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(71) Applicant (for all designated States except US): **IDEAL CURES PVT. LTD** [IN/IN]; A-223 to 229, 2nd Floor, Virwani Industrial Estate, Off Western Express Highway Goregaon, (East), IN-400063 Mumbai (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **PAREEK, Suresh** [IN/IN]; IDEAL CURES PVT. LTD, |A-223 to 229, 1st Floor, Virwani Industrial Estate, Off Western, Express Highway Goregaon (EAST), IN-400063 Mumbai (IN). **RAJSHARAD, Chetan** [IN/IN]; IDEAL CURES PVT. LTD, |A-223 to 229, 1st Floor, Virwani Industrial Estate, Off Western, Express Highway Goregaon (EAST), IN-400063 Mumbai (IN). **LUINI, Dario** [IT/IT]; IDEAL CURES PVT. LTD, |A-223 to 229, 1st Floor, Virwani Industrial Estate, Off Western, Express Highway Goregaon (EAST), IN-400063 Mumbai (IT).

(74) Agent: **ARVIND, Chitra**; Rajeshwari & Associates, 1039, First Floor, C-Block129, Sushant Lok-I, Haryana, 122002 Gurgaon (IN).

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(54) Title: COMPOSITION AND METHOD FOR CONTROLLING RELEASE OF ACTIVE INGREDIENT

(57) Abstract: A coating composition based on sodium alginate, is designed to release the active ingredient of pharmaceutical substances, veterinary substances, nutraceutical products, and food and confectionery products after a pre-determined lag period, and a method of preparing the coating composition is also provided.



COMPOSITION AND METHOD FOR CONTROLLING RELEASE OF ACTIVE INGREDIENT

FIELD OF THE INVENTION

The present invention relates to development of film coating compositions designed to release active ingredient of pharmaceutical substances, veterinary substrates, nutraceutical products, and food and confectionery products over a predetermined period and a process of producing such a composition.

BACKGROUND OF THE INVENTION:

Currently, most commercially available edible film coatings comprise a combination of synthetic cellulosic polymer such as hydroxyl-propyl-methyl-cellulose (HPMC), a film former such as ethylcellulose, methylcellulose, polyvinylpyrrolidone, and polydextrose together with other ingredients including fillers, for example, lactose or maltodextrin; plasticizers, such as polyethylene glycols, dibutylsebacate, and triethyl citrate; surfactants; and often coloring materials such as a food dye or pigment, including opacifiers such as titanium dioxide and the like. These coatings are usually used for immediate release of a given active ingredient.

Most of the commercially available film coating compositions are used either for immediate release where the coated substrate disintegrates quickly in stomach and releases the active component in the acidic environment of the stomach or designed for enteric release where the substrate is coated with a pH dependent polymer so that the coating remains intact in acidic pH of stomach but dissolves quickly as soon as it confronts alkaline pH of the intestine to release the active ingredient. The release of the active ingredient from such pH dependent polymeric film takes anything from 2 hours to 4 hours depending on the physiology of the patient, the solubility of the polymer at different pH and the kind of food available in the stomach.

US Patent 4,792,452 describes one such controlled release composition where the active ingredient is released at a controlled rate regardless of the pH of the environment. The composition comprises a pH dependent polymer particularly sodium salt of alginic acid, a pH

dependent hydrocarbon gelling agent such as hydroxypropyl methyl cellulose along with other pharmaceutical excipients.

WO9813029 (also published as US6183780) describes an oral delayed immediate release formulation that comprises a non swellable core containing the active ingredient and is surrounded by a coating. The active ingredient is released by the rupture of the coating upon exposure to the gastrointestinal fluids. The coating composition comprises a polymeric material such as ethyl cellulose, a water soluble plasticizing agent, and a brittleness inducing agent.

WO2008110577 (US 2010028426) discloses a time specific delayed/pulsatile release dosage forms that releases the active ingredient after a predetermined lag period independently of the physiological pH variations that occur in the gastrointestinal tract. The dosage form comprises a core with active ingredient, a sealing layer and an outer coating layer. Both the sealing layer and coating layer contain atleast one polymer that exhibits pH independent water solubility. The polymers preferred for the composition include alkylcellulosic polymers.

WO02076429 discloses a sustained release drug delivery composition comprising about 20-40% of sodium alginate, about 4-12% of propylene glycol alginate, and about 40-80% of a pharmaceutical medicament. The invention aims at providing a composition which provides a dissolution rate of about 20% of drug within 2 hrs at an acidic pH, and the rest of 80% of the drug is released within at least 10 hrs at alkaline or neutral pH.

There are several products that must be consumed after food and if consumed before food, the efficacy of the active ingredient is lost or not fully realized due to exposure to very low pH in the empty stomach. There are certain coating compositions that provide sustained release formulation, wherein the dose is provided to obtain a sustained release effect. Sustained release effect releases the active substance at regular time interval rather than all together, which may be desired at certain points of time.

Hence, though there are several types of coating compositions in prior art, there is still a need of a coating composition whereby, an active ingredient may be programmed to be released after a pre-determined lag period.

OBJECT OF INVENTION

An object of the invention is to provide a coating composition, which releases the active ingredient after a pre-determined lag period,

Another object of the invention is to provide a method for preparing the coating composition of the present invention.

SUMMARY OF THE INVENTION:

The invention provides a coating composition based on sodium alginate, which composition is designed to release the active ingredient after a pre-determined lag period.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a coating composition based on sodium alginate as film forming polymer and is designed such that the active ingredient is released after a predetermined lag period.

