	6.94	3.64	**5.09**
188	0.53	2.09	1.26
336	0.17	0.68	0.16
362	0.23	0.62	0.18
385	2.36	1.14	1.45
482	**5.62**	**3.35**	**4.44**
525	0.31	1.61	0.77
817	0.18	0.24	0.06
1030	0.11	0.11	0.02
1055	3.06	1.39	2.14
1222	**6.71**	**4**	**5.54**
1366	0.22	0.78	0.15
1414	0.2	0.5	0.1
1486	0.18	0.28	0.05
1678	0.15	0.11	0.02
1702	2.55	0.94	1.81
1726	3.48	1.85	2.58
1870	**9.09**	**5.08**	**7.21**
1990	0.42	1.35	0.42
2134	0.23	0.15	0.07

The use of montmorrilonit (Veegum HS) did not considerably change the moisture permeability of the coating systems comprising HPMC (Pharmacoat 606) as it is shown in Figure 4.

As the used amount of montmorrilonit is increasing, the moisture impermeability of the coating compositions containing polyvinyl alcohol modified with montmorillonit is improving. Considering the results of mechanical tests, the presence of more than 10% of montmorillonit based on the film-composition can result in a brittle film, therefore 10% of montmorrilonit content seems to be optimal in systems which contain only polyvinyl alcohol. If the coating system also contains

more pigments (e.g. titan dioxide, talc), 3-7% of montmorillonit is used based on the weight of the film-coating polymer preferably.

More particularly, the present invention relates to a coating composition comprising a polyvinyl alcohol firm-forming agent and montmorillonit which comprises 10-30%, preferably 2-20%, more preferably 5-15% of montmorillonit on the basis of the weight of the polyvinyl alcohol film-forming agent. The coating composition can comprise preferably further accessory agents, preferably a softener, an anti-adhesive agent, a pigment or a dye. It can comprise preferably polyethyleneglycol as softener, preferably talc as anti-adhesive, preferably titanium dioxide as pigment and preferably ferrous oxide pigments as dye.
The coating composition of the present invention is used for the coating of solid compositions, preferably tablets, pellets, granules or active ingredient particles containing a pharmaceutical active ingredient, a nutrition agent or a supplement.

Furthermore, the present invention relates to the use of such coating compositions containing polyvinyl alcohol and montmorillonit for the coating of tablets, pellets, granules or active ingredient particles, which comprises 10-30%, preferably 2-20%, more preferably 5-15% of montmorillonit on the basis of the weight of the polyvinyl alcohol film-forming agent.

The used coating composition can preferably comprise further accessory agents, preferably a softener, an anti-adhesive agent, a pigment or a dye. It can contain preferably polyethyleneglycol as softener, preferably talc as anti-adhesive, preferably titanium dioxide as pigment, preferably ferrous oxide pigments as dye.

The coating composition of the present invention is used for the coating of solid compositions, preferably tablets, pellets, granules or active ingredient particles containing a pharmaceutical active ingredient, a nutrition agent or a supplement.

Another aspect of the present invention is a coating composition, which comprises a polyvinyl alcohol firm-forming agent and montmorillonit. According to a preferred embodiment of the present invention the coating composition comprises 10-30%,

preferably 2-20%, more preferably 5-15% of montmorillonit on the basis of the weight of the film-forming agent. Preferably, the coating composition can comprise further accessory agents, preferably a softener, an anti-adhesive agent, a pigment or a dye. It can comprise preferably polyethyleneglycol as softener, preferably talc as anti-adhesive, preferably titanium dioxide as pigment, preferably ferrous oxide pigments as dye.

Moreover the present invention refers to solid compositions comprising a pharmaceutical active ingredient, a nutrition agent or a supplement or a mixture thereof and coated with a coating containing a polyvinyl alcohol film-forming agent and motmorillonit. These compositions comprise 1-30%, preferably 2-20%, more preferably 5-15% of montmorillonit based on the weight of the film-forming agent. The coatings of these compositions can contain accessory agents, preferably a softener, an anti-adhesive agent, a pigment or a dye if necessary. They can contain preferably polyethyleneglycol as softener, preferably talc as anti-adhesive, preferably titanium dioxide as pigment, preferably ferrous oxide pigments as dye.

The present invention refers to a process for the preparation of a coating composition comprising polyvinyl alcohol and montmorillonit in which the polyvinyl alcohol and the montmorillonit are mixed in a powder form, or the mixture is granulated by means of a suitable process, or besides the polyvinyl alcohol and montmorillonite advantageously further accessory agents, such as a softener, an anti-adhesive agent, a pigment or a dye are added to the composition in a powder form.

Furthermore, the present invention relates to the preparation of a coating suspension containing polyvinyl alcohol and montmorillonit, in which the coating composition containing polyvinyl alcohol and montmorillonit is suspended in water. Besides the polyvinyl alcohol and montmorillonit the coating composition can comprise further accessory agents, such as a softener, an anti-adhesive agent, a pigment or a dye.

The present invention also relates to a process for the preparation of an aqueous coating suspension comprising polyvinyl alcohol and montmorillonit, in which the montmorillonit is suspended in water, then the polyvinyl alcohol or an aqueous solution thereof is added to the stirred suspension and the obtained suspension is homogenized. According to the present invention 1-30%, preferably 2-20%, more preferably 5-15 % of montmorillonit is used based on the weight of the film-forming polymer.

