FORM 2
THE PATENTS ACT, 1970
[39 of 1970]
&
THE PATENTS (AMENDMENT) RULES, 2006
PROVISIONAL SPECIFICATION
[See Section 10 and Rule 13]

Abstract

The lungs are explored as an attractive route for non-invasive drug delivery with efficient release of therapeutics for systemic and local site. Incorporating therapeutics with polymeric nanoparticles offers additional advantages including sustained release and site specific release of drug. However, nanoparticle delivery to the lungs has many challenges including formulation instability and poor inhalation efficiency due to particle interaction and low-inertia nanoparticles. Thus, novel methods formulating nanoparticles into the form of micronscale dry powders have been developed where carrier particles exhibited improved fluidization and deposition property.

Recently various particle engineering techniques are explored where nanoparticulate drug carrier are converted in to microparticles to achieve the required range of MMAD which decides the regional deposition of the particles in the respiratory tract. Engineering of the budesonide drug particle by the aqueous controlled gellation system with highest entrapment efficiency of drug was useful for delivery at the targeted site. The system which was capable of delivering the dry powder in the pulmonary route is largely influenced by physical characteristics such as size, shape, density, crystallinity, surface topography etc. In this formulation every ingredient has a specific role to form the engineered complexes of polymers incorporating the maximum quantity of drug which in turn depends upon the extent of gellation of this system.

The objective of this study, therefore, was to engineering of budesonide and optimization of these physical characteristics and related attributes which gives maximum entrapment efficiency and pulmonary deposition of engineered drug particles.

Claims

1. Nanoparticulate delivery system for hydrophobic drugs with improved entrapment efficiency wherein the system comprises one or more gellating agent or more of surfactant, one or more of the cationic agent surrounds the nanoparticles.

2. Nanoparticulate delivery system in the form of dry powder comprising the particle size range from 1.5 μm to 3.5 μm.

3. Nanoparticulate delivery system wherein the entrapment efficiency ranges from 80% to 93%.

5. Nanoparticulate delivery system according to claim 1, wherein the gelling agent comprises one or more of sodium alginate, chitosan, polyglycolic acid.

6. Nanoparticulate delivery system according to claim 1, wherein the surfactant comprises pluronic.

7. Method of preparation of nanoparticulate delivery system according to claim 1, wherein controlled gellation of anionic polymers was carried out due to specific ratio of anionic polymers and multivalent cations.

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FIELD OF THE INVENTION

The invention disclosed herein relates to development of micro particulate pulmonary delivery system for budesonide or salts or hydrates thereof, with entrapment efficiency wherein the system converts into hydrogel upon deposition in the respiratory tract. The invention further provides method of making such micro particulate pulmonary delivery system.

BACKGROUND OF THE INVENTION

India is a country with different geographical, natural diversitities with high population which is a major cause for immergence of various chronic diseases. Chronic respiratory disease (CRD) is becoming one of the major disease in India. CRD includes asthama and chronic respiratory disease (COPD) which are responsible for major burden of 100 million patients in India. Both the conditions are characterized by inflammation of airways and important cause of disability and healthcare burden. Along with inflammation, asthama is found to be associated with airway hyper-responsiveness, recurrent episodes of wheezing, breathlessness, chest tightness and coughing which raise due to variety of specific and nonspecific inhalation stimuli. This condition is mainly responsible for airflow limitation, broncho-constriction, chronic mucus plug formation and airway swelling. As compared to asthama, development of COPD is multifactorial and risk factors mainly include genetic and environmental factors. In this condition excess secretion of mucus causes inflammation ofairways and narrowing of terminal bronchioles. Major pathological changes in COPD are observed in central and large airways adjascent to the alveolar space. In asthama and COPD, Tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) are implicated as a potent inflammatory cytokines. The TNF-α production gets triggered by various

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cells such as epithelium, endothelium, activated macrophages, monocytes, smooth muscle, eosinophils and neutrophils by various stimuli. IL-6, a multifunctional pro-inflammatory cytokine is also involved in inflammation of lungs. Therefore in order to get better anti-inflammatory activity, high concentration of active drug in the lung is useful to exhibit anti-inflammatory activity via the inhibition of inflammatory mediators such as TNF-α and IL-6.