The coating composition of the present invention essentially comprises a pH independent polymer, a plasticizer, a detackifier. It also includes other additives such as a preservative, flavoring agent, opacifiers, fillers/diluents, and coloring agents.

These and other objects of the invention are achieved by developing a composition that employs sodium alginate as film forming polymer in an amount from 25 to 85%w/w, together with a plasticizer, detackifier, preservative and other additives.

Sodium Alginate is polymer soluble in aqueous solutions with pH greater than 3.0. In aqueous acidic solutions with pH less than 3, it is poorly soluble. Thus, sodium alginate is a pH independent polymer (like enteric coating polymers which are completely insoluble in acidic pH but dissolve quickly in alkaline pH). It has been found that when used in a coating composition, the coating composition remains stable at highly acidic pH of empty stomach (the pH of empty stomach varies from 1.5 to 2.5 whereas the pH of the fed stomach varies from 2.0 to 4.5 depending on the nature of food and the amount of water taken along with food).

Sodium alginate is a sodium salt of alginic acid. Alginic acid extracted from various species of deep-sea weed like Phaeophyceae. Sodium alginate is a polysaccharide, like starch and cellulose. It is composed of several building units (typically 100-3000) linked together in a flexible chain. Long molecules constructed from identical or nearly identical building units are called polymers, while the building units themselves are called monomers. Polymers of natural origin are commonly called biopolymers.

Sodium alginate is built upon the basis of two sugars, which are both uronates, the salts of mannuronic and guluronic acid. When producing alginates, uronic acid is converted into the salt-form mannuronate (M) and guluronate (G).

Generally, Sodium alginate in the pharmaceutical field is used as a stabilizing agent, suspending agent, tablet and capsule disintegrant, tablet binder and viscosity increasing agent.

Sodium alginate occurs as an odorless and tasteless, white to pale yellowish-brown colored powder. A 1% w/v aqueous solution has a pH of about 7.2. It is practically insoluble in ethanol, ether, chloroform and ethanol/water mixtures in which the ethanol content is greater than 30%. It is practically insoluble in other organic solvents and aqueous acidic solutions in which pH is less than 3. It is slowly soluble in water, forming a viscous colloidal solution. Various grades of sodium alginate are commercially available that yield aqueous solutions of varying viscosity. A 1% w/w aqueous solution, at 20° C., has a viscosity of 20-400

mPas (20-400 cP). Viscosity may vary depending upon concentration, pH, temperature or the presence of metal ions. Above pH 10, viscosity decreases.

Sodium alginate has been used in tablet formulations, both a binder and disintegrant; it has also been used as a diluents in capsule formulations. In topical formulations, Sodium alginate has been widely used as a thickening and suspending agent in a variety of pastes, creams and gels and as a stabilizing agent for oil-in-water emulsions. Sodium alginate solutions are susceptible on storage to microbial spoilage, which may affect solution viscosity. Heating sodium alginate solutions to temperatures above 70°C, causes depolymerization with a loss in viscosity. Autoclaving solutions of sodium alginate may also cause a decrease in viscosity depending upon the nature of any other substances present. Gamma irradiation should not be used to sterilize sodium alginate solutions since this process severely reduces solution viscosity.

Viscosity of Sodium- alginate used in examples are lower as well as higher i.e. 10 cps more preferably 5-10cps and higher grade of 15 to 20cps.

Sodium alginate is generally less susceptible to microbial attack. However, even if the issue of microbial attack arises, it may be prevented by adding appropriate preservatives to the composition. Sodium alginate has been used in the art as a film forming polymer. However, it has met with limited success. At best, sodium alginate has been used for immediate release. However, the inventors have found that it is possible to achieve disintegration of a tablet coating after a pre-determined time lag; whereby the active ingredient is released. The lag-time or predetermined lag time referred is the period during which the drug substance is held captive and protected by the coating. Thereafter, the coating disintegrates and releases the drug into gastric media, the desired lag-time may be in the range of 20-120 minutes.

The amount of pH independent polymer used in the composition of the present invention may be in the range of 25% w/w to 85% w/w of the composition.

The plasticizer used in the composition may be selected from the group consisting of polyethylene glycol, propylene glycol, glycerin, triacetin, triethyl citrate, diethyl phthalate, dibutyl phthalate, liquid paraffin, castor oil, triglycerides, coconut oil etc.

The amount of plasticizer may vary from 3% w/w to 15% w/w of the composition.

The present invention includes a detackifier which helps in reducing the tackiness so that the composition has lesser tendency to agglomerate. The detackifier may be selected any of talc, stearic acid, stearates of calcium, magnesium or zinc, kaolin, Glyceryl mono stearate.

The amount of detackifier may vary from 1% w/w to 35% w/w of the composition.

The composition of the present invention would optionally include additives such as preservative, pigments (coloring agent), opacifier, diluents, lubricant, sweetener and flavoring agent.

A preservative selected from any of sorbic acid, potassium sorbate, benzoic acid, sodium benzoate or esters of hydroxybenzoic acid, parabens etc, may be employed in the composition to avoid attack by fungi/bacteria.

The amount of preservative may be in the range of 0.1% w/w to 2% w/w of the composition.

The colouring agent or the pigment may be selected from any colors and lakes approved by the FD & C. A non limiting list of pigments that may be used in the composition of present invention includes, iron oxide colors, Lake colours, natural colours, CandurinTM colors and the like.