Particularly the process can be carried out as follows:

a.)

to the stirred aqueous suspension of montmorillonit polyvinyl alcohol is added and the obtained mixture is homogenized, then further accessory agents are added under stirring to the mixture, or

b.)

to the stirred aqueous suspension of montmorillonit a previously prepared premix of polyvinyl alcohol and accessory agents is added.

The premix according to present invention is a mixture containing polyvinyl alcohol and such accessory agents, which are necessary in the coating system. The premixes can be prepared by adding the accessory agents to a solution of polyvinyl alcohol, then homogenized. Numerous commercially available film-coating compositions (e.g. Opadry Clear) can be used as premix alone or mixed with other accessory agents.

Another aspect of the present invention is a process for the preparation of solid compositions containing a pharmaceutical, a nutrition agent or a supplement or a mixture thereof, in which the solid composition is coated with a coating containing polyvinyl alcohol and motmorillonit using a known method.

According to the prior art tablets can be coated e.g. in a coating pan, so that the aqueous suspension of the coating composition is sprayed onto the tablets, then the coated tablets are dried. Granules, pellets and active ingredient particles are coated most preferably using fluidisation equipment. The coating process of tablets, granules, pellets and active ingredient particles is a part of the general knowledge of the person skilled in the art. In the course of the use of different equipments different technological parameters have to be adjusted, but the

selection and optimisation of these parameters are also a part of the general knowledge of the person skilled in the art.

In the course of the coating of solid compositions the used coating composition contains 1-30%, preferably 2-20%, more preferably 1-15% montmorillonit based on the weight of the film-forming composition. If necessary, the process is carried out in such a way that further accessory agents, preferably a softener, an anti-adhesive agent, a pigment and a dye are admixed to the composition.

According to the present invention pharmaceuticals are such compositions which are used for the treatment or prevention of illnesses or used for diagnostic purposes. The effects of the pharmaceuticals to the organisms are examined by pharmaceutical sciences. Pharmaceuticals are compositions containing one or more synthetically produced or herbal active ingredients. The pharmaceuticals can be classified by their effects, e.g. according to the ATC codes of WHO. Nutritions are special nutriments, namely artificially mixed nutriments, which contain natural nutriments or other biologically valuable compounds, e.g. vitamins. Nutritions can be e.g. medical nutritions, infant formulas, diet preparations etc. Supplement compositions are used regularly or occasionally for replacement of elements which are missing from normal food. These can be combined compositions containing several ingredients, e.g. multivitamins or protein and vitamin combinations, fibre and vitamin combinations.

According to the present invention the active ingredients are active ingredients of pharmaceuticals, natural nutriments and other biologically useful compounds of nutrition compositions and biologically active ingredients of supplements and mixtures thereof. The coated solid pharmaceutical compositions, nutritions and supplements according to the present invention can be used for healing, treating or feeding either human beings or animals depending on the quality and quantity and indications of the used active ingredient.

The solid compositions according to the present invention, e.g. tablets, pellets and granules can preferably contain accessory agents used in the pharmaceutical or food industry. Such accessory agents can be organic and inorganic filling agents. As inorganic filling agent inorganic salts, e.g. mono- and dibasic potassium

phosphate, potassium carbonate, as organic filler organic polymers, e.g. microcrystalline cellulose, starch, sugars, e.g. dextrose, sugar derivatives, e.g. mannitol can be used. As binder polymers, e.g. polyvinyl pyrrolidone or hydroxypropylmethylcellulose can be used. As disintegrating agent starch derivatives, e.g. sodium starch glycolate or other swelling polymer, such as crospovidon can also be used. As glidant colloidal silica, magnesium stearate or e.g. glycerylbehanate can also be used.

The preparation of the tablets, pellets and granules and the selection of the suitable accessory agents belong to the general knowledge of the person skilled in the art. Depending on the used active ingredients and accessory agents the tablets can be prepared with direct compression or alternatively, the active ingredients and accessory agents are granulated, then the obtained granules are mixed with the compounds of the outer phase, then pressed into tablets. Granules can be prepared using wet granulation processes such as extrusion, extrusion-spheronization or fluid bed granulation process. Dry granulation processes such as briquetting and compaction processes can also be used. The use and optimisation of the specified processes belong to the general knowledge of the person skilled in the art.

The tablets containing a pharmaceutical active ingredient coated with a coating according to the present invention can contain any active ingredient which is not incompatible with polyvinyl alcohol. Nevertheless, such ingredients can also be used if the tablet or granule has a layered structure and the layer containing polyvinyl alcohol is isolated with another water-dissoluble layer. If the active ingredient particles are incompatible with the coating containing polyvinyl alcohol, the active ingredient particles are coated with a water-soluble separating layer, e.g. a layer containing hydroxypropylmethylcellulose and the coating comprising polyvinyl alcohol and montmorillonit is layered onto it.

The advantage of the process of the present invention is that the mositure barrier coatings prepared according to the present invention have a better moisture impermeability than the commercially available water-soluble coatings.

The coating composition according to the present invention does not become sticky during the coating process.