Management of asthama and COPD is mainly achieved by pharmacological and nonpharmacological agents. Drugs used for the treatment of asthama and COPD are inhaled bronchodilators and corticosteroids, oral theophylline and phosphodiesterase-4 inhibitor. Among these medications, recently inhaled corticosteroids (ICSs) are accepted as a first line therapy for asthama management with effective control on the inflammation which reduces morbidity and mortality in patients. Moreover, ICSs are effective in management of COPD by controlling the chances of exacerbations and helps to impart quality life for the patient. Therefore, it is logical to use drugs like budesonide exhibiting high glucocorticoid receptor activity which helps to reduce the inflammatory symptoms such as edema and vascular hyper-permeability. Budesonide has a low molecular weight of 430.53 Da and less oral bioavailability of 6 -11% with a half life of 2-3 h. It is well accepted that long term use of steroid is mainlyassociated with potential side effects such as nausea, anorexia, headache, thinning of the skin and easy bruising.

Conventionally dry powder inhalers (DPI's)for treatment of COPD are prepared by micronization methods which are often blends of fine drug particles and inert lactose (carrier) where drug particles are expected to adhere to the carrier surface. The particle morphology, density and composition cannot be controlled during micronization process which seems to influence cohesive, surface and electrostatic properties of conventional DPI.Moreover, most of the DPI formulations rely on lactose monohydrate as a carrier where lactose has major

drawbacks such as presence of transmissible spongiform encephalopathy and endotoxins obtained from bovine source. Also it can-not be used in the compounds with the reducing sugar such as proteins, peptides, budesonide and formoterol. To overcome these constrains various drug delivery systems have been developed. Darvari et al reported a method of processing microparticles comprising: a plurality of solid microparticles and at least one non-volatile material; providing a non-solvent comprising an aqueous solution containing at least one free multivalent cation; exposing the composition to the non-solvent to form a mixture containing one or more liquid phases and the solid microparticles.Tarara et al reported a pharmaceutical formulation for pulmonary administration, comprising a plurality of particulates having a mass median diameter less than 20 μm wherein each particulate comprises: (a) a lipid matrix; and (b) at least one particle of an active agent in the lipid matrix, said active agent having an aqueous solubility of less than 1.0 mg/ml, wherein at least 90% of the active agent particles in the formulation have a geometric diameter less than 3 μm.Vehring et al designedparticulate drug delivery compositions comprising water-insoluble active agents and their methods of production. The invention is particularly suited for producing particles for pulmonary drug delivery application. Donovan, et al prepared a dry powder inhaler includes a chamber holding a bead-like actuator to which a powdered medicament is adhered. Air is drawn into the chamber through an inlet flow channel and exits through an outlet flow channel. The bead-like actuator oscillates in response to the air flow, dislodging powdered medicament to be entrained in the air flow and delivered to the patient. Blizzar et al provides improved pharmaceutical formulations for pulmonary delivery having improved chemical and physical stability of the therapeutic, prophylactic or diagnostic agent as compared to formulations known in the art. The improved pharmaceutical formulations of the invention for administration to the respiratory system of a

patient for the treatment of a variety of disease conditions comprise a mass of biocompatible particles comprising an active agent, and a hydrogenated starch hydrosylate (HSH). The invention further relates to a method of treating diseases comprising administering the pharmaceutical formulations of the present invention to the respiratory system of a patient in need of treatment.

Successful lung deposition of drug is achieved by controlling the particle size, shape and surface properties of the drug incorporating delivery system. For preparation of suitable dry powder inhaler (DPI), micronization is usually employed to reduce the particle size to less than 5μm. However administration of therapeutically active drugs through conventional DPI's has shown least deposition efficiency in the lung due to agglomeration on account of large particle size and minimum fluidization due to micronization process. Typically particles with mean mode aerodynamic diameter (MMAD) smaller than 5 μm with large geometrical size distribution (GSD) may be delivered to deep lung. Moreover, fine particle fraction (FPF) of the currently available DPI formulation is not more than 30% which means that only 30% of total dose reaches at the site of action.To overcome these constrains there is need ofbiodegradable inhaled carriers for pulmonary drug delivery which possesses adequate aerodynamic properties, shows efficient drug release and overcome the lung clearance of drug.There have been a variety of carriers investigated such as liposomes, biodegradable polymeric microspheres, bioresponsive carriers, prodrugs, co-precipitates, porous particles and polymeric micelles.