Opacifiers of the present invention may be selected from the group comprising titanium dioxide, zinc oxide, calcium carbonate, magnesium oxide and the like.

Diluent used in the composition may be any of Tri basic calcium phosphate, Lactose, Micro-crystalline cellulose, calcium phosphate and the like.

Lubricants used in the composition may be any of magnesium stearate, calcium stearate, zinc stearate, stearic acid, mineral oil, and combinations thereof.

Sweeteners may be such as comprising glucose, fructose, sorbitol, aspartame, glycerol, saccharin, xylitol and the like.

Flavoring agents of the present invention may be selected from the group comprising powder, liquid, encapsulated flavors either natural or synthetic origin.

Substrates of the present invention comprise but are not limited to pharmaceutical materials, nutritional supplements, food, confectionery forms.

The coating composition of the present invention comprises the pH independent polymer, preferably sodium alginate in the range of more preferably 25 to 85% w/w, plasticizer in the range of 3-15 % w/w, preferably 4-12% w/w, a detackifier in the range of 1-35% w/w, a preservative in the range of 0.1-2% w/w and optionally a pigment in the range of 0.1-35% w/w, an opacifier in the range of 0.1-30 % w/w and other excipients in the range of 0.1-20 % w/w.

The invention has also found that the content of sodium alginate and coating weight gain on the tablet is related to the lag time for disintegration of the coating. In other words by increasing the coating weight gain on the tablet, the lag-period may be varied. 'Weight gain' as used herein means the amount of coating applied to the. The release of the active ingredient may be favorably altered by a pre-determined lag period, by varying the weight gain from 5 to 20%.

The lag period may be determined based on the amount of sodium alginate employed and/or the weight gain in the coating process. Upon testing disintegration time at pH 1.2 the coated tablet remained intact from about 30 minutes to 120 minutes at coating weight gain

varying from 4% to 16% w/w respectively. Further size and shape of the oral substrate like tablet/soft-gel capsule and physical properties of active ingredient may lead to variation in disintegration time.

Some non-limiting examples of the same is presented below:

TABLE 1

SN	Active content	Disintegration Time at pH 1.2	
1	Mint oil soft gel Capsule	60 mins at 9% Weight Gain	120 mins at 16% Weight Gain
2	Fish oil soft gel Capsule	60 mins at 10% Weight Gain	
2	Creatin tablet	60 mins at 8% Weight Gain	120 mins at 15% Weight Gain
3	Chilly extract tablet	45 mins at 10% Weight Gain	60 mins at 15% Weight Gain
4	Ten herbs tablet (laxative)	60 mins at 7% Weight Gain	120 mins at 13% Weight Gain
5	BioscalinHPMC Matrix tablet (VitB, Metionin)	45 mins at 4.5% Weight Gain	60 mins at 6.5% Weight gain,
		100 mins at 9% Weight Gain	120 mins at 13% Weight Gain

The composition of the invention may be manufactured either as a dry ready to use powder which may be constituted at the user's end or may be developed as an aqueous composition.

Tablet Cores are manufactured in standard manner. The active ingredient and optionally other ingredients are first blended in a mixer, and then the solution or suspension of binder is sprayed onto this mix in a granulator. For example, fluidized bed granulators can be used for this operation. An alternative process can be to use a conventional or high shear mixer to achieve granulation to obtain granules. Granules once dried can be mixed with the other excipients, especially with the lubricant, but also with glidants and any other excipient suitable to improve processing. The mixture of granules (preferably with lubricant), and optionally glidant is pressed into tablets. Alternatively, tablets containing the active ingredient can be obtained by standard techniques, and are hereinafter referred as tablet cores. These tablet cores are then coated with the coating composition of the invention to achieve a desired time release of the active ingredient.

The relative amounts of ingredients in the coating are preferably as follows. The proportion of pH independent polymer such as sodium alginate in the coating may vary between 25 to 85.0% of the coating dry weight. The proportion of plasticizer in the coating may vary between 3 to 15% of the coating dry weight. The proportion of detackifier in the coating may vary between 1 to 35% of the coating dry weight. The relative proportion of the pH independent polymer may be varied depending on the release profile to be obtained (where a more delayed release is generally obtained with a higher amount of pH independent film-forming polymer is used and *vice versa*). Further, the amount of sodium alginate, plasticizer and detackifier are varied to achieve a fine balance between these ingredients and prepare suitable film coating composition.

The lag-period may also be modified to desired level by varying amount of coating applied to the substrate. For example the lower concentration of polymer in the coating composition reduces the time-lag; however, the lesser duration of time lag can be increased significantly by increasing the total coating applied to the substrate, which may be measured in terms of the coating weight on the tablet. Similarly, the higher concentration of polymer results in greater time lag and same can be reduced by decreasing the coating weight gain on the tablet. This finding gives flexibility to the formulator to design a system with most optimized results in terms of desired delaying action. An important aspect of the invention is that the delay in release of active ingredient can be achieved without the use of any pore-forming agent.

The coating process may be as follows. The composition of the present invention may easily be dispersed in water with the use of a propeller stirrer. The prepared suspension/solution is then sprayed onto the substrate using standard coating machine and standard coating parameters used for aqueous film coating process. The coating weight gain on the core tablet may vary from 5% w/w to anything up to 20% w/w depending on the desired delaying action.

For instance, the inventive composition may be sprayed by SchlickTM spray gun having 0.8-1.2 mm nozzle size and by adapting the following coating parameters, such as Inlet air temperature in the range of 65-70 degree Celsius, Tablet bed temperature in the range of 30-45degree Celsius, suitable pump speed, pan speed, an atomizing air pressure in the range of 1.4-3.0KG/cm sq. as per requirement of lot size to be coated.