Using a coating having a better moisture impermeability broadens the selection of the usable accessory agents, since some of them, which are generally excluded as being incompatible in the presence of humidity, may be used in this case. Such a coating improves the physical and chemical stability of the composition.
It reduces the change of the dissolution rates of active ingredients during the shelf life. A less moisture sensitive composition can be used in broader geographical territories.

Drawings:
Drawing 1, Figure 1 shows the increase of weight of tablets coated with different commercially available coatings, which tablets were preconditioned in a place having 33% humidity for 48 hours then were stored in a place having 75% relative humidity.
Drawing 2, Figure 2 shows the increase of the weight of tablets coated with Opadry Clear and modified coatings according to the present invention, which tablets were preconditioned in a place having 33% humidity for 48 hours, then were put in a place having 75% relative humidity.
Drawing 3, Figure 3 shows the increase and decrease of the weight of uncoated tablets, tablets coated with Opadry Clear II+ 10% MMT and tablets coated with Opadry AMD coatings, which tablets were preconditioned at 33% of humidity for 48 hours, at room temperature then were stored in a place where the relative humidity was changed from 33% to 75% and back cyclically.
Drawing 4, Figure 4 shows the increase of the weight of tablets coated with Pharmacoat containing HPMC and tablets coated with coatings containing Pharmacoat coating modified with 5 and 10% of montmorillonit compared with uncoated tablets stored in a place having 75% relative humidity.
Drawing 5, Figure 5 shows the size of montmorillonit.
Drawing 5, Figure 6 shows the crystal structure of montmorillonit.

Further details of the present invention are to be found in the following Examples without limiting the scope of protection to said Examples.

Example 1

Process for the preparation of test tablets:

Composition of tablets:

Compound	Function	Amount/ Tablet	Weight
Zincum aspartas anhidricum	Active ingredient	5.0 mg	2.25 g
Magnesii aspartas tetrahydricus	Active ingredient	424.0 mg	190.8 g
Kalii dihydrogenophosphas	Active ingredient	59.0 mg	26.55 g
Dikalii phosphas	Active ingredient	76.0 mg	34.2 g
Povidonum	Binding agent	10.0 mg	4.5 g
Crospovidonum	Disintegrant	100.0 mg	45 g
Silica colloidalis anhydrica	Hydrating agent and glidant	13.0 mg	5.85 g
Magnesii stearas	Lubricant	9.0 mg	4.05 g
Summary		696 mg	313.2 g

Nominal weight of tablets is 696.0mg

The active ingredients are mixed in a high-shear mixer, then granulated with an aqueous solution of povidonum and dried below 3 % of humidity in a fluid bed dryer, the obtained granules regranulated to reduce the particle size to be less than 1 mm, then homogenized with other accessory agents in a drum mixer and pressed into tablets.

Example 2

Coating of tablets

The coating process was carried out using the commercially available coating compositions in all cases as follows:

The coating process was carried out in a Glatt GC 250 film-coating machine. The film-coating composition (40g) was suspended under permanent stirring in water (260g) at room temperature for 1 hour in every case, then sieved if it was necessary. The tablet cores (800g) filled into the machine were heated with an inlet airflow of 55 °C under rotation of the cauldron at 3 rpm until the outlet airflow increased to 45 °C. The spraying of the coating dispersions was carried out at a dosage rate of 6g/min and under 3 bar of spraying pressure of air and the rotation of the cauldron was increased to 6 rpm during the spraying process. The spraying process was carried out until achieving 4% of weight gain.

Example 3

Examination of the humidity absorption and desorption properties of tablets:

Before the tests of humidity absorption the samples were preconditioned by being placed in a hygrostat having 33% relative humidity (until constant weight, ~ 48 hours, 0 point), then the samples were placed into a hygrostat having 75% of relative humidity and the weight gain of the samples was measured several times in 24 hours. The weight gain is given in percent on the basis of the initial weight in percent.

The formula of calculation is as follows:

m/m%= (tablet weight/conditioned weight of the tablet)*100

Example 4

Tablets coated with a coating containing of polyvinyl alcohol and motmorillonit

(montmorillonit compositon= 4.2%)

The uncoated tablets were prepared according to Example 1.

450 tablets (313.2g) were coated.

Nominal weight of the tablets was 696.0mg.

Nominal composition of the coating of a tablet was: 23.0 mg of Opadry II 85 F and 1.0 mg of Veegum HS

The coating was carried out in a film coating machine of ProCept 4m8.

Process for the preparation of film coating suspension:

At room temperature 1.0 g Veegum HS is suspended in 150 ml of deionized water under stirring with a magnetic stirrer, then 23.0 g of Opadry II 85F are added and the mixture is stirred for additional 45 minutes.

Coating process:

The tablet cores (450g) filled into the machine were heated with an inlet airflow of 55 °C under rotation of the cauldron at 3 rpm, until the temperature of the core bed increased to 45 °C. The spraying of the coating dispersions was carried out at a dosage rate of 2 g/min and under 1.5 bar of spraying pressure of air and the rotation of the cauldron was increased to 10 rpm during the spraying process. The temperature of the inlet air was controlled to keep the temperature of the core bed between 42-45°C. The coating process was carried out until achieving a weight gain of 24 mg/tablet.

