IMPROVED PHARMACEUTICAL FORMULATIONS

FIELD OF THE INVENTION

The present invention relates to pharmaceutical formulations, to methods of making them and to their use in the treatment and prophylaxis of diseases in mammals, particularly humans.

BACKGROUND OF THE INVENTION

Pharmaceutical dosage forms which rapidly dissolve when placed in the mouth of the patient, thereby delivering the desired dose of the pharmaceutically active substances, are particularly useful when the dosage form can be taken without water. Such dosage forms are generally preferred by children and old people and also by people with difficulties in swallowing and/or taking tablets or capsules.

Rapidly dissolving dosage forms are generally prepared using a multistep process. Some of these processes use a lyophilization step during which solvent is removed from a solution and/or suspension comprising a pharmaceutically active substance, carrier material and solvent.

Pharmaceutical formulations manufactured by lyophilization have various advantages but also various challenges such as issues of free flow, moisture absorption, bitter taste, dose uniformity and content uniformity. The present invention aims at overcoming these challenges.

SUMMARY OF THE INVENTION

The present invention provides a novel blend composition of sorbitol and liquid paraffin for use in the improvement of formulation properties of pharmaceutical formulations in several parameters, i.e. flow properties, moisture protection, antistatic properties and compressibility (Carr Index). The blend composition may also contain citric acid and has the ability to mitigate the taste of bitter drugs.

The present invention thus provides a free-flowing solid pharmaceutical formulation comprising one or more active ingredients and a blend composition comprising or consisting of sorbitol, liquid paraffin and optionally citric acid.

The present invention further provides a blend, comprising or consisting of sorbitol, liquid paraffin and optionally citric acid, for use in the manufacture of a pharmaceutical formulation comprising one or more active ingredients.

The present invention also provides a process for the manufacture of a solid pharmaceutical formulation of the invention comprising:

(a) forming a lyophilized powder by subliming the solvent from a preparation comprising one or more active ingredients and the solvent;

(b) forming a blend composition comprising or consisting of sorbitol, liquid paraffin and optionally citric acid;

(c) mixing the blend composition obtained in step (b) with the lyophilized powder obtained in step (a).

FIGURES

Figure 1 compares the Compressibility Index (Carr Index) of the formulations of Example 1 and Comparative Examples A-E.

Figure 2 compares the Hausner Ratio of the formulations of Example 1 and Comparative Examples A-E.

Figure 3 depicts the % Moisture Content of the formulations of Example 1 and Comparative Examples A-E as a function of storage time.

Figure 4 compares the % Residual Content of the formulations of Example 1 and Comparative Examples A-E.

Figure 5 is a photograph of a stick pack of the invention.

Figure 6 compares the Compressibility Index (Carr Index) of the formulations of Example 2 and Comparative Examples F-K.

Figure 7 compares the Hausner Ratio of the formulations of Example 2 and Comparative Examples F-K.

Figure 8 depicts the % Moisture Content of the formulations of Example 2 and Comparative Examples F-K as function of storage time.

Figure 9 compares the % Residual Content of the formulations of Example 2 and Comparative Examples F-K.

Figure 10 compares the Compressibility Index (Carr Index) of the formulations of Example 3-4 and Comparative Examples L-Q.

Figure 11 compares the Hausner Ratio of the formulations of Example 3-4 and Comparative Examples L-Q.

Figure 12 depicts the % Moisture Content of the formulations of Example 3-4 and Comparative Examples L-Q as function of storage time.

Figure 13 compares the % Residual Content of the formulations of Example 3-4 and Comparative Examples L-Q

Figure 14 compares the Compressibility Index (Carr Index) of the formulations of Example 5 and Comparative Examples R-W.

Figure 15 compares the Hausner Ratio of the formulations of Example 5 and Comparative Examples R-W.

Figure 16 depicts the % Moisture Content of the formulations of Example 5 and Comparative Examples R-W as function of storage time.

Figure 17 compares the % Residual Content of the formulations of Example 5 and Comparative Examples R-W

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a novel blend composition of sorbitol and liquid paraffin for use in the improvement of formulation properties of pharmaceutical formulations in several parameters, i.e. flow properties, moisture protection, antistatic

properties and compressibility. The blend composition may also contain citric acid and has ability to mitigate the taste of bitter drugs.

The novel blend, when mixed with lyophilized powder, provides a pharmaceutical formulation with improved properties, e.g., flow properties, moisture protection, antistatic properties and compressibility.

The present invention thus provides a free-flowing solid pharmaceutical formulation comprising one or more active ingredients and a blend composition comprising or consisting of sorbitol, liquid paraffin and optionally citric acid.

The formulation preferably comprises 0.01% to 30% by weight of one or more active ingredients, 70% to 99.99% by weight of the blend composition, and 0% to 30% by weight of one or more other pharmaceutically acceptable excipients. More preferably, the formulation comprises 0.1% to 28% by weight of one or more active ingredients, 72% to 99.9% by weight of the blend composition, and 5% to 30% by weight of one or more other pharmaceutically acceptable excipients. In an embodiment of the invention, the formulation is obtained by a process including steps of forming the blend composition by blending sorbitol, liquid paraffin and optionally citric acid, and adding the blend composition to the active ingredient(s), which is preferably a lyophilized powder.

The present invention further provides a blend composition comprising or consisting of sorbitol, liquid paraffin and optionally citric acid for use in the manufacture of a pharmaceutical formulation comprising one or more active ingredients. The blend composition preferably comprises 95 to 99.9% by weight of sorbitol, 0.1% to 5% by weight of liquid paraffin, and 0 to 4% by weight of citric acid. More preferably, the blend composition comprises 96 to 99.5% by weight of sorbitol, 0.5% to 4% by weight of liquid paraffin, and 0.5 to 2% by weight of citric acid. In one embodiment, the blend composition consists of the indicated components, in the indicated preferred and more preferred proportions.

The present invention also provides a process for the manufacture of a solid pharmaceutical formulation of the invention comprising:

(a) forming a lyophilized powder by subliming the solvent from a preparation comprising one or more active ingredients and the solvent;

(b) forming a blend composition comprising or consisting of sorbitol, liquid paraffin and optionally citric acid;

(c) mixing the blend composition obtained in step (b) with the lyophilized powder obtained in step (a).

The process of the invention allows obtaining a solid pharmaceutical formulation in the form of a free-flowing powder.

Preferred proportions of active ingredient(s), sorbitol, liquid paraffin, citric acid and blend composition in the process of the present invention are the same as in the pharmaceutical formulation of the present invention.

The solvent used in the preparation to be lyophilized, comprising active ingredient(s) and solvent, typically is water.

The terms "*active ingredient*" and "*pharmaceutically active ingredient*" are used interchangeably herein.