The composition may be practiced as transparent, translucent, opaque or coloured by adding suitable opacifier, colours and pigments. The composition may also be easily modified by adding other excipients like sweeteners, flavours, other taste or flavor enhancing agents to improve its organoleptic properties.

The above principles may be employed to successfully coat a wide range of tablets having a wide variety of active ingredients incorporated therein. For example, the composition of the present invention may be used to coat suitable dosage forms containing the active pharmaceutical ingredient. Suitable active pharmaceutical ingredients include, but are not limited to: adrenergic blocking agent; acetyl-choline-esterase inhibitor; analgesic or antipyretics; angiotensin modulator; anthelmintic agents; anti-anxiety agent; antibacterial; antibiotic; anticoagulant; anticonvulsant; antidepressant; antifungal; antihistamine; antimalarial; antimicrobial agent; antipsychotic agent; Antiviral agents; blood glucose lowering drug; calcium channel modulator; diuretic; erectile dysfunction; gastric acid secretion inhibitor; histamine H₂-receptor antagonist; inhibitor of steroid Type II 5[alpha]-reductase including; lipid regulating agents; selective H₁- receptor antagonist; vasodilator; vitamins.

The composition of the present invention was found to be synergistic and optimum results were obtained by using a combination of all components of the composition.

In another embodiment, the present invention provides a method for delaying the release of an active ingredient into biological environment by a predetermined lag period, comprising the steps of:

- (i) providing active ingredient in a suitable dosage form and
- (ii) coating the product of step (i) with the composition of the present invention.

ADVANTAGES

1. Present invention provides tailor-made composition for pre-defined release of active ingredient.
2. Present invention also provides release modification based on polymer concentration and relative coatingweight gain.
3. The present invention also provides flexibility in terms of compositions wherein the time of delay in release of the active ingredient may be engineered as per the requirement of the manufacturer.

The invention is not limited to the specific embodiments described above but may bevaried within broad limits by the skilled man.

EXAMPLES:

The following examples will further serve to provide details of the invention. However they do not in any way limit the scope of the invention. All units and percentages in the examples are by weight.

DISINTEGRATION TEST:

The disintegration tests of coated tablet performed as specified in IP (Indian Pharmacopoeia) or USP (United States Pharmacopoeia).It is to be understood that the composition of the present invention may also be tested by other disintegration tests. Indeed, various modifications of the described modes for carrying out the invention that are

apparent to those skilled in the art are intended to be within the scope of the present invention.

EXAMPLE 1 :-

All Inventive composition ingredients are weighed as per table 2 and mixed in a standard blender or mixer.

TABLE 2

Ingredient	Percentage by weight	Weight in grams
Sodium Alginate	60	600
Polyethylene Glycol	9.4	94
Talc	10	100
Sodium methyl paraben	0.5	5
Sodium benzoate	0.1	1
Stearic acid	2	20
TiO ₂	18	180
Total	100	1000

The coating composition of the present invention is prepared as a ready to use dry blend and is reconstituted in purified water. Further composition as prepared is coated on Creatine tablets having raw weight of 1400 mg Capsule shape, dimensions (length- 15 mm & thickness 7 mm). Tablets were coated on **Logica Progetti** coating machine having Pellegrini drum and spray gun type of Schlick ABC (0.8 mm). For instance, the inventive composition may be sprayed by adapting the following coating parameters, such as Inlet air temperature in the range of 65-70 degree Celsius, Tablet bed temperature in the range of 40-45 degree Celsius, suitable pump speed, pan speed, an atomizing air pressure of 2.0 Bar or as per requirement of lot size to be coated.

Additionally other active ingredients are coated as per standard protocol. Upon testing disintegration at pH 1.2 of coated oral substrate obtained from above composition displayed following results at Table 2.1:-

TABLE 2.1

SN	Active ingredient	Disintegration time at pH 1.2	
1	Creatine tablets Capsule shape (15x7mm)	60 mins at 8% Weight Gain	120 mins at 15% Weight Gain
2	Chilly extract tablet Capsule shape (12x5 mm)	45 mins at 10% Weight Gain	60 mins at 15% Weight Gain
3	Ten herbs tablet (laxative) Round shape (10 mm standard radius)	60 mins at 7% Weight Gain	120 mins at 13% Weight Gain
4	Bioscalin HPMC Matrix tablet	45 mins at 4.5% Weight Gain	60 mins at 6.5% Weight gain,
	Almond shape (15x9 mm)	100 mins at 9% Weight Gain	120 mins at 13% Weight Gain

EXAMPLE 2

Inventive composition as prepared in example 1 is coated on Mint oil Soft-gel capsule having fish oil weight of 750 mg, Almond shape dimensions (length- 11 mm & thickness 6 mm). Tablets were coated on **Logica Progetti** coating machine having Pellegrini drum and spray gun type of Schlick ABC (0.8 mm). For instance, the inventive composition may be sprayed by adapting the following coating parameters, such as Inlet air temperature in the range of 65-70 degree Celsius, Tablet bed temperature in the range of 35-36 degree Celsius, suitable pump speed, pan speed, an atomizing air pressure of 2.4 bar or as per requirement of lot size to be coated.