Example 5

Tablets coated with a coating containing polyvinyl alcohol and motmorillonit

(montmorillonit/coating composition = 6.2%)

The uncoated tablets were prepared according to Example 1 using the composition as follows:

Compound	Amount
Zincum aspartas anhidricum	10.0 mg
Magnesii aspartas tetrahydricus	848.0 mg
Kalii dihydrogenophosphas	118.0 mg
Dikalii phosphas	152.0 mg
Povidonum	20.0 mg
Crospovidonum	200.0 mg
Silica colloidalis anhydrica	26.0 mg
Magnesii stearas	18.0 mg

Nominal weight of the tablets: 1392.0mg.

450g of tablets were coated.

Nominal composition of coating of a tablet: 45.0 mg of Opadry II 85 F and 3.0mg of Veegum HS.

The coating was carried out in a film coating machine of ProCept 4m8.

Process for the preparation of a film-coating suspension:

At room temperature 1.5 g Veegum HS is suspended in 150 ml of deionized water under stirring with a magnetic stirrer, then 22.5 g of Opadry II 85F are added and the mixture is stirred for additional 45 minutes.

Coating process:

The tablet cores (450g) filled into the machine were heated with inlet airflow of 55 °C under rotation of the cauldron at 3 rpm until the temperature of the core bed increased to 45 °C. The spraying of the coating dispersions was carried out at a dosage rate of 2 g/min and under 1.5 bar of spraying pressure of air. The rotation of the cauldron was increased to 10 rpm during the spraying process. The temperature of the inlet air was controlled to keep the temperature of the core bed between 42-45°C. The coating process was carried out until achieving a weight gain of 48 mg/tablet.

Example 6

Tablet coated with a coating containing polyvinyl alcohol-montmorillonit composite

a.) Process for the preparation of tablet cores:

Uncoated tablets were prepared according to Example 1.

b.) Tablets coated with Opadry Clear:

The coating process was carried out according to Example 2 using Opadry Clear as coating composition.

c.) Process for the preparation of tablets coated with a coating containing Opadry Clear + 5 % of montmorrilonit:

The coating suspension is prepared according to Example 5 with the difference that 1.2 g of montmorillonit and 22.5 g of Opadry Clear are used.

The coating process was carried out according to Example 5.

d.) Process for the preparation of tablets coated with a coating containing Opadry Clear + 10 % of montmorrilonit:

The coating suspension is prepared according to Example 5 with the difference that 2.3 g of montmorillonit and 22.5 g of Opadry Clear are used.

The coating process was carried out according to Example 5.

e.) Process for the preparation of tablets coated with a coating containing Opadry Clear + 20 % of montmorrilonit:

The coating suspension is prepared according to Example 5 with the difference that 4.5 g of montmorillonit and 22.5 g of Opadry Clear are used.

The coating process was carried out according to Example 5.

The moisture absorption of the tablets is shown in Table 3 and in Figure 2.

Example 7

Tablet coated with a coating containing polyvinyl alcohol-montmorillonit composite

a.) Process for the preparation of tablet cores:

Uncoated tablets were prepared according to Example 1.

b.) Process for the preparation of tablets coated with coatings containing Opadry White:

The coating of the tablets is carried out according to Example 2 with the difference that the used coating composition is Opadry Clear.

c.) Process for the preparation of tablets coated with a coating containing Opadry White + 5 % of montmorrilonit:

The coating suspension is prepared according to Example 5 with the difference that 1.2 g of montmorillonit and 22.5 g of Opadry Clear are used.

d.) Process for the preparation of tablets coated with a coating containing Opadry White + 10 % of montmorrilonit:

The coating suspension is prepared according to Example 5 with the difference that 2.3 g of montmorillonit and 22.5 g of Opadry Clear are used.

The coating process was carried out according to Example 5.

The damp-proof properties of tablets are shown in the following Table:

	Uncoated tablet	Opadry White coating	Opadry White +5%MMT	Opadry White +10%MMT
T [h]	m/m [%]	m/m [%]	m/m [%]	m/m [%]
0	0%	0%	0%	0%
2	34%	6.35%	4.74%	4.75%
5	63%	16.66%	12.63%	13.08%
24	191%	96.80%	68.69%	78.47%

Claims:

1. Use of a coating composition comprising a polyvinyl alcohol film-forming agent and montmorillonit for the coating of tablets, pellets, granules or active ingredient particles.
2. Use according to Claim 1 characterized in that the coating composition comprises 1-30%, preferably 2-20%, more preferably 5-15% of montmorillonit based on the weight of the film-forming agent.
3. Use according to Claim 1 or 2, characterized in that the coating composition contains at least one further accessory agent, preferably a softener, an anti-adhesive agent, a pigment or a dye.
4. Use according to any of Claims 1-3, characterized in that the coating composition contains a pharmaceutical active ingredient, a nutrition agent or a supplement as active ingredient.
5. A coating composition comprising a polyvinyl alcohol film-forming agent and montmorillonit.
6. A coating composition according to Claim 5 comprising 1-30%, preferably 2-20%, more preferably 5-15% of montmorillonit based on the weight of the film-forming agent.
7. A coating composition according to Claims 5 or 6 comprising at least one additional accessory agent, preferably a softener, an anti-adhesive agent, a pigment or a dye.
8. A solid composition containing a pharmaceutical, a nutrition agent, a supplement or a mixture thereof coated with a coating which comprises a polyvinyl alcohol film-forming agent and montmorillonit.
9. A solid composition according to Claim 8 comprising 1-30%, preferably 2-20%, more preferably 5-15% of montmorillonit based on the weight of the film-forming agent.