The pharmaceutical formulation of the present invention comprises one or more pharmaceutically active ingredients. They may be selected from, e.g., oligopeptides, polypeptides (proteins), nucleotides, polynucleotides and "small molecules". Non-limiting examples of pharmaceutically active ingredients which can be used in the present invention are analgesics, alpha blockers, anti-allergy agents, anti-asthma agents, anti-rhinitis agents, anti-uticaria agents, anti-inflammatory agents, anti-arrhythmic agents, anti-bacterial agents, anti-psychotics, anti-diabetics, anti-diuretics, anti-epileptics, anti-fungal agents, anti-gout agents, anti-hypertensive agents, anti-incontinence agents, anti-migraine agents, anti-muscarinic agents and immunosuppressants, antivirals, anxiolytics, sedatives, hypnotics and neuroleptics, anti-benign hyperplasia (BPH agents), decongestants, diuretics, enzymes, anti-parkinsonian agents, gastro-intestinal agents, histamine receptor antagonists, infertility agents, endometriosis agents, hormone replacement therapy agents, lipid regulating agents, local anesthetics, neuromuscular agents, motion sickness agents,

nutritional agents, oral vaccines, proteins, peptides and recombinant drugs, proton pump inhibitors, anti-schizophrenia agents, hormones, contraceptives, seizure/panic disorder agents, sexual dysfunction (male and female) agents and so forth .

Specific non-limiting examples of these active ingredients are:

Anti-allergics: desloratadine, loratadine, Montelukast, Montelukast sodium, Cetirizin, Fexofenadin, Ebastine.

Alfa blockers: Tamsulosin, Silodosin

Analgesics and anti-inflammatory agents: aspirin, aloxiprin, auranofin, azapropazone, benorylate, diflunisal, etodolac, fenbufen, fenoprofen calcium, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, paracetamol.

Anti-arrhythmic agents: amiodarone HCl, disopyramide, flecainide acetate, quinidine sulphate.

Anti-bacterial agents: benethamine penicillin, cinoxacin, ciprofloxacin HCl, clarithromycin, clofazimine, cloxacillin, demeclocycline, doxycycline, erythromycin, ethionamide, imipenem, nalidixic acid, nitrofurantoin, rifampicin, spiramycin, sulphabenzamide, sulphadoxine, sulphamerazine, sulphacetamide, sulphadiazine, sulphafurazole, sulphamethoxazole, sulphapyridine, tetracycline, trimethoprim.

Anti-psychotics: amoxapine, ciclazindol, maprotiline HCl, mianserin HCl, nortriptyline HCl, trazodone HCl, trimipramine maleate.

Anti-diabetics: acetohexamide, chlorpropamide, glibenclamide, gliclazide, glipizide, tolazamide, tolbutamide.

Anti-diuretics: desmopressin and its analog, desmopressin acetate.

Anti-epileptics: beclamide, carbamazepine, clonazepam, ethotoin, methoin, methsuximide, methylphenobarbitone, oxcarbazepine, paramethadione, phenacemide, phenobarbitone, phenytoin, phensuximide, primidone, sulthiame, valproic acid.

Anti-fungal agents: amphotericin, butoconazole nitrate, clotrimazole, econazole nitrate, fluconazole, flucytosine, griseofulvin, itraconazole, ketoconazole, miconazole, natamycin, nystatin, sulconazole nitrate, terbinafine HCl, terconazole, tioconazole, undecenoic acid.

Anti-gout agents: allopurinol, probenecid, sulphinpyrazone.

Anti-hypertensive agents: amlopidine, benidipine, darodipine, dilitazem HCl, diazoxide, felodipine, guanabenz acetate, indoramin, isradipine, minoxidil, nicardipine HCl, nifedipine, nimodipine, phenoxybenzamine HCl, prazosin HCl, reserpine, terazosin HCl.

Anti-migraine agents: rizatriptan, dihydroergotamine mesylate, ergotamine tartrate, methysergide maleate, pizotifen maleate, sumatriptan succinate, caffeine.

Anti-muscarinic agents: oxybutinin, tolterodin, atropine, benzhexol HCl, biperiden, ethopropazine HCl, hyoscine butyl bromide, hyoscyamine, mepenzolate bromide, orphenadrine, oxyphencylcimine HCl, tropicamide.

Anti-rhinitis agents, anti-uticaria agents: Cetirizin, fexofenadin, ebastine, loratadine, montelukast.

Antivirals: acyclovir, amantadine hydrochloride, famciclovir, zidovadine, didanosine, zalcitabine, foscarnet sodium.

Anxiolytic agents, sedatives, hypnotics and neuroleptics: alprazolam, amylobarbitone, barbitone, bentazepam, bromazepam, bromperidol, brotizolam, butobarbitone, carbromal, chlordiazepoxide, Chlorpheniramine, chlormethiazole, chlorpromazine, clobazam, clonazepan, clotiazepam, clozapine, diazepam, droperidol, ethinamate, flunanisone, flunitrazepam, fluopromazine, flupenthixol decanoate, fluphenazine decanoate, flurazepam, haloperidol, lorazepam, lormetazepam, medazepam, meprobamate, methaqualone, midazolam, nitrazepam, oxazepam, pentobarbitone, perphenazine phenylephrine, pimozide, prochlorperazine, pseudoephedrineHCL, sulpride, temazepam, thioridazine, triazolam, zopiclone.

Contraceptives: clomiphene citrate, danazol, desogestrel, ethinyloestradiol, ethynodiol, ethynodiol diacetate, levonorgestrel, medroxyprogesterone acetate, mestranol, methyltestosterone, norethisterone, norethisterone enanthate, norgestrel, estradiol, conjugated estrogens, dydrogesterone, progesterone, stanozolol, stilboestrol, testosterone, tibolone.

Decongestants: pseudoephedrine hydrochloride.

Diuretics: acetazolamide, amiloride, bendrofluazide, bumetanide, chlorothiazide, chlorthalidone, ethacrynic acid, frusemide, metolazone, spironolactone, triamterene.

Enzymes: pancreatin, pepsin, lipase.

Epilepsy: Gabapentin

Anti-parkinsonian agents: bromocriptine mesylate, lysuride maleate, selegiline, para-fluoroselegiline, lazabemide, rasagiline, 2-BUMP [N-(2-butyl)-N-methylpropargylamine], M-2-PP [N-methyl-N-(2-pentyl)-propargylamine], MDL-72145 [beta-(fluoromethylene)-3,4-dimethoxy-benzeneethanamine], mofegiline, apomorphine, N-propylnoraporphine, cabergoline, metergoline, naxagolide, pergolide, piribedil, ropinirole, terguride, quinagolide.

Gastro-intestinal agents: bisacodyl, cimetidine, cisapride, diphenoxylate HCl, domperidone, metoclopramide, famotidine, loperamide, mesalazine, nizatidine, esomeprazole, metopimazine, pantoprazole, ondansetron HCl, Granisetron, tropisetron, dolasetron, ranitidine HCl, sulphasalazine. Lanzoprazole.