Accordingly in the present invention, there is provided development of micro particulate pulmonary delivery system for budesonide. The system converts into hydrogel upon deposition in the respiratory tract and helps to improve deep lung deposition. Further the delivery system produced by controlled gellation as disclosed herein exhibits entrapment efficiency in the range

of 60% to 93% w/v, desired aerosolization and physical characteristics in terms of MMAD, GSD and FPF. The invention further provides method of making such micro particulate pulmonary delivery system.In one aspect of the invention there is provided micro particulate pulmonary delivery system for budesonide with entrapment efficiency efficiency in the range of 60% to 93% w/v wherein the system comprises one or more gelling agent, one or more of surfactant, one or more of the cationic agent surrounding the budesonide and wherein the delivery system converts into hydrogel upon deposition in the respiratory tract.

In another aspect of the invention there is provided micro particulate pulmonary delivery system for budesonide drug with entrapment efficiency efficiency in the range of 60% to 93% w/v wherein the system comprises one or more gelling agent, one or more of surfactant, one or more of the cationic agent surrounding thebudesonide and wherein the system exhibits mean more aerodynamic diameter (MMAD) in the range of 0.5 μm to 5 μm, fine particle fraction (FPF) in the range of 30% to 50%.

In yet another aspect of the invention there is provided method of making micro particulate pulmonary delivery system for budesonide wherein the method involves:

a. Mixing drug and surfactant with organic solvent which was added in to the sodium alginate solution with continuous stirring.
b. Addition of calcium chloride and chitosan solutions to the mixture with continuous stirring until complete evaporation of organic solvent.
c. Lyophilization of microparticles using mannitol as a cryoprotectant.

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DETAILED DESCRIPTION OF THE INVENTION

The inventors have disclosed herein a micro particulate delivery system for budesonide. An objective of the invention is to overcome deposition obstacles and clearance mechanisms ofactive drugs such as budesonide, improving deposition efficiency, reducing the dosing frequency thereby achieving patient compliance as well as reducing the potential cost involved in treatment of chronic respiratory disease. The invention discloses preparation of such delivery system using naturally originated biocompatible and biodegradable excipients. Further the delivery system as disclosed herein exhibits desired micromeritic properties, mean mode aerodynamic diameter (MMAD) and maximum fine particle fraction (FPF) essential for better lung deposition.

In one aspect of the invention there is provided micro particulate pulmonary delivery system for budesonide with entrapment efficiency efficiency in the range of 60% to 93% w/v wherein the system comprises one or more gelling agent, one or more of surfactant, one or more of the cationic agent surrounding thebudesonide and wherein the delivery system converts into hydrogel upon deposition in the respiratory tract.

The term microparticulate pulmonary delivery system relates to the system in the form of dry powder having particle size in the range of 0.5 to 5μm which incorporates the drug particles in it. Fabrication of the delivery system in the form of stable dry powder inhalation (DPI) as disclosed herein is achieved by controlled gelation of hydrophilic polymer in the presence of wide variety of hydrophilic or cationic polymer, multivalent cations and surfactants which upon inhalation gives the maximum lung deposition and subsequently converts in to microgel with prolonged anti-inflammatory activity as compared to the conventional DPI. The invention relates to composition of controlled release hydrogels where negatively charged hydrophilic polymer such

as sodiumalginate microparticles encapsulates budesonide. The formulated system achieves desired aerosolization and physical characteristics essential to improve the lung deposition. In the present study controlled gelation of hydrophilic polymer like sodium alginate was carried out where calcium ions react with guluronic acid units of the sodium alginate to form the negative charged calcium alginate complex which was enveloped by addition of cationic polymer such as chitosan to form uniform alginate particles. The drug molecules were entrapped in the formed polyelectrolyte complex during gelation. It was observed that amount of divalent cation like calcium chloride and the cationic polymer such as chitosan has pronounced effect on formation of biopolymer based DPI.An important object is to prepare microparticles by controlled gelatin of sodium alginate with specific ratio of cationic polymers and multivalent cations. One more object of invention is use of pluronic F-68 expecting that itmight help in encapsulation and dispersion of drug in alginate hydrogels. Yet another object is to provide negatively charged particle which is further helpful to increase time of flight and lung deposition. The process involves addition of organic solution of drug and surfactant into the sodium alginate solution under continuous stirring after which calcium chloride and chitosan solution was added with continuous stirring. The stirring was carried out until complete evaporation of organic solvent. It is also an object of said invention to provide a composition having good deposition and minimum undesirable side effects in comparison to marketed formulation.