10. A solid composition according to Claim 8 or 9 in which the coating comprises at least one further accessory agent, preferably a softener, an anti-adhesive agent, a pigment or a dye.

11. Process for the preparation of a composition comprising polyvinyl alcohol and montmorillonit, characterized in that the polyvinyl alcohol and the montmorillonit are mixed in a powder form and granulated in a known manner if necessary.

12. Process according to Claim 11 characterized in that further accessory agents, preferably a softener, an anti-adhesive agent, a pigment or a dye are added to the mixture.

13. Process for the preparation of a composition comprising polyvinyl alcohol and montmorillonit, characterized in that the montmorillonit is suspended in water and the polyvinyl alcohol or an aqueous solution thereof is admixed and the obtained mixture is homogenized.

14. Process according to Claim 13, characterized in that 1-30%, preferably 2-20%, more preferably 1-15% of montmorillonit based on the weight of the film-forming agent is used.

15. Process according to Claim 13 or 14 characterized in that

a.)

polyvinyl alcohol is added to the aqueous suspension of montmorillonit under stirring and the mixture thus obtained is homogenized, then a further accessory agent or agents, preferably a softener, an anti-adhesive agent, a pigment or a dye is/are admixed, or

b.)

a premix comprising polyvinyl alcohol and accessory agents is added to the aqueous suspension of montmorillonit under stirring.

16. Process for the coating of the solid compositions containing a pharmaceutical, a nutrition agent or a supplement characterized in that the solid composition is coated in a known manner with a coating composition comprising polyvinyl alcohol and montmorillonit.

17. Process according to Claim 16, characterized in that the used coating composition comprises 1-40%, preferably 2-20%, more preferably 1-15% of montmorillonit based on the weight of the film-forming agent.

18. Process according to any of Claims 16-17 characterized in that the coating composition contains at least one further accessory agent, preferably a softener, an adhesive agent, a pigment or a dye.