Histamine Receptor Antagonists: acrivastine, astemizole, cinnarizine, cyclizine, cyproheptadine HCl, dimenhydrinate, flunarizine HCl, loratadine, meclozine HCl, oxatomide, terfenadine, triprolidine.

Hormones: Human Growth hormone (HGH), Follicle Stimulating Hormone (FSH), Gonadotropin-releasing hormone (GnRH) agonists or antagonists, nafarelin Triptorelin, cetrorelix, atosiban.

Hormone replacement therapy agents: dydrogesterone.

Anti-hypertension agents: Enalapril.

Lactation agents: Oxytocin, oxytocin agonists.

Lipid regulating agents: bezafibrate, clofibrate, fenofibrate, gemfibrozil, probucol.

Local anaesthetics: amethocaine, amylocaine, benzocaine, bucricaine, bupivacaine, butacaine, butanilicaine, butoxycaine, butyl aminobenzoate, carticaine, chloroprocaine, cinchocaine, clibucaine, clormecaine, coca, cocaine, cyclomethycaine, dimethisoquin, diperodon, dyclocaine, ethyl chloride, ethyl p-piperidinoacetylaminobenzoate, etidocaine, hexylcaine, isobutamben, ketocaine, lignocaine, mepivacaine, meprylcaine, myrtecaine, octacaine, oxethazaine, oxybuprocaine, parethoxycaine, pramoxine, prilocaine, procaine, propranocaine, propoxycaine, proxymetacaine, ropivacaine, tolycaine, tricaine, trimecaine, vadocaine.

Motion sickness agents: diphenhydramine.

Neuro-muscular agents: pyridostigmine.

Nonsteroidal antiandrogens: Enzalutamide.

Nutritional agents: betacarotene, vitamins, such as vitamin A, vitamin B_2, vitamin D, vitamin E, vitamin K, minerals.

Oral vaccines: to prevent or reduce the symptoms of diseases such as Influenza, Tuberculosis, Meningitis, Hepatitis, Whooping Cough, Polio, Tetanus, Diphtheria, Malaria, Cholera, Herpes, Typhoid, HIV, AIDS, Measles, Lyme disease, Traveller's Diarrhea, Hepatitis A, B and C, Otitis Media, Dengue Fever, Rabies, Parainfluenza, Rubella, Yellow Fever, Dysentery, Legionnaires Disease, Toxoplasmosis, Q-Fever, Haemorrhegic Fever, Argentina Haemorrhegic Fever, Caries, Chagas Disease, Urinary Tract Infection caused by E. coli, Pneumococcal Disease, Mumps, Chikungunya, Hay fever, Asthma, Rheumatoid Arthritis, Carcinomas, Coccidiosis, Newcastle Disease, Enzootic pneumonia, Feline leukemia, Atrophic rhinitis, Erysipelas, Foot and Mouth disease and Swine pneumonia, or to prevent or reduce the symptoms of diseases caused by Vibrio species, Salmonella species, Bordetella species, Haemophilus species, Toxoplasmosis gondii, Cytomegalovirus, Chlamydia species, Streptococcal species, Norwalk Virus, Escherischia coli, Helicobacter pylori, Rotavirus, Neisseria gonorrhae, Neisseria meningiditis, Adenovirus, Epstein Barr Virus, Japanese Encephalitis Virus, Pneumocystis carini, Herpes simplex, Clostridia species, Respiratory Syncytial Virus, Klebsiella species, Shigella species, Pseudomonas aeruginosa, Parvovirus, Campylobacter species, Rickettsia species, Varicella zoster, Yersinia species, Ross River Virus, J.C. Virus, Rhodococcus equi, Moraxella catarrhalis, Borrelia burgdorferi and Pasteurella haemolytica, BCG.

Agents for voiding dysfunctions: Tamsulosin, trospium chloride, tolterodine , oxybutynin, Solifenacin.

Proteins, peptides and recombinant drugs: recombinant hormones and iso-hormones, recombinant cytokines, recombinant plasminogens, TNF receptor fusion protein, monoclonal antibodies, nucleic acids, antisense oligonucleotides, oligonucleotides, glycoproteins and adhesion molecules, Calcitonin, octreotide, insulin and insulin analogs, etanercept, pegfilgrastim, liraglutide, bivalirudin, nesiritide, ceruletide, bentiromide, exenatide, gonadorelin, enfuvirtide, vancomycin, icatibant, secretin, leuprolide, glucagon recombinant, oxytocin, sermorelin, gramicidin D, Insulin recombinant, capreomycin, vasopressin, cosyntropin, bacitracin, abarelix, vapreotide, thymalfasin, mecasermin, teriparatide, corticotropin, pramlintide.

Phosphate Binders: Sevelamer.

Sexual dysfunction agents: Cabergolin, oxytocin, tadalafil, sildenafil, vardenafil.

Stimulants: amphetamine, dexamphetamine, dexfenfluramine, fenfluramine.

In a specific embodiment, the active ingredient of a formulation of the invention is selected from the group consisting of desloratadine, montelukast, solifenacin, silodosin, sildenafil and any pharmaceutically acceptable salt thereof.

In a specific embodiment, the active ingredient of a formulation of the invention is desloratadine.

In a specific embodiment, the active ingredient of a formulation of the invention is sildenafil.

In a specific embodiment, the active ingredient of a formulation of the invention is solifenacin.

In addition to the components discussed above, the formulation may also include other excipients (auxiliary agents, accessory agents) such as, but not limited to fillers, thickeners (including but not limited to guar gum and xanthan gum), binders, diluents, lubricants, pH adjusting agents, protecting agents, viscosity enhancers, wicking agents, non-effervescent disintegrants, effervescent disintegrants, surfactants, anti-oxidants, wetting agents, colorants, flavoring agents, taste-masking agents, sweeteners, preservatives and so forth.

A suitable route of administration for a dosage form of the present invention is oral administration.

In one embodiment, a pharmaceutical formulation of the invention can be administered to a patient in the form of a powder.

In another aspect, a pharmaceutical formulation of the invention is contained in a package dispensing single doses of the formulation, also named a unit dosage form. Non-limiting examples of a package/unit dosage form are a sachet and a stick pack.

In another embodiment, a pharmaceutical formulation of the invention, e.g., in the form of a powder, is packed in a multi-dosage form, i.e. a dosage form allowing withdrawing multiple doses of arbitrary size. Non-limiting examples of a multi-dosage form are a bottle and any other container capable of holding a powder.

A patient administered with a free-flowing powder formulation of the invention will be certain that he receives the entire dosage, i.e. there will be no residue left in the package/unit dosage form.

In one embodiment, the oral administration is carried out by emptying a sachet, stick pack or (any other) unit pack containing the powder onto the tongue and swallowing the content.

In another embodiment, the oral administration is carried out by dissolving the powder in a solvent (e.g. a glass of water) and then drink the solution.