Additionally other active ingredients are coated as per standard protocol. Upon testing disintegration at pH 1.2 of coated oral substrate obtained from above Soft-gel capsule displayed following results:-

TABLE 3

SN	Active ingredient	Disintegration time at pH 1.2	
1	Mint oil soft gel Capsule Almond shape (11x6 mm)	60 mins at 9% Weight Gain	120 mins at 16% Weight Gain
2	Fish oil soft gel Capsule	60 mins at 10% Weight Gain	

EXAMPLE 3:

The active ingredient and optionally other ingredients are first blended in a mixer, and then the solution or suspension of binder is sprayed onto this mix in a granulator. For example, fluidized bed granulators can be used for this operation. An alternative process can be to use a conventional or high shear mixer to achieve granulation to obtain granules. Granules once dried can be mixed with the other excipients, especially with the lubricant, but also with glidants and any other excipient suitable to improve processing. The mixture of granules (preferably with lubricant), and optionally glidant is pressed into tablets. Alternatively, tablets containing the active ingredient can be obtained by standard techniques, and are hereinafter referred as tablet cores.

Individual ingredients (with individual plasticizers) are weighed as per table 5 and mixed in a standard blender or mixer.

TABLE 5

Ingredient	Percentage by weight	Weight in grams
Sodium Alginate	60	600
Triacetin/Di-ethyl phthalate/CastorOil/Glycerine/ Polyethylene Glycol	9.4	94

Talc	14	140
Sodium methyl paraben	0.5	5
Sodium benzoate	0.1	1
TiO ₂	16	160
Total	100	1000

The coating composition of the present invention is prepared as a ready to use dry blend and is reconstituted in purified water.

These tablet cores are then coated with the coating composition of the invention to achieve a desired timed release of the active ingredient. For instance, the inventive composition may be sprayed by adapting the following coating parameters, such as Inlet air temperature in the range of 65-70 degree Celsius, Tablet bed temperature in the range of 40-45 degree Celsius, suitable pump speed, pan speed, an atomizing air pressure in the range of 1.4-3.0KG/cm sq. as per requirement of lot size to be coated.

When any of the composition of Example 1 was coated, different lag periods could be predetermined by varying the weight of the composition. It is inferred that plasticizer acts in a synergistic manner with the polymer.

EXAMPLE 4

The tablet cores with the active ingredient are prepared in a similar manner as described in Example 3. Individual ingredients are weighed as per Table 6 and mixed in a standard blender or mixer.

TABLE 6

Ingredient	Percentage by weight	Weight in grams
Sodium Alginate	60	600
Castor oil	4.4	44
Glycerine	5	50
Talc	14	140
Sodium methyl paraben	0.5	5
Sodium benzoate	0.1	1

TiO ₂	16	160
Total	100	1000

The coating composition of the present invention is prepared as a ready to use dry blend and is reconstituted in purified water. The tablet cores are coated in a similar manner as described in example 3.

Upon testing disintegration at pH 1.2 of coated oral substrate obtained from above, tablet remain stable for 120 mins at 15 % weight gain.

EXAMPLE 5 The effect of polymer concentration

The tablet cores with the active ingredient are prepared in a similar manner as described in Example 3. Individual ingredients are weighed as per Table 7 and mixed in a standard blender or mixer.

TABLE 7

Ingredient	Percentage by weight	Weight in grams
Sodium Alginate	80	800
Plasticizer	9.4	94
Talc	5	50
Sodium methyl paraben	0.5	5
Sodium benzoate	0.1	1
TiO ₂	5	50
Total	100	1000

The coating composition of the present invention is prepared as a ready to use dry blend and is reconstituted in purified water. The tablet cores are coated in a similar manner as described in example 3.

Upon testing disintegration at pH 1.2 of coated oral substrate obtained from above, tablet remain stable for 120 mins at 12 % weight gain.

EXAMPLE 6

The tablet cores with the active ingredient are prepared in a similar manner as described in example 3. Individual ingredients are weighed as per table 8 and mixed in a standard blender or mixer.

TABLE 8

Ingredient	Percentage by weight	Weight in grams
Sodium Alginate	40	400
Plasticizer	9.4	94
Talc	24	240
Sodium methyl paraben	0.5	5
Sodium benzoate	0.1	1
TiO ₂	26	260
Total	100	1000

The coating composition of the present invention is prepared as a ready to use dry blend and is reconstituted in purified water. The tablet cores are coated in a similar manner as described in example 3.

Upon testing disintegration at pH 1.2 of coated oral substrate obtained from above, tablet remain stable for 120 mins at 18 % weight gain.

EXAMPLE 7

The tablet cores with the active ingredient are prepared in a similar manner as described in example 3. Individual ingredients are weighed as per table 9 and mixed in a standard blender or mixer.

TABLE 9

Ingredient	Percentage by weight	Weight in grams
Sodium Alginate	30	300
Plasticizer	9.4	94
Talc	28	280

Sodium methyl paraben	0.5	5
Sodium benzoate	0.1	1
TiO ₂	28	280
Total	100	1000

The coating composition of the present invention is prepared as a ready to use dry blend and is reconstituted in purified water. The tablet cores are coated in a similar manner as described in example 3.

Upon testing disintegration at pH 1.2 of coated oral substrate obtained from above, tablet remain stable for 120 mins at 20 % coating weight gain.

Further the compositions of the present invention may also contain other pigments or colors.

EXAMPLE 8

The tablet cores with the active ingredient are prepared in a similar manner as described in example 3. Individual ingredients are weighed as per table 10 and mixed in a standard blender or mixer.