Figure 1

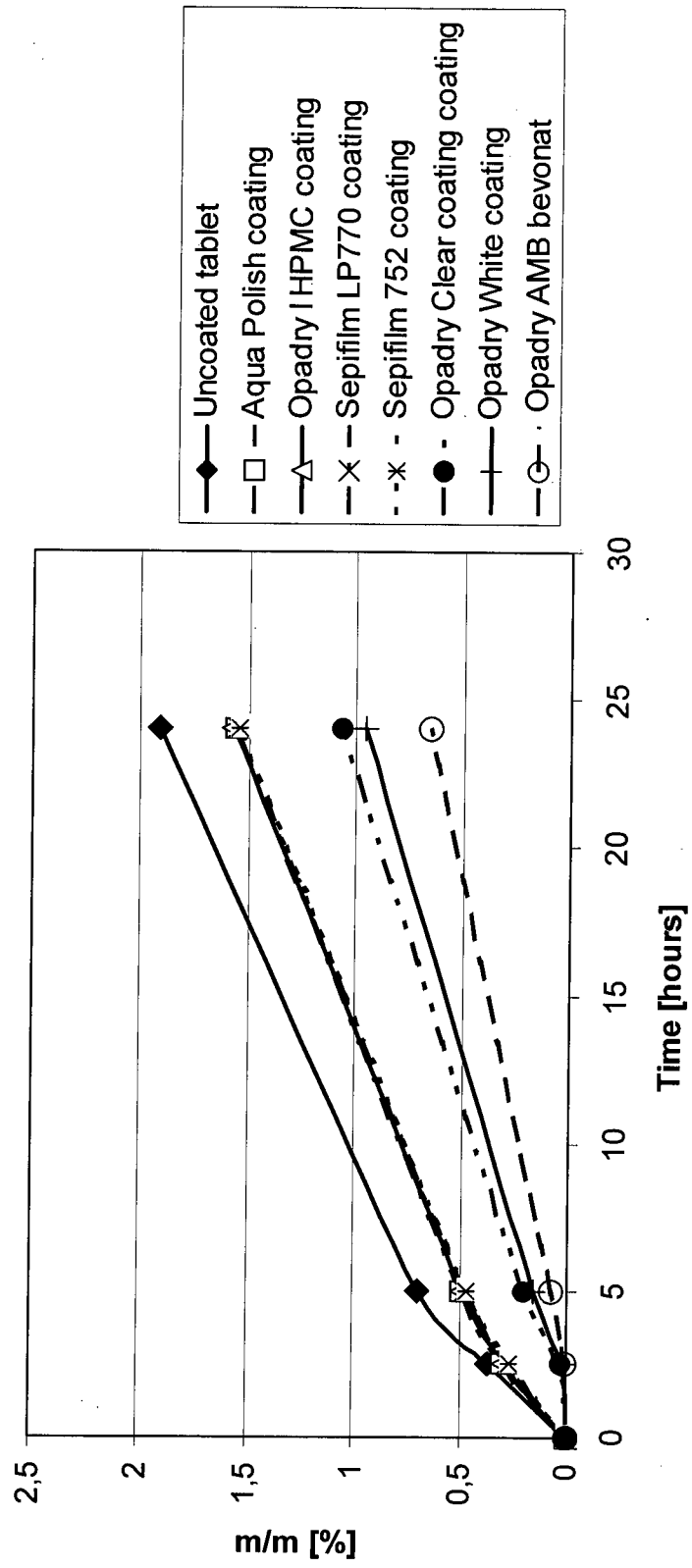

Uncoated tablet
Aqua Polish coating
Opadry I HPMC coating
Sepifilm LP770 coating
Sepifilm 752 coating
Opadry Clear coating coating
Opadry White coating
Opadry AMB bevonat
m/m [%]
2,5
2
1,5
1
0,5
0
0
5
10
15
20
25
30
Time [hours]

Figure 2

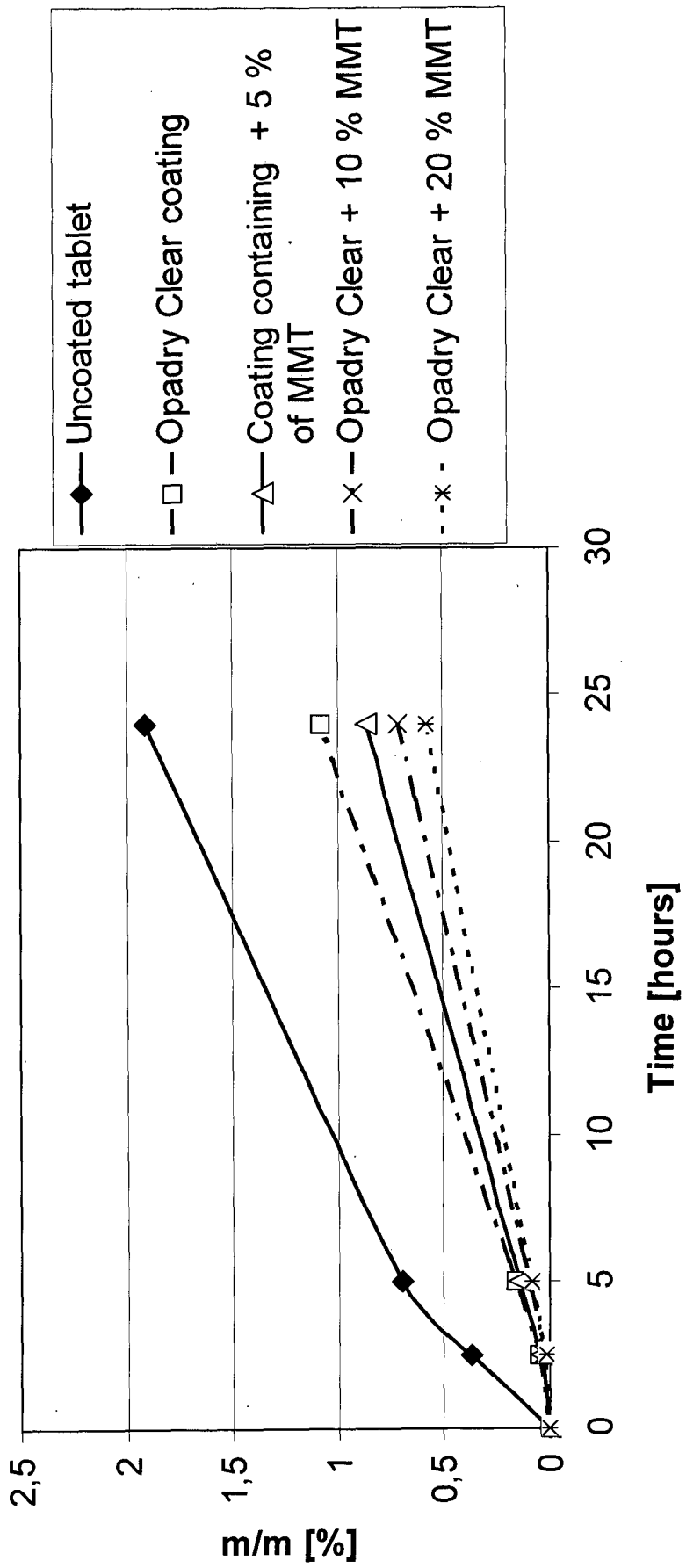

Uncoated tablet
Opadry Clear coating
Coating containing + 5 % of MMT
Opadry Clear + 10 % MMT
Opadry Clear + 20 % MMT
m/m [%]
2,5
2
1,5
1
0,5
0
Time [hours]
0
5
10
15
20
25
30