The exact dose and regimen of administration of the dosage form will necessarily depend upon the therapeutic effect to be achieved and may vary with the particular active ingredient, the route of administration, and the age and condition of the individual subject to whom the formulation is to be administered. At times patients may be instructed to take two or any other number of unit dosage forms, e.g. stick packs, in a single administration or at times only a portion, such as half or a quarter, of the unit dosage form in a single administration.

The formulations of the invention are unique in that they have improved flow properties, moisture content, antistatic properties and compressibility.

The pharmaceutical formulation of the invention may be obtained by:

(a) forming a lyophilized powder by subliming the solvent (e.g. water), for example in a freeze drying process, from a preparation that comprises the active ingredient(s) and the solvent;

(b) forming a blend composition comprising sorbitol and liquid paraffin. The blend composition may optionally contain citric acid;

(c) mixing the blend composition with the lyophilized powder obtained in step (a) to obtain a pharmaceutical composition with improved flow properties, moisture protection, antistatic properties and compressibility.

According to one embodiment, the resulting free flowing composition is introduced into a stick pack.

According to another embodiment, the resulting free flowing composition is introduced into a sachet.

The free flowing blend composition of sorbitol and liquid paraffin is mixed with a lyophilized powder by methods known in the art such as geometric mixing or mixing with any type of blender.

EXAMPLES

The invention is further described in the following examples, which are not in any way intended to limit the scope of the inventions as claimed.

Materials and methods

Material	Manufactured by	Supplied by
Polacrillin Potassium (resin)	Dow France S.A.S	Colorcon India
Maltodextrin	Roquette France	Signet India
Citric acid	Merck	Merck
Talc	Imerys Talc	Signet India
Magnesium stearate	Sun-shine	Sun-shine
Liquid paraffin	Ashwini chemicals pvt. Ltd.	Ashwini chemicals pvt. Ltd.
Sorbitol	Roquette	Signet India
Desloratadine	Enaltec	Enaltec
Sodium Hydroxide	Merck	Merck
Mannitol	Roquette France	Signet India
Hydroxypropyl cellulose L	Ashland	Ashland
Tartaric acid pellets	Ideal cures	Ideal cures
Sildenafil citrate	Rakshit drugs	Rakshit drugs
Solifenacin	MSN Lab	MSN Lab

Example 1: Placebo Formulation

A (placebo) formulation was prepared using the following ingredients:

	Ingredients	Quantity per 1000 Stick Packs (g)
Lyophilized Granules prepared from liquid composition composed of:		
1	Resin	20.0
2	Maltodextrin	77.0
3	Citric acid	3.0
4	Water	q.s. to 400 g
Blend Composition		
5	Sorbitol	394.5
6	Citric acid	3.0
7	Liquid paraffin	2.5

Manufacturing procedure:

I. Lyophilized Granules

1. Citric acid was dissolved in 200 g of water using a magnetic/overhead stirrer for 5 minutes.
2. Resin was added under continuous stirring and the dispersion formed was kept under stirring for 1 hour.
3. Maltodextrin was added under continuous stirring.
4. The final weight of the solution/dispersion was made to 400 g using purified water.
5. Mixing of the solution/dispersion was continued for 10 minutes in a magnetic/overhead stirrer.
6. This solution/dispersion was filled in stainless steel tray and freeze-dried in a lyophilizer.
7. After complete freeze drying, the lyophilized cake was sieved through a #40 sieve to obtain the lyophilized granules.

II. Blend Composition

8. Sorbitol was passed through a #40 sieve and mixed with crushed and sieved citric acid in a double cone blender for 2 minutes at 10 RPM.
9. Liquid paraffin was added dropwise to 40 g of the mixture from step 8, and mixed manually to obtain a uniformly distributed blend composition.
10. The blend composition was sieved through a #60 sieve and then mixed with remaining mixture from step 8 using a double cone blender for 3 minutes at 10 RPM to obtain the final blend composition.

III. Formulation

11. The lyophilized granules from step 7 were mixed with the final blend composition from step 10 in a double cone blender for 5 minutes at 10 RPM to obtain the free flowing (placebo) composition.
12. The free flowing composition was filled into stick packs and sealed, at 500 mg per stick pack (see Figure 5).

Example 2: Desloratadine Composition

A formulation of desloratadine was prepared using the following ingredients:

	Ingredients	Quantity per 1000 Stick Packs (g)
Lyophilized Granules prepared from liquid composition composed of:		
1	Desloratadine	10.0
2	Resin	20.0
3	Maltodextrin	67.0
4	Citric acid	3.0
5	Water	q.s. to 400 g
Blend Composition		
6	Sorbitol	394.5
7	Citric acid	3.0
8	Liquid paraffin	2.5

Manufacturing procedure

I. Lyophilized Granules

1. Citric acid was dissolved in 200 g of water using a magnetic/overhead stirrer for 5 minutes.
2. Desloratadine was added under continuous stirring using a magnetic/overhead stirrer.
3. Resin was added under continuous stirring and the dispersion formed was kept under stirring for 1 hour.
4. Maltodextrin was added under continuous stirring.
5. The final weight of the solution/dispersion was made to 400 g using purified water.
6. Mixing of the solution/dispersion was continued for 10 minutes in a magnetic/overhead stirrer.
7. This solution/dispersion was filled in stainless steel tray and freeze-dried in a lyophilizer.
8. After complete freeze drying, the lyophilized cake was sieved through a #40 sieve to obtain the lyophilized granules.

II. Blend Composition

9. Sorbitol was passed through a #40 sieve and mixed with crushed and sieved citric acid in a double cone blender for 2 minutes at 10 RPM.

10. Liquid paraffin was added dropwise to 40 g of the mixture from step 9, and mixed manually to obtain a uniformly distributed blend composition.
11. The blend composition was sieved through a #60 sieve and then mixed with remaining mixture from step 9 using a double cone blender for 3 minutes at 10 RPM to obtain the final blend composition.

III. Formulation

12. The lyophilized granules from step 8 were mixed with the final blend composition from step 11 in a double cone blender for 5 minutes at 10 RPM to obtain the free flowing desloratadine formulation.
13. The free flowing composition was filled into stick packs and sealed, at 500 mg per stick pack (see Figure 5).