TABLE 10

Ingredient	Percentage by weight	Weight in grams
Sodium Alginate	60	600
Plasticizer	9.4	94
Talc	14	140
Sodium methyl paraben	0.5	5
Sodium benzoate	0.1	1
L. Sunset Yellow/ Red Iron Oxide	5	50
TiO ₂	11	110
Total	100	1000

The coating composition of the present invention is prepared as a ready to use dry blend and is reconstituted in purified water. The tablet cores are coated in a similar manner as

described in example 3. DT values were ranging from 24 to 120 minutes when the coating weight gain was varied from 7-20%

EXAMPLE 9

The tablet cores with the active ingredient are prepared in a similar manner as described in example 3. Individual ingredients are weighed as per table 11 and mixed in a standard blender or mixer.

TABLE 11

Ingredient	Percentage by weight	Weight in grams
Sodium Alginate	60	600
Glycerin	7.5	75
Stearic acid	4	40
Talc	13	130
Sorbic acid	0.5	5
TiO ₂	15	150
Total	100	1000

The coating composition of the present invention is prepared as a ready to use dry blend and is reconstituted in purified water. The tablet cores are coated in a similar manner as described in example 3.

Upon testing disintegration at pH 1.2 of coated oral substrate obtained from above , tablet remain stable for 20-100 minutes when the coating weight gain was varied from 7-15%.

EXAMPLE 10

The tablet cores with the active ingredient are prepared in a similar manner as described in example 3. Individual ingredients are weighed as per table 12 and mixed in a standard blender or mixer.

TABLE 12

Ingredient	Percentage by weight	Weight in grams
Sodium Alginate	60	600
Glycerin	6	60

Talc	13.5	135
Sorbic acid	0.5	5
TiO ₂	20	200
Total	100	1000

The coating composition of the present invention is prepared as a ready to use dry blend and is reconstituted in purified water. The tablet cores are coated in a similar manner as described in example 3.

Upon testing disintegration at pH 1.2 of coated oral substrate obtained from above, tablet remain stable for 60 mins at 12 % weight gain.

Use of different diluents and fillers was studied by way of following examples;

EXAMPLE 11

The tablet cores with the active ingredient are prepared in a similar manner as described in example 3. Individual ingredients are weighed as per table 13 and mixed in a standard blender or mixer.

TABLE 13

Ingredient	Percentage by weight	Weight in grams
Sodium Alginate	50	500
Plasticizer	9.4	94
MCC PH 105	10	100
Talc	14	140
Sodium methyl paraben	0.5	5
Sodium benzoate	0.1	1
TiO ₂	16	160
Total	100	1000

The coating composition of the present invention is prepared as a ready to use dry blend and is reconstituted in purified water. The tablet cores are coated in a similar manner as described in example 3.

Upon testing disintegration at pH 1.2 of coated oral substrate obtained from above, tablet remains stable for 70 mins at 15 % weight gain.

EXAMPLE 12

The tablet cores with the active ingredient are prepared in a similar manner as described in example 3. Individual ingredients are weighed as per table 14 and mixed in a standard blender or mixer.

TABLE 14

Ingredient	Percentage by weight	Weight in grams
Sodium Alginate	50	500
Plasticizer	9.4	94
Lactose	10	100
Talc	14	140
Sodium methyl paraben	0.5	5
Sodium benzoate	0.1	1
TiO ₂	16	160
Total	100	1000

The coating composition of the present invention is prepared as a ready to use dry blend and is reconstituted in purified water. The tablet cores are coated in a similar manner as described in example 3.

Upon testing disintegration at pH 1.2 of coated oral substrate obtained from above , tablet remain stable for 60 at 10% weight gain, and remain intact for 120 mins at 15 % weight gain.

EXAMPLE 13

The tablet cores with the active ingredient are prepared in a similar manner as described in example 3. Individual ingredients are weighed as per table 15 and mixed in a standard blender or mixer.

TABLE 15

Ingredient	Percentage by weight	Weight in grams
Sodium Alginate	60	600
Plasticizer	9.4	94
PVPK30	4	40
Talc	14	140
Sodium methyl paraben	0.5	5
Sodium benzoate	0.1	1
TiO ₂	12	120
Total	100	1000

The coating composition of the present invention is prepared as a ready to use dry blend and is reconstituted in purified water. The tablet cores are coated in a similar manner as described in example 3.

The coated oral substrate as obtained from above displayed a disintegration time 65 mins at 10 % weight gain and more than 120 mins at 15 % weight gain.

EXAMPLE 14

The tablet cores with the active ingredient are prepared in a similar manner as described in example 3. Individual ingredients are weighed as per table 16 and mixed in a standard blender or mixer.

TABLE 16

Ingredient	Percentage by weight	Weight in grams
Sodium Alginate	60	600
Plasticizer	9.4	94
Sodium Lauryl Sulphate	1	10
Talc	14	140
Sodium methyl paraben	0.5	5
Sodium benzoate	0.1	1
TiO ₂	15	150
Total	100	1000

The coating composition of the present invention is prepared as a ready to use dry blend and is reconstituted in purified water. The tablet cores are coated in a similar manner as described in example 3.

Upon testing disintegration at pH 1.2 of coated oral substrate obtained from above , tablet remain stable for 60 mins at 10 % weight gain and remain intact for 120 mins at 15 % weight gain.

EXAMPLE 15

The tablet cores with the active ingredient are prepared in a similar manner as described in example 3. Individual ingredients are weighed as per table 17 and mixed in a standard blender or mixer.