In one aspect of the invention there is provided micro particulate pulmonary delivery system for budesonide with entrapment efficiency efficiency in the range of 60% to 93% w/v wherein the system comprises one or more gelling agent, one or more of surfactant, one or more of the cationic agent surrounding thebudesonide and wherein the system exhibits MMAD in the range of 0.5 μm to 5 μm, FPF in the range of 30% to 50%.

The micro-particles have a tap density less than 0.4 g/cm^3 and a mean diameter between 0.5 μm to 5 μm which in combination yield MMAD of between 1 – 5 μm, preferably between 0.5–3 μm by using andersen cascade impactor. The MMAD or aerodynamic diameter of a particle is the diameter of a fictitious sphere of unit density which under the action of gravity settles with the same velocity. The aerodynamic diameter is calculated to provide for maximum deposition within the lungs, achieved by the use of very small particles of less than five microns in diameter, preferably between 1 and 3 μm, which are then subject to phagocytosis.

The particles can be used for controlled local delivery of therapeutic agents to respiratory tract after aerolization. Administration of the particles to the deep lung was observed at 1.5 μm to 3.5 μm with least density which was useful for the improved aerolization. The particles can be used to form a composition that includes particles and a pharmaceutically acceptable carrier for administration to a patient, preferably for administration via inhalation. Suitable carriers include those typically used for inhalation therapy.

The prepared particles are responsible for higher percentage of FPF which is more than 30% of marketed formulations. The FPF is defined as percent of drug that reaches to deep lung. The particle size, shape, density, surface charge and nature are major contributing factors for maximum FPF which was calculated by using twin stage impinger.

In one of the embodiment of the invention there is provided a micro particulate pulmonary delivery system, wherein the system comprises dry powder for inhalation exhibiting the particle size in the range of 0.5 to 5μm.

Entrapement efficiency is defined as the ratio of weight of drug entrapped in to a carrier system to the total drug added.The amount of drug entrapped in the formulations was calculated by estimating the amount of unentrapped drug by centrifugation at 25,000 rpm for 30 min. The

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obtained supernatant was assayed spectrophotometrically at 246 nm for free drug content.

The % EE of drug is calculated by following equation

% EE = Total drug concentration /Initial drug concentration × 100

In one of the embodiments of the invention there is provided a micro particulate pulmonary delivery system wherein the system exhibits entrapment efficiency in the range of 60% to 93% w/v.

The invention also relates to micro particulate pulmonary delivery systemwith maximum entrapement efficiency for budesonidein sodium alginate microparticles was achieved due to intercalation of precipitated drug molecules in polymer matrix.

Ther term gelling agent refers to water soluble natural or synthetic polymers which have a capacity of crosslinking and absorb a large amount of water in to the developed network structure. The examples of gelling agents include one or more of naturally occurring polysaccharides such as sodium alginate, sclereglucan,carrageenans,hyaluronic acid, chitosan, polyglycolic acid, polyacrylamide,gelatins and the like.

The term surfactant refers to compounds that lower the surface tension (or interfacial tension) between two liquids or between a liquid and a solid. Surfactants may act as detergents, wetting agents, emulsifiers, foaming agents, and dispersants. The examples of surfactants include pluronic F-68, pluronic F-107, polyethylene glycols and similar classes of surfactants.

In one of the embodiment of the invention there is provided micro particulate pulmonary delivery system wherein the surfactant comprises pluronic.The divalent cationic agents have the capacity to form ionic interaction with the negatively charged polymers or agents. The term divalent cationic agent refers to calcium, barium, magnesium, Zinc etc.

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FORMULATION OF DELIVERY SYSTEM

The organic solution of drug and surfactantsuch as pluronic F 68 is added in the aqueous solution of hydrophilic polymer like sodium alginate with continuous stirring. To this specific concentration of divalent cation solution like calcium chloride and chitosan is added to carry out controlled gelation of anionic polymer which yields micron size particles. The stirring is continued for complete evaporation of the organic solvent and the obtained microparticles are lyophilized to get stable dry powder for inhalation.