Comparative Example A

A granule formulation was prepared essentially as described in Example 1 using the following ingredients:

	Ingredients	**Quantity per 1000 Stick Packs (g)**
1	Resin	33.0
2	Maltodextrin	129.0
3	Citric acid	8.0
4	Water	q.s. to 200 g

Comparative Example B

A comparative pharmaceutical formulation was prepared essentially as described in Example 1 by using a blend composition containing talc and the other following ingredients**:**

	Ingredients	Quantity per 1000 Stick Packs (g)
Lyophilized Granules prepared from liquid composition composed of:		
1	Resin	33.0
2	Maltodextrin	127.0
3	Citric acid	5.0
4	Water	q.s. to 200 g
Blend Composition		
5	Citric acid	3.0
6	Talc	2.5

Comparative Example C

A comparative pharmaceutical formulation was prepared essentially as described in Example 1 by using a blend composition containing Magnesium stearate and the other following ingredients:

	Ingredients	Quantity per 1000 Stick Packs (g)
Lyophilized Granules prepared from liquid composition composed of:		
1	Resin	33.0
2	Maltodextrin	127.0
3	Citric acid	5.0
4	Water	q.s. to 200 g
Blend Composition		
5	Citric acid	3.0
6	Magnesium stearate	2.5

Comparative Example D

A comparative pharmaceutical formulation was prepared essentially as described in Example 1 by using a blend composition containing Talc, Magnesium stearate and the other following ingredients:

	Ingredients	Quantity per 1000 Stick Packs (g)
Lyophilized Granules prepared from liquid composition composed of:		
1	Resin	33.0
2	Maltodextrin	127.0
3	Citric acid	5.0
4	Water	q.s. to 200 g
Blend Composition		
5	Citric acid	3.0
6	Talc	1.3
7	Magnesium stearate	1.3

Comparative Example E

A comparative pharmaceutical formulation was prepared essentially as described in Example 1 by using a blend composition containing only liquid paraffin and the other following ingredients:

	Ingredients	Quantity per 1000 Stick Packs (g)
Lyophilized Granules prepared from liquid composition composed of:		
1	Resin	33.0
2	Maltodextrin	127.0
3	Citric acid	5.0
4	Water	q.s. to 200 g
Blend Composition		
5	Citric acid	3.0
6	Liquid paraffin	2.5

Comparative Example F

A granule formulation was prepared essentially as described in Example 2 using the following ingredients:

	Ingredients	Quantity per 1000 Stick Packs (g)
1	Desloratadine	16.7
2	Resin	33.40
3	Maltodextrin	111.89
4	Citric acid	8.0
5	Water	q.s. to 668 g

Comparative Example G

A comparative pharmaceutical formulation was prepared essentially as described in Example 2 by using a blend composition containing talc and the other following ingredients:

	Ingredients	Quantity per 1000 Stick Packs (g)
Lyophilized Granules prepared from liquid composition composed of:		
1	Desloratadine	16.45
2	Resin	33.0
3	Maltodextrin	110.0
4	Citric acid	5.0
5	Water	q.s. to 658 g
Blend Composition		
6	Citric acid	3.0
7	Talc	2.5

Comparative Example H

A comparative pharmaceutical formulation was prepared essentially as described in Example 2 by using a blend composition containing Magnesium stearate and the other following ingredients:

	Ingredients	Quantity per 1000 Stick Packs (g)
Lyophilized Granules prepared from liquid composition composed of:		
1	Desloratadine	16.45
2	Resin	33.0
3	Maltodextrin	110.0
4	Citric acid	5.0
5	Water	q.s. to 658 g
Blend Composition		
6	Citric acid	3.0
7	Magnesium stearate	2.5

Comparative Example I

A comparative pharmaceutical formulation was prepared essentially as described in Example 2 by using a blend composition containing Talc, Magnesium stearate and the other following ingredients:

	Ingredients	Quantity per 1000 Stick Packs (g)
Lyophilized Granules prepared from liquid composition composed of:		
1	Desloratadine	16.45
2	Resin	33.0
3	Maltodextrin	110.0
4	Citric acid	5.0
5	Water	q.s. to 658 mg
Blend Composition		
6	Citric acid	3.0
7	Talc	1.3
8	Magnesium stearate	1.3

Comparative Example J

A comparative pharmaceutical formulation was prepared essentially as described in Example 2 by using a blend composition containing only liquid paraffin and the other following ingredients:

	Ingredients	Quantity per 1000 Stick Packs (g)
Lyophilized Granules prepared from liquid composition composed of:		
1	Desloratadine	16.45
2	Resin	33.0
3	Maltodextrin	127.0
4	Citric acid	5.0
5	Water	q.s. to 200 g
Blend Composition		
6	Citric acid	3.0
7	Liquid paraffin	2.5

Comparative Example K

A comparative pharmaceutical formulation was prepared essentially as described in Example 2 by using a blend composition containing only Sorbitol and the other following ingredients:

	Ingredients	Quantity per 1000 Stick Packs (g)
Lyophilized Granules prepared from liquid composition composed of:		
1	Desloratadine	10.0
2	Resin	20.0
3	Maltodextrin	67.0
4	Citric acid	3.0
5	Water	q.s. to 400 g
Blend Composition		
6	Sorbitol	400.0

Example 3: Sildenafil Composition

A formulation of sildenafil was prepared using the following ingredients:

	Ingredients	Quantity per 1000 Stick Packs (g)
Lyophilized Granules prepared from liquid composition composed of:		
1	Sildenafil Citrate	140.48
2	Sodium hydroxide	30.12
3	Mannitol	149.45
4	HPC-L	4.0
5	Purified Water	q.s to 1000 g
Blend Composition		
6	Sorbitol	604.87
7	Citric acid	64.63
8	Liquid paraffin	3.0

Manufacturing procedure

I. Lyophilized Granules

1. Sodium hydroxide was dissolved in 370 mL of purified water under stirring on overhead stirrer for 10 min at 1000 RPM
2. Sildenafil citrate was dispersed uniformly in the solution of step 1 under stirring for 30 min.
3. The dispersion obtained in step 2 was homogenized at 10000 RPM for 60 min using homogenizer and overhead stirrer.
4. Hydroxypropyl cellulose L was dissolved in water (166.5 g) and the solution was added to dispersion of step 2 under stirring.
5. Mannitol was added to the dispersion.
6. The final weight of the solution/dispersion was made to 1000 g using purified water.
7. Mixing of the solution/dispersion was continued for 10 minutes in a magnetic/overhead stirrer.
8. This solution/dispersion was filled in stainless steel tray and freeze-dried in a lyophilizer.
9. After complete freeze drying, the lyophilized cake was sieved through a #40 sieve to obtain the lyophilized granules.

II. Blend Composition

10. Sorbitol was passed through a #40 sieve and mixed with crushed and sieved citric acid in a double cone blender for 2 minutes at 10 RPM.
11. Liquid paraffin was added dropwise to 40 g of the mixture from step 10, and mixed manually to obtain a uniformly distributed blend composition.
12. The blend composition was sieved through a #60 sieve and then mixed with remaining mixture from step 9 using a double cone blender for 3 minutes at 10 RPM to obtain the final blend composition.

III. Formulation

13. The lyophilized granules from step 9 were mixed with the final blend composition from step 12 in a double cone blender for 5 minutes at 10 RPM to obtain the free flowing Sildenafil Citrate formulation.
14. The free flowing formulation was filled into stick packs and sealed, at 500 or 1000 mg per stick pack (see Figure 5).