TABLE 17

Ingredient	Percentage by weight	Weight in grams
Sodium Alginate	50	500
Plasticizer	9.4	94
Modified Starch	10	100
Talc	14	140
Sodium methyl paraben	0.5	5

Sodium benzoate	0.1	1
TiO ₂	16	160
Total	100	1000

The coating composition of the present invention is prepared as a ready to use dry blend and is reconstituted in purified water. The tablet cores are coated in a similar manner as described in example 3.

Upon testing disintegration at pH 1.2 of coated oral substrate obtained from above , tablet remain stable for 120 mins at 15 % weight gain

EXAMPLE 16

The tablet cores with the active ingredient are prepared in a similar manner as described in example 3. Individual ingredients are weighed as per table 18 and mixed in a standard blender or mixer.

TABLE 18

Ingredient	Percentage by weight	Weight in grams
Sodium Alginate	45	450
Plasticizer	9.4	94
HPMC3cps	15	150
Talc	14	14
Sodium methyl paraben	0.5	5
Sodium benzoate	0.1	1
TiO ₂	16	160
Total	100	1000

The coating composition of the present invention is prepared as a ready to use dry blend and is reconstituted in purified water. The tablet cores are coated in a similar manner as described in example 3.

Upon testing disintegration at pH 1.2 of coated oral substrate obtained from above , tablet remain stable for 40mins at 15% weight gain.

EXAMPLE 17

The tablet cores with the active ingredient are prepared in a similar manner as described in example 3. Individual ingredients are weighed as per table 19 and mixed in a standard blender or mixer.

TABLE 19

Ingredient	Percentage by weight	Weight in grams
Sodium Alginate FMP	30	300
Plasticizer	9.4	94
Talc	30	300
Sodium methyl paraben	0.5	5
Sodium benzoate	0.1	1
TiO ₂	30	300
Total	100	1000

The coating composition of the present invention is prepared as a ready to use dry blend and is reconstituted in purified water. The tablet cores are coated in a similar manner as described in example 3.

Upon testing disintegration at pH 1.2 of coated oral substrate obtained from above , tablet remain stable for 120 mins at 15 % weight gain.

Further it was also observed that the incorporation of higher viscosity grade of Sodium Alginate only affect the viscosity of the coating suspension and thereby affecting the polymer carrying capacity of the suspension, however the same can also be used to delay the drug release from the coated substrate.

Sodium alginate FMP is a higher viscosity grade (having viscosity of 15-20cps) whereas the viscosity of Sodium- alginate used in other examples was less than 10 cps more preferably 5-10cps.

EXAMPLE 18

The tablet cores with the active ingredient are prepared in a similar manner as described in example 3. Individual ingredients are weighed as per table 20 and mixed in a standard blender or mixer.

TABLE 20

Ingredient	Percentage by weight	Weight in grams
Sodium Alginate	60	600
Plasticizer	9.4	94
Talc	14.6	146
TiO ₂	16	160
Total	100	1000

The coating composition of the present invention is prepared as a ready to use dry blend and is reconstituted in a suitable solvent. The tablet cores are coated in a similar manner as described in example 3.

Upon testing disintegration at pH 1.2 of coated oral substrate obtained from above , tablet remain stable for 120 mins at 15 % weight gain.

EXAMPLE 19

The tablet cores with the active ingredient are prepared in a similar manner as described in example 3. Individual ingredients are weighed as per table 21 and mixed in a standard blender or mixer.

TABLE 21

Ingredient	Percentage by weight	Weight in grams
Sodium Alginate	60	600
Polyethylene Glycol	9.4	94

Talc	10	100
Sodium methyl paraben	0.5	5
Sodium benzoate	0.1	1
Stearic acid	2	20
TiO ₂	18	180
Total	100	1000

The coating composition of the present invention is prepared as a ready to use dry blend and is reconstituted in purified water.

These tablet cores are then coated with the coating composition of the invention to achieve a desired timed release of the active ingredient. For instance, the inventive composition may be sprayed by adapting the following coating parameters, such as Inlet air temperature in the range of 65-70 degree Celsius, Tablet bed temperature in the range of 40-45 degree Celsius, suitable pump speed, pan speed, an atomizing air pressure in the range of 1.4-3.0KG/cm sq. as per requirement of lot size to be coated.

Upon testing disintegration at pH 1.2 of coated oral substrate obtained from above , tablet remain stable for 120mins at 15 % weight gain. It is to be understood that various modifications and variations of the methods and compositions of the invention described herein will be apparent to those skilled in the art without departing from the scope and spirit of the invention. It may also be noted that the specific embodiments disclosed in the examples do not in any way limit the scope of the present invention.

Indeed, various modifications of the described modes for carrying out the invention that are apparent to those skilled in the art are intended to be within the scope of the present invention.