The final formulation has shown -17.5mv of surface charge. This may have resulted from inadequate deacylation of chitosan used in the final formulation. Degree of deacetylation of chitosan affects overall charge density. An increasing presenceof ammonium groups results in decrease in the crosslinking density related to hydrogenbonding and hydrophobic interactions which can be calculated as

% Deacylation = Absorbance of carbonyl stretch of amide /Absorbance of NH stretch of free amine × 115

IR spectra of chitosan showed the characteristic peaks for N-H stretch (V max 3414 cm^{-1}) for free amine and C=O stretch (Vmax1101 cm^{-1}) for amide carbonyl. Deacetylation was calculated as 37% which was below the acceptable limit.

Moreover the mass ration ranging from 0.0:6 mg to 0.8:6 mg of chitosan: sodium alginate has been documented to impart positive charge on particles by forming uniform coat, however in the current invention, specific ratio of chitosan with alginate (0.031 to 0.126) results in imparting negative charge on the particles. This can be attributed to incomplete stretching of deacetylated chains of chitosan on account of the electrostatic repulsion between the NH_3 groups yielding into irregular and non-uniform coating of chitosan on the particles. The charge on the human

respiratory tract is negative due to presence of mucin.As per the charge theory, similar charged particles are responsible for repulsion in between the particles. Therefore, negative charge on the respiratory tract and formulated DPI responsible for prominent repulsive forces and increase the time of flight of DPI.

Following inhalation, biocompatible and biodegradable particles can deposit in lungs and subsequently undergo swelling and gelation in the presence of respiratory secretions, without particles being phagocytosed by alveolar macrophages. Due to formation of hydrogels, drug can be delivered relatively slowly into alveolar fluid and at a controlled rate into blood stream which helps to minimize the possible toxic effects of the present anti-inflammatory drugs used in the asthama.

Rotahaler was used as the delivery device for determinations using Twin stage impinger (TSI), Andersen cascade impactor (ACI) and Dosage unit sampling apparatus (DUSA). Initially respirable fraction of optimized budesonide and commercial DPI was determined by TSI (Model No: WP-SSGI-0289, Westech instruments, UK) after aerolization at 60±5L/min for 5 sec with 7 ml and 30 ml of phosphate buffer saline (PBS pH 7.4) in the stage 1 and 2 of the impinger respectively. Each stage was rinsed with PBS and drug content was determined by UV spectrophotometry methodat 246nm (Jasco-v-530) after appropriate dilution.The formulation having the highest respirable fraction was chosen for further deposition studies using an ACI.

Following are the exemplary examples illustrating embodiments of the invention that are presently best known.

Example 1

Acetone solution (10 ml) of budesonide (25 mg) and pluronic - F 68 (100 mg) was added into the sodium alginate (0.063%w/v) solution under magnetic stirring (250 rpm). To which, 1 ml of calcium chloride (10 mM) solution was added drop wise for 15 min followed by 2 ml of chitosan (2 mg/ml) solution were added, stirring was continued until to complete evaporation of organic solvent. The obtained microparticle suspension was lyophilized using mannitol as a cryoprotectant to get budesonide DPI.

Example 2

Acetone solution (10 ml) of budesonide (25 mg) and pluronic - F 68 (100 mg) was added into the sodium alginate (0.063%w/v) solution under magnetic stirring (250 rpm). To which, 1 ml of calcium chloride (10 mM) solution was added drop wise for 15 min followed by 3 ml of chitosan (2 mg/ml) solution were added, stirring was continued until to complete evaporation of organic solvent. The obtained microparticles suspension was lyophilized using mannitol as a cryoprotectant to get budesonide DPI.

Example 3

Acetone solution (10 ml) of budesonide (25 mg) and pluronic - F 68 (100 mg) was added into the sodium alginate (0.063%w/v) solution under magnetic stirring (250 rpm). To which, 1 ml of calcium chloride (10 mM) solution was added drop wise for 15 min followed by 4 ml of chitosan (2 mg/ml) solution were added, stirring was continued until to complete evaporation of organic solvent. The obtained microparticles suspension was lyophilized using mannitol as a cryoprotectant to get budesonide DPI.

Example 4

Acetone solution (10 ml) of budesonide (25 mg) and pluronic - F 68 (100 mg) was added into the sodium alginate (0.063%w/v) solution under magnetic stirring (250 rpm). To which, 2 ml of calcium chloride (10 mM) solution was added drop wise for 15 min followed by 2 ml of chitosan (2 mg/ml) solution were added, stirring was continued until to complete evaporation of organic solvent. The obtained microparticles suspension was lyophilized using mannitol as a cryoprotectant to get budesonide DPI.