Example 4: Sildenafil Composition

A formulation of Sildenafil was prepared essentially as described in Example 3 using the following ingredients:

	Ingredients	**Quantity per 1000 Stick Packs (g)**
Lyophilized Granules prepared from liquid composition composed of:		
1	Sildenafil Citrate	140.48
2	Sodium hydroxide	30.12
3	Mannitol	149.45
4	HPC-L	4.0
5	Purified Water	q.s to 1000 g
Blend Composition		
6	Sorbitol	604.87
7	Tartaric acid pellets	64.63
8	Liquid paraffin	3.00

Comparative Example L

A granule formulation was prepared essentially as described in Example 3 using the following ingredients:

	Ingredients	**Quantity per 1000 Stick Packs (g)**
1	Sildenafil Citrate	140.48
2	Sodium hydroxide	30.12
3	Mannitol	149.45
4	HPC-L	4.0
5	Purified Water	q.s to 1000 g

Comparative Example M

A comparative pharmaceutical formulation was prepared essentially as described in Example 3 by using a blend composition containing talc and the other following ingredients**:**

	Ingredients	**Quantity per 1000 Stick Packs (g)**
Lyophilized Granules prepared from liquid composition composed of:		
1	Sildenafil Citrate	140.48
2	Sodium hydroxide	30.12
3	Mannitol	149.45
4	HPC-L	4.0
5	Purified Water	q.s to 1000 g
Blend Composition		
6	Citric acid	64.63
7	Talc	3.0

Comparative Example N

A comparative pharmaceutical formulation was prepared essentially as described in Example 3 by using a blend composition containing Magnesium stearate and the other following ingredients**:**

	Ingredients	Quantity per 1000 Stick Packs (g)
Lyophilized Granules prepared from liquid composition composed of:		
1	Sildenafil Citrate	140.48
2	Sodium hydroxide	30.12
3	Mannitol	149.45
4	HPC-L	4.0
5	Purified Water	q.s to 1000 g
Blend Composition		
6	Citric acid	64.63
7	Magnesium stearate	3.0

Comparative Example O

A comparative pharmaceutical formulation was prepared essentially as described in Example 3 by using a blend composition containing Talc, Magnesium stearate and the other following ingredients:

	Ingredients	Quantity per 1000 Stick Packs (g)
Lyophilized Granules prepared from liquid composition composed of:		
1	Sildenafil Citrate	140.48
2	Sodium hydroxide	30.12
3	Mannitol	149.45
4	HPC-L	4.0
5	Purified Water	q.s to 1000 g
Blend Composition		
6	Citric acid	64.63
7	Talc	1.50
8	Magnesium stearate	1.50

Comparative Example P

A comparative pharmaceutical formulation was prepared essentially as described in Example 3 by using a blend composition containing liquid paraffin and the other following ingredients:

	Ingredients	Quantity per 1000 Stick Packs (g)
Lyophilized Granules prepared from liquid composition composed of:		
1	Sildenafil Citrate	140.48
2	Sodium hydroxide	30.12
3	Mannitol	149.45
4	HPC-L	4.0
5	Purified Water	q.s to 1000 g
Blend Composition		
6	Citric acid	64.63
7	Liquid paraffin	3.0

Comparative Example Q

A comparative pharmaceutical formulation was prepared essentially as described in Example 3 by using a blend composition containing Sorbitol and the other following ingredients:

	Ingredients	Quantity per 1000 Stick Packs (g)
Lyophilized Granules prepared from liquid composition composed of:		
1	Sildenafil Citrate	140.48
2	Sodium hydroxide	30.12
3	Mannitol	149.45
4	HPC-L	4.0
5	Purified Water	q.s to 1000 g
Blend Composition		
6	Sorbitol	604.87

Example 5: Solifenacin Composition

A formulation of Solifenacin was prepared using the following ingredients:

	Ingredients	Quantity per 1000 Stick Packs (g)
Lyophilized Granules prepared from liquid composition composed of:		
1	Solifenacin	10.0
2	Polacrillin Potassium (Resin)	20.0
3	Maltodextrin	67.0
4	Citric acid	3.0
5	Water	q.s. to 400 g
Blend Composition		
6	Sorbitol	394.5
7	Citric acid	3.0
8	Liquid paraffin	2.5

Manufacturing procedure

I. Lyophilized Granules

1. Solifenacin was dissolved in 140 g of water using a magnetic/overhead stirrer for 5 minutes.
2. Citric acid was added under continuous stirring using a magnetic/overhead stirrer.
3. Resin was added under continuous stirring and the dispersion formed was kept under stirring for 1 hour.
4. Maltodextrin was dissolved in 140 g of water in separate beaker & then added in to step 3 under continuous stirring.
5. The final weight of the solution/dispersion was made to 400 g using purified water.
6. Mixing of the solution/dispersion was continued for 10 minutes in a magnetic/overhead stirrer.
7. This solution/dispersion was filled in stainless steel tray and freeze-dried in a lyophilizer.
8. After complete freeze drying, the lyophilized cake was sieved through a #40 sieve to obtain the lyophilized granules.

II. Blend Composition

9. Sorbitol was passed through a #40 sieve and mixed with crushed and sieved citric acid in a double cone blender for 2 minutes at 10 RPM.

10. Liquid paraffin was added dropwise to 40 g of the mixture from step 9, and mixed manually to obtain a uniformly distributed blend composition.
11. The blend composition was sieved through a #60 sieve and then mixed with remaining mixture from step 9 using a double cone blender for 3 minutes at 10 RPM to obtain the final blend composition.

III. Formulation

12. The lyophilized granules from step 8 were mixed with the final blend composition from step 11 in a double cone blender for 5 minutes at 10 RPM to obtain the free flowing Solifenacin formulation.
13. The free flowing composition was filled into stick packs and sealed, at 500 mg per stick pack (see Figure 5).

Comparative Example R

A granule formulation was prepared essentially as described in Example 5 using the following ingredients:

	Ingredients	**Quantity per 1000 Stick Packs (g)**
1	Solifenacin	16.5
2	Polacrillin Potassium (Resin)	33.0
3	Maltodextrin	110.5
4	Citric acid	5.0
5	Water	q.s. to 682 g

Comparative Example S

A comparative pharmaceutical formulation was prepared essentially as described in Example 5 by using a blend composition containing talc and the other following ingredients:

	Ingredients	Quantity per 1000 Stick Packs (g)
Lyophilized Granules prepared from liquid composition composed of:		
1	Solifenacin	16.5
2	Polacrillin Potassium (Resin)	33.0
3	Maltodextrin	110.5
4	Citric acid	5.0
5	Water	q.s. to 682 g
Blend Composition		
6	Citric acid	3.0
7	Talc	2.5

Comparative Example T

A comparative pharmaceutical formulation was prepared essentially as described in Example 5 by using a blend composition containing Magnesium stearate and the other following ingredients:

	Ingredients	Quantity per 1000 Stick Packs (g)
Lyophilized Granules prepared from liquid composition composed of:		
1	Solifenacin	16.5
2	Polacrillin Potassium (Resin)	33.0
3	Maltodextrin	110.5
4	Citric acid	5.0
5	Water	q.s. to 682 g
Blend Composition		
6	Citric acid	3.0
7	Magnesium stearate	2.5