Figure 3

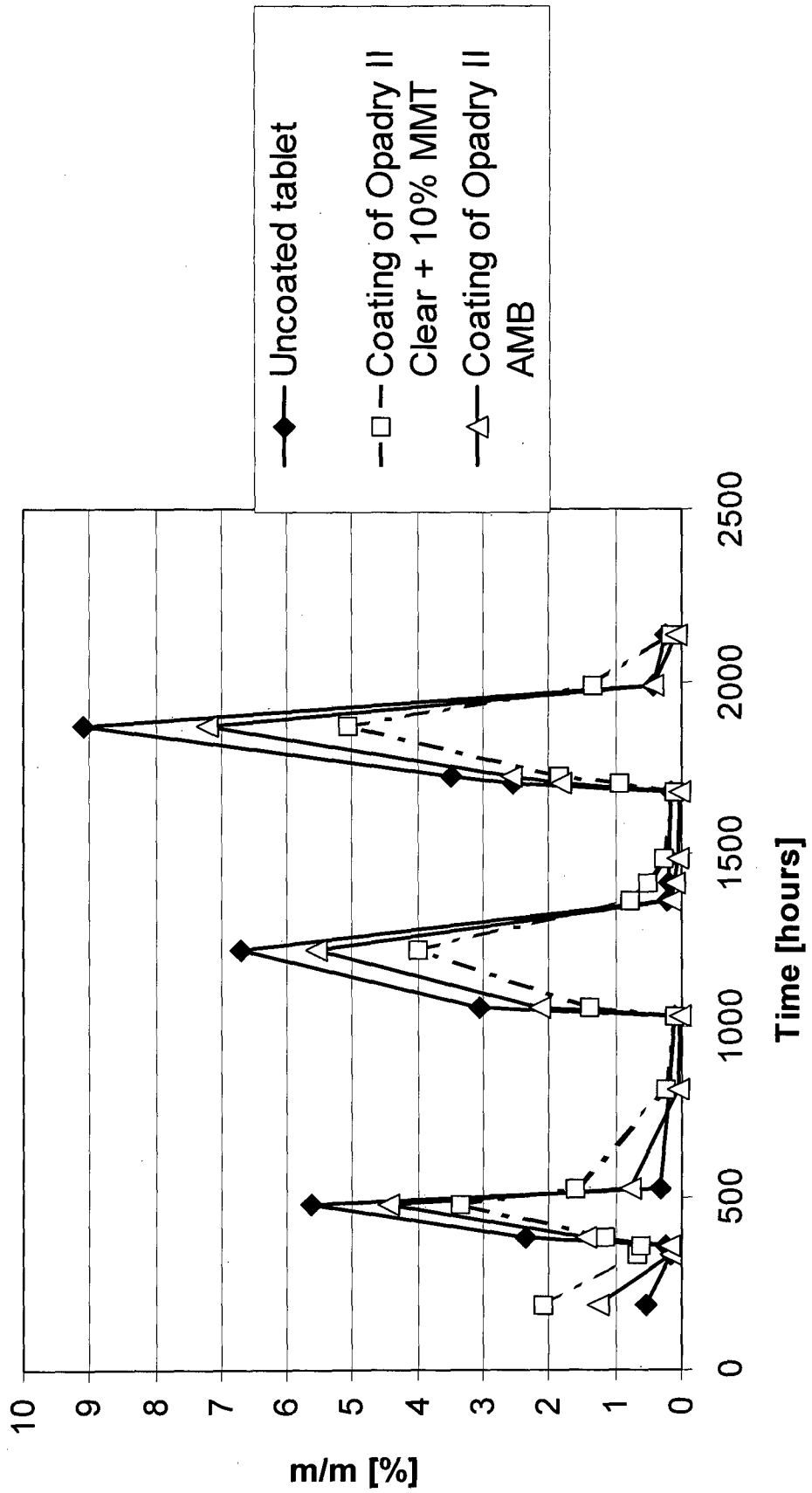

Uncoated tablet
Coating of Opadry II Clear + 10% MMT
Coating of Opadry II AMB
m/m [%]
Time [hours]
0
1
2
3
4
5
6
7
8
9
10
0
500
1000
1500
2000
2500