Example 5

Acetone solution (10 ml) of budesonide (25 mg) and pluronic - F 68 (100 mg) was added into the sodium alginate (0.063%w/v) solution under magnetic stirring (250 rpm). To which, 2 ml of calcium chloride (10 mM) solution was added drop wise for 15 min followed by 3 ml of chitosan (2 mg/ml) solution were added, stirring was continued until to complete evaporation of organic solvent. The obtained microparticles suspension was lyophilized using mannitol as a cryoprotectant to get budesonide DPI

.Example 6

Acetone solution (10 ml) of budesonide (25 mg) and pluronic - F 68 (100 mg) was added into the sodium alginate (0.063%w/v) solution under magnetic stirring (250 rpm). To which, 2 ml of calcium chloride (10 mM) solution was added drop wise for 15 min followed by 4 ml of chitosan (2 mg/ml) solution were added, stirring was continued until to complete evaporation of organic solvent. The obtained microparticles suspension was lyophilized using mannitol as a cryoprotectant to get budesonide DPI.

Example 7

Acetone solution (10 ml) of budesonide (25 mg) and pluronic - F 68 (100 mg) was added into the sodium alginate (0.063%w/v) solution under magnetic stirring (250 rpm). To which, 3 ml of calcium chloride (10 mM) solution was added drop wise for 15 min followed by 2 ml of chitosan (2 mg/ml) solution were added, stirring was continued until to complete evaporation of organic solvent. The obtained microparticles suspension was lyophilized using mannitol as a cryoprotectant to get budesonide DPI.

Example 8

Acetone solution (10 ml) of budesonide (25 mg) and pluronic F-68 (100 mg) was added into the sodium alginate (0.063%w/v) solution under magnetic stirring (250 rpm). To which, 3 ml of calcium chloride (10 mM) solution was added drop wise for 15 min followed by 3 ml of chitosan (2 mg/ml) solution were added, stirring was continued until to complete evaporation of organic solvent. The obtained microparticles suspension was lyophilized using mannitol as a cryoprotectant to get budesonide DPI.

Example 9

Acetone solution (10 ml) of budesonide (25 mg) and pluronic - F68 (100 mg) was added into the sodium alginate (0.063%w/v) solution under magnetic stirring (250 rpm). To which, 3 ml of calcium chloride (10 mM) solution was added drop wise for 15 min followed by 4 ml of chitosan (2 mg/ml) solution were added, stirring was continued until to complete evaporation of organic solvent. The obtained microparticles suspension was lyophilized using mannitol as a cryoprotectant to get budesonide DPI.

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Claims

1. Micro particulate pulmonary delivery system of budesonide or salts or hydrates thereof, with entrapment efficiency wherein the system comprises one or more gelling agent, one or more of surfactant, one or more of the cationic agent surrounding the drug particles wherein the delivery system converts into hydrogel upon deposition in the respiratory tract.
2. Micro particulate pulmonary delivery system for budesonide or salts or hydrates thereof, with entrapment efficiency wherein the system comprises one or more gelling agent, one or more of surfactant, one or more of the cationic agent surrounding the budesonide and wherein the system exhibits MMAD in the range of 0.5 μm to 5 μm, FPF in the range of 30% to 50%.
3. Micro particulate pulmonary delivery system according to claim 2, wherein the system comprises dry powder for inhalation exhibiting the particle size in the range of 0.5 to 5μm.
4. Micro particulate pulmonary delivery system according to claim 2 wherein the system exhibits entrapment efficiency in the range of 60% to 93% w/v.
5. Micro particulate pulmonary delivery system according to claim 2, wherein the gelling agent comprises one or more of sodium alginate, chitosan and polyglycolic acid.
6. Micro particulate pulmonary delivery system according to claim 2 wherein the surfactant comprises pluronic F 68.
7. Micro particulate pulmonary delivery system according to claim 2 wherein the divalent cation such as calcium chloride, barium sulphate etc.

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8. Method of making micro particulate pulmonary delivery system for budesonide wherein the method involves:

   a) Mixing organic solution of drug and surfactant in to the sodium alginate solution with continuous stirring.

   b) Addition of calcium chloride and chitosan solutions to the mixture with continuous stirring until complete evaporation of organic solvent.

   c) Lyophilization of microparticles using mannitol as a cryoprotectant.

DATE AND SIGNATURE

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