Comparative Example U

A comparative pharmaceutical formulation was prepared essentially as described in Example 5 by using a blend composition containing Talc, Magnesium stearate and the other following ingredients:

	Ingredients	Quantity per 1000 Stick Packs (g)
Lyophilized Granules prepared from liquid composition composed of:		
1	Solifenacin	16.5
2	Polacrillin Potassium (Resin)	33.0
3	Maltodextrin	110.5
4	Citric acid	5.0
5	Water	q.s. to 682 g
Blend Composition		
6	Citric acid	3.0
7	Talc	1.3
8	Magnesium stearate	1.3

Comparative Example V

A comparative pharmaceutical formulation was prepared essentially as described in Example 5 by using a blend composition containing liquid paraffin and the other following ingredients:

	Ingredients	Quantity per 1000 Stick Packs (g)
Lyophilized Granules prepared from liquid composition composed of:		
1	Solifenacin	16.5
2	Polacrillin Potassium (Resin)	33.0
3	Maltodextrin	110.5
4	Citric acid	5.0
5	Water	q.s. to 682 g
Blend Composition		
6	Citric acid	3.0
7	Liquid paraffin	2.5

Comparative Example W

A comparative pharmaceutical formulation was prepared essentially as described in Example 5 by using a blend composition containing Sorbitol and the other following ingredients:

	Ingredients	Quantity per 1000 Stick Packs (g)
Lyophilized Granules prepared from liquid composition composed of:		
1	Solifenacin	10.0
2	Polacrillin Potassium (Resin)	20.0
3	Maltodextrin	67.0
4	Citric acid	3.0
5	Water	q.s. to 400 g
Blend Composition		
6	Sorbitol	400.0

Example 6: Bulk Density & Tapped Density results

Bulk and tapped density are important to understand flow properties of formulations. The bulk density of a material is the ratio of the mass to the volume (including the interparticulate void volume) of an untapped powder sample. The tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample. The tapped density is obtained by mechanically tapping a graduated cylinder containing the sample until little further volume change is observed. Because the interparticulate interactions influencing the bulking properties of a powder are also the interactions that interfere with powder flow, a comparison of the bulk and tapped densities can give a measure of the relative importance of these interactions in a given powder. Such a comparison is often used as an index of the ability of the powder to flow, for example the Compressibility Index or the Hausner Ratio:

Compressibility Index (Carr Index):

$$\frac{100(V_0 - V_f)}{V_0}$$

Hausner Ratio:

$$\frac{V_0}{V_f}$$

V_0 = unsettled apparent volume (bulk volume) V_f = final tapped volume

The lower the values of Compressibility Index and Hausner Ratio, the better the flow properties of the powder.

Procedure for determining bulk density:

According to US Pharmacopoeia (USP) Chapter <616>, Method I, using a 100-mL cylinder readable to 1 mL and an amount of powder such that its untapped apparent volume is between 50 and 100 mL.

Procedure for determining tapped density:

According to US Pharmacopoeia (USP) Chapter <616>, Method I, with the following details:

- A 100-mL graduated cylinder (readable to 1 mL) weighing 130 ± 16 g is mounted on a holder weighing 240 ± 12 g.
- 10, 500, and 1250 taps on the powder sample are conducted and corresponding volumes V_{10}, V_{500}, and V_{1250} to the nearest graduated unit are measured.
- If the difference between V_{500} and V_{1250} is less than or equal to 1 mL, V_{1250} is the tapped volume.
- If the difference between V_{500} and V_{1250} exceeds 1 mL, the measurement is repeated in increments such as 1250 taps, until the difference between succeeding measurements is less than or equal to 1 mL.

- **Results:**

Formulations	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr Index	Hausner Ratio
Example 1	**0.476**	**0.652**	**26.984**	**1.370**
Example 2	**0.50**	**0.64**	**21.67**	**1.28**
Comparative Example A	0.192	0.333	42.308	1.733
Comparative Example B	0.200	0.341	41.333	1.705
Comparative Example C	0.231	0.385	40.000	1.667
Comparative Example D	0.208	0.366	43.056	1.756
Comparative Example E	0.160	0.273	41.489	1.709
Comparative Example F	0.24	0.37	33.87	1.51
Comparative Example G	0.24	0.41	41.27	1.70
Comparative Example H	0.27	0.39	30.91	1.45
Comparative Example I	0.26	0.39	34.48	1.53
Comparative Example J	0.21	0.41	49.32	1.97
Comparative Example K	0.44	0.63	29.41	1.42
Example 3	**0.417**	**0.690**	**39.69**	**1.655**
Example 4	**0.444**	**0.714**	**37.77**	**1.607**
Comparative Example L	0.278	0.488	43.065	1.756
Comparative Example M	0.308	0.541	43.07	1.757
Comparative Example N	0.323	0.556	41.93	1.722
Comparative Example O	0.323	0.541	40.32	1.676
Comparative Example P	0.286	0.513	44.28	1.795
Comparative Example Q	0.408	0.667	38.77	1.633
Example 5	**0.429**	**0.667**	**35.714**	**1.556**
Comparative Example R	0.217	0.375	42.029	1.725
Comparative Example S	0.224	0.395	43.284	1.763
Comparative Example T	0.238	0.395	39.683	1.658
Comparative Example U	0.238	0.395	39.683	1.658
Comparative Example V	0.188	0.375	50.000	2.000
Comparative Example W	0.435	0.667	34.783	1.533

Example 7: Angle of Repose:

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to interparticulate friction or resistance to movement between particles. The angle of repose is a constant, three-dimensional angle (relative to the horizontal base) assumed by a cone-like pile of material.

Procedure (as per USP General Chapter <1174>):

The angle of repose is formed on a fixed base with a retaining lip to retain a layer of powder on the base. The base should be free of vibration. The height of the funnel is varied to carefully build up a symmetrical cone of powder. Care should be taken to prevent vibration as the funnel is moved. The funnel height should be maintained approximately 2–4 cm from the top of the powder pile as it is being formed in order to minimize the impact of falling powder on the tip of the cone. If a symmetrical cone of powder cannot be successfully or reproducibly prepared, this method is not appropriate. The angle of repose is determined by measuring the height of the cone of powder and calculating the angle of repose (a) from the following equation:

tan (a) = height/0.5 base.