We claim,

1. A coating composition comprising, a pH independent polymer, a plasticizer, a detackifier, and optionally, pharmaceutically acceptable additive wherein the amount of pH independent polymer and weight gain of the tablet is relative to a lag period in disintegration of the coating.
2. The coating composition as claimed in claim 1, wherein the lag period is for a period of 20-120 mins.
3. A coating composition as claimed in claim 1, wherein, the pH independent polymer is sodium alginate.
4. The composition as claimed in claim 1, wherein the polymer is present in the range from about 25% to about 85% by weight of the composition.
5. The composition as claimed in claim 1, wherein the plasticizer is selected from the group consisting of polyethylene glycol, propylene glycol, glycerin, triacetin, triethyl citrate, diethyl phthalate, dibutyl phthalate, liquid paraffin, castor oil, triglycerides, coconut oil.
6. The composition as claimed in claim 1, wherein the plasticizer is present in the range from about 3 to 15 % by weight of the composition.
7. The composition as claimed in claim 1, wherein the detackifier is selected from the group consisting of talc, stearic acid, stearates of calcium, magnesium or zinc, kaolin, glycerol mono stearate, preferably talc
8. The composition as claimed in claim 1, wherein the detackifier is present in the range from about 3 to about 35% by weight of the composition.
9. The composition as claimed in claim 1, wherein the pharmaceutically acceptable additives comprise a preservative, a coloring agent, an opacifier, a diluent, a lubricant, a sweetener and a flavoring agent.

10. The composition as claimed in claim 1, wherein the preservative is selected from the group consisting of sorbic acid, potassium sorbate, benzoic acid, sodium benzoate or esters of hydroxybenzoic acid, parabens
11. The composition as claimed in claim 1, wherein the preservative is present in range from about 0.1 to about 2.0 % by weight of the composition.
12. The composition as claimed in claim 1, wherein the coloring agent is selected from the group comprising colors and lakes approved by the FD & C, preferably selected from the group consisting of iron oxide colours, Lake colours, natural colours, CandurinTM color and the like.
13. The composition as claimed in claim 1, wherein the opacifier is selected from the group comprising titanium dioxide, zinc oxide, calcium carbonate, magnesium oxide.
14. The composition as claimed in claim 1, wherein the diluent is selected from the group comprising Tri basic calcium phosphate, Micro-crystalline cellulose, calcium phosphate, lactose.
15. The composition as claimed in claim 1, wherein the lubricant is selected from the group comprising magnesium stearate, calcium stearate, zinc stearate, stearic acid, mineral oil, and combinations thereof.
16. The composition as claimed in claim 1, wherein the sweetener is selected from the group comprising glucose, fructose, sorbitol, aspartame, glycerol, saccharin, xylitol.
17. The composition as claimed in claim 1, wherein the flavoring agent is selected from the group comprising powder, liquid, encapsulated flavors either natural or synthetic origin.
18. The composition as claimed in claim 1, wherein the pH independent polymer, preferably sodium alginate in the range 25 to 85% w/w, plasticizer in the range of 3-15 % w/w, preferably 4-12% w/w, a detackifier in the range of 1-35% w/w, a preservative in the range of 0.1-2% w/w and optionally a pigment in the range of 0.1-35% w/w, an opacifier in the range of 0.1-30 % w/w and other excipients in the range of 0.1-20 % w/w.
19. A method of making a dry coating composition comprising the steps of mixing a pH independent polymer, adding a plasticizer, further adding a detackifier and mixing until the combined mix is blended to form the dry coating composition, wherein the

pH independent polymer, preferably sodium alginate in the range 25 to 85% w/w, plasticizer in the range of 3-15 % w/w, preferably 4-12% w/w, a detackifier in the range of 1-35% w/w, a preservative in the range of 0.1-2% w/w and optionally a pigment in the range of 0.1-35% w/w, an opacifier in the range of 0.1-30 % w/w and other excipients in the range of 0.1-20 % w/w

20. A method of coating using the composition as claimed in claim 1 comprising the steps of

- (i) providing active ingredient in a suitable dosage form and
- (ii) coating the product of step (i) with the composition of claim-1 –

“A coating composition comprising, a pH independent polymer, a plasticizer, a detackifier, and optionally, pharmaceutically acceptable additive wherein the amount of pH independent polymer and weight gain of the tablet is relative to a lag period in disintegration of the coating.”

21. The method as claimed in claim 20, wherein the coating weight gain is from about 4 to 50%, preferably 4 to 25% w/w.

22. A substrate coated with composition of claim 1.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2012/000625

A. CLASSIFICATION OF SUBJECT MATTER

SEE EXTRA SHEET

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)

IPC: A61K9/-; A61K47/-

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)

WPI; EPODOC; CNPAT; CNKI; CNABS; CNTXT; ideal w cures, sodium w alginate, plastici+, glycol, glycerin, triacetin, phthalate, paraffin, detackif+, talc, stear+, color+, colour+, titanium w dioxide

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2008312345 A1 (IDEAL CURES PVT. LTD.) 18 Dec. 2008 (18.12.2008) claims 16, 21, paragraphs 0037, 0053-0056, 0065	1-22
X	US 2009054533 A1 (PAREEK, Suresh Rukmanand et al.) 26 Feb. 2009 (26.02.2009) paragraphs 0021-0029, 0032-0037, 0042, 0047	1-9, 12-18, 20-22
X	US 2009252767 A1 (DURIG, Thomas et al.) 08 Oct. 2009 (08.10.2009) paragraphs 0017-0018, 0030, 0035-0036, 0047-0049	1-3, 5-9, 13, 15, 20-22

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:	"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
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier application or patent but published on or after the international filing date	"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
"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)	"&" document member of the same patent family
"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	

Date of the actual completion of the international search 20 June 2012 (20. 06. 2012)	Date of mailing of the international search report 30 Aug. 2012 (30.08.2012)
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer HU, Xinliang Telephone No. (86-10)82246918

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2012/000625

Continuation of:

A. CLASSIFICATION OF SUBJECT MATTER

A61K47/38 (2006.01) i

A61K47/36 (2006.01) i

A61K9/28 (2006.01) i

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/IB2012/000625

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