Figure 4

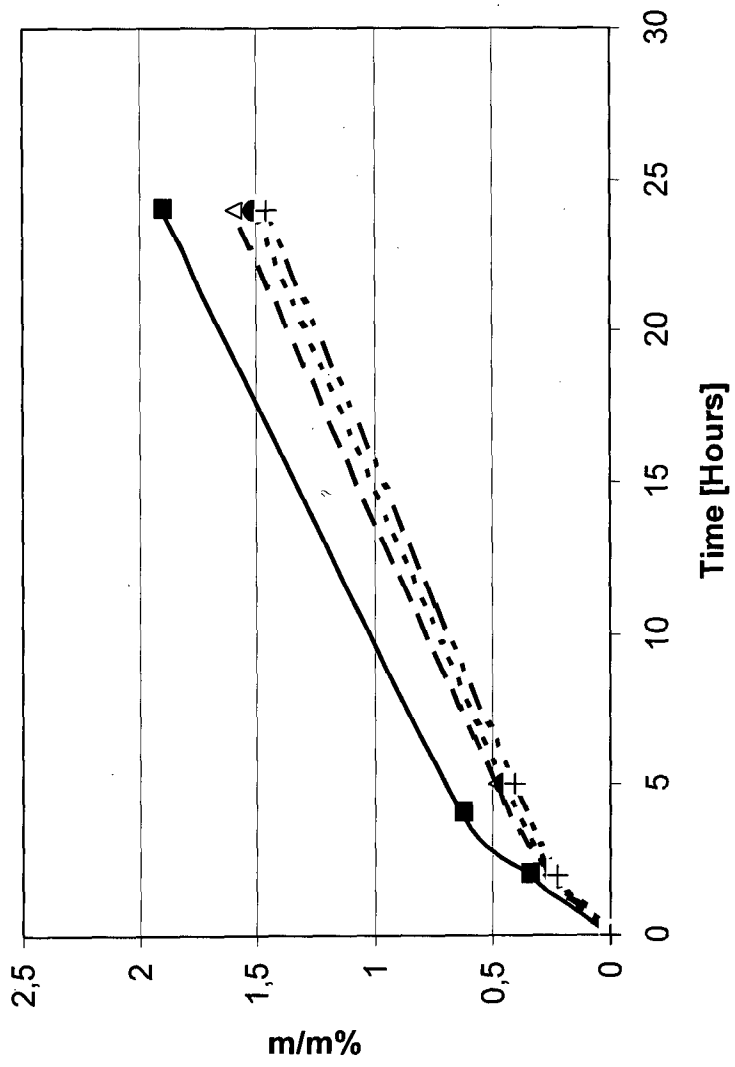

uncoated tablet
Pharmacoat
Pharmacoat + 5% MMT
Pharmacoat + 10% MMT
m/m%
2,5
2
1,5
1
0,5
0
Time [Hours]
0
5
10
15
20
25
30

Figure 5

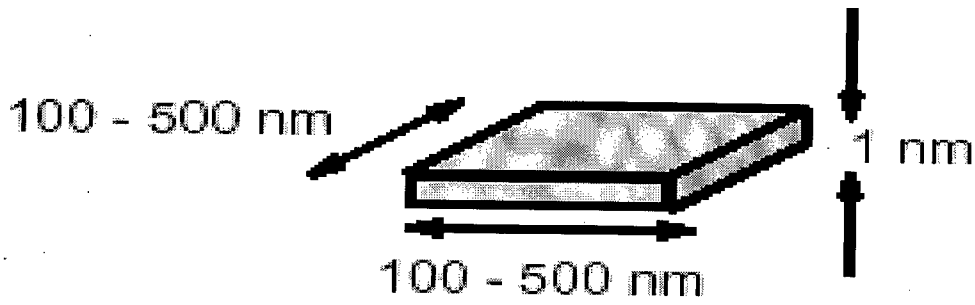
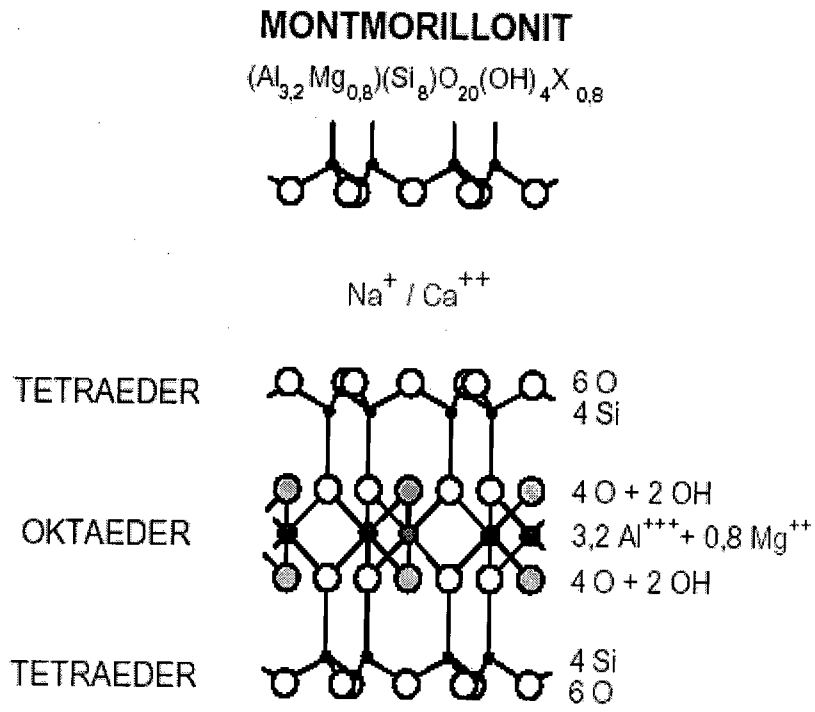


Figure 6



INTERNATIONAL SEARCH REPORT

International application No
PCT/HU2011/000095

A. CLASSIFICATION OF SUBJECT MATTER
INV. 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)
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, 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	DATABASE WPI Week 200414 Thomson Scientific, London, GB; AN 2004-137307 XP002676820, & JP 2003 286108 A (SUMITOMO CHEM CO LTD) 7 October 2003 (2003-10-07) abstract -----	1,3-5,7, 8,10-12, 16,18
X	WO 2011/105539 A1 (TORAY INDUSTRIES [JP]; FUJISAKI YUKI [JP]; YOSHII RYOJI [JP]; HORIUCHI) 1 September 2011 (2011-09-01) the whole document -----	1-10, 13-18

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
31 May 2012	08/06/2012

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/HU2011/000095

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 2003286108 A	07-10-2003	NONE	
WO 2011105539 A1	01-09-2011	NONE	