Results:

Formulations	**Angle of repose (degree)**	**Flow behavior**
Example 1	**34**	**Good**
Example 2	**36.66**	**Fair**
Comparative Example A	These formulations did not pass through the funnel as such due to rat hole formation and poor flow properties and hence could not be analyzed	
Comparative Example B		
Comparative Example C		
Comparative Example D		
Comparative Example E		
Comparative Example F		
Comparative Example G		
Comparative Example H		
Comparative Example I		
Comparative Example J		
Comparative Example K	41.10	weak
Example 3	**34**	**Good**
Example 4	**35**	**Good**
Comparative Example L	37	Fair
Comparative Example M	Formulations did not pass through the funnel as such due to rat hole formation and poor flow properties and hence could not be analyzed	
Comparative Example N		
Comparative Example O	36	Fair
Comparative Example P	Formulations did not pass through the funnel as such due to rat hole formation and poor flow properties and hence could not be analyzed	
Comparative Example Q	32	Good
Example 5	**31**	**Good**
Comparative Example R	36	Fair
Comparative Example S	Formulations did not pass through the funnel as such due to rat hole formation and poor flow properties and hence could not be analyzed	
Comparative Example T	36	Fair

Comparative Example U	37	Fair
Comparative Example V	Formulations did not pass through the funnel as such due to rat hole formation and poor flow properties and hence could not be analyzed	
Comparative Example W	35	Good

Example 8: Moisture Content:

The pharmaceutical formulations were placed in open petri dishes, which were then placed in a Climacel maintained at 25°C/75% RH for simulating exposure to high humidity. The moisture content of each formulation was analyzed after 1, 2 and 6 hours in the Climacel. Moisture content was evaluated by using USP General Chapter 921 – Water Determination method.

Results:

Formulations	Moisture Content (wt%)			
	Initial	1 hour	2 hours	6 hours
Example 1	**1.19**	**2.27**	**3.65**	**6.82**
Example 2	**1.49**	**3.08**	**5.80**	**7.88**
Comparative Example A	4.24	5.33	8.10	12.49
Comparative Example B	4.40	5.12	8.31	13.11
Comparative Example C	4.57	5.77	6.98	13.28
Comparative Example D	4.11	5.45	8.67	14.54
Comparative Example E	4.34	5.48	7.96	13.64
Comparative Example F	5.30	6.97	10.60	14.54
Comparative Example G	5.31	8.16	11.65	15.23
Comparative Example H	4.95	7.77	9.96	14.11
Comparative Example I	5.10	7.91	9.78	14.23
Comparative Example J	6.32	9.00	10.92	14.57
Comparative Example K	1.66	4.60	5.86	9.77
Example 3	**2.1**	**3.01**	**4.45**	**10.95**
Example 4	**2.09**	**2.89**	**4.68**	**11.39**
Comparative Example L	4.73	6.72	9.12	14.24
Comparative Example M	4.08	5.94	7.57	12.92
Comparative Example N	4.07	6.69	7.9	12.75
Comparative Example O	4.1	5.83	8.26	13.43
Comparative Example P	4.03	6.54	8.54	13.41
Comparative Example Q	2.05	3.2	4.86	12.06
Example 5	**1.17**	**2.98**	**3.8**	**5.65**
Comparative Example R	4.65	10.19	14.64	13
Comparative Example S	4.46	13.56	10.87	13.26
Comparative Example T	4.14	10.24	10.11	13.42
Comparative Example U	4.62	14.82	8.59	10.14
Comparative Example V	4.95	12.68	8.58	12.42
Comparative Example W	1.94	2.49	3.11	8.37

Example 9: Anti-Sticking Properties

The anti-sticking properties of the formulation was measured by determining the residual content using the following procedure:

Procedure:

The pharmaceutical formulations were filled uniformly in 10 stick packs made from flexible laminates as depicted in Figure 5. The fill weight of each stick pack was noted down for further reference. Filled stick packs were sealed using a sealing machine. The sealed stick packs were kept on vibratory shifter for 30 minutes for entrapping the formulations into the corners of the stick pack. Each stick pack was opened by cutting from one sealed side. The formulation from each stick pack was removed and weighed on a calibrated balance to measure the amount of formulation recovered from each stick pack. The residual content was calculated using the following formula:

(Fill weight of stick pack) – (Content recovered from stick pack) = Residual content

Results

Formulations	% Residual content	Standard Deviation
Example 1	**2.04**	**0.39**
Example 2	**1.35**	**0.35**
Comparative Example A	6.49	1.14
Comparative Example B	4.98	0.99
Comparative Example C	7.39	0.73
Comparative Example D	5.11	1.03
Comparative Example E	4.10	0.99
Comparative Example F	4.76	0.80
Comparative Example G	4.75	0.91
Comparative Example H	4.02	0.56
Comparative Example I	4.04	0.34
Comparative Example J	3.02	2.20
Comparative Example K	1.94	0.50
Example 3	**0.63**	**0.11**
Example 4	**0.6**	**0.11**
Comparative Example L	2.28	0.86
Comparative Example M	2.78	0.57
Comparative Example N	2.08	0.43
Comparative Example O	2.25	0.34
Comparative Example P	1.42	0.65
Comparative Example Q	0.96	0.20
Example 5	**2.15**	**0.22**
Comparative Example R	4.72	1.22
Comparative Example S	8.19	3.88
Comparative Example T	10.65	4.50
Comparative Example U	10.68	5.85
Comparative Example V	* Wet Mass with very poor flow	
Comparative Example W	4.73	3.09

CLAIMS

1. A free-flowing solid pharmaceutical formulation comprising (1) lyophilizing granules comprising one or more active ingredients and (2) a blend composition comprising sorbitol and liquid paraffin, wherein

the blend composition comprises 95% to 99.9% by weight of sorbitol, 0.1% to 5% by weight of liquid paraffin, and 0% to 4% by weight of citric acid, and

the formulation comprises 0.01% to 30% by weight of active ingredient(s), 70% to 99.99% by weight of the blend composition, and 0% to 30% by weight of the other pharmaceutically acceptable excipients.

2. The formulation according to claim 1 comprising 0.1% to 28% by weight of active ingredient(s), 72% to 99.9% by weight of the blend composition, and 5% to 30% by weight of one or more other pharmaceutically acceptable excipients.

3. The formulation according to claim 1 or 2 wherein the blend composition comprises 96% to 99.5% by weight of sorbitol, 0.5% to 4% by weight of liquid paraffin, and 0.5% to 2% by weight of citric acid.

4. The formulation according to claim 1 or 2 wherein the blend composition consists of 95% to 99.9% by weight of sorbitol, 0.1% to 5% by weight of liquid paraffin, and 0% to 4% by weight of citric acid.

5. The formulation according to claim 4 wherein the blend composition consists of 96% to 99.5% by weight of sorbitol, 0.5% to 4% by weight of liquid paraffin, and 0.5% to 2% by weight of citric acid.

6. The formulation according to any one of claims 1 to 5 wherein the active ingredient is selected from the group consisting of desloratadine, montelukast, solifenacin, silodosin, sildenafil and pharmaceutically acceptable salts of the

aforementioned active ingredients, and desmopressin and desmopressin acetate.

7. The formulation according to any one of claims 1 to 5 wherein the active ingredient is desloratadine, or a pharmaceutically acceptable salt thereof.

8. The formulation according to any one of claims 1 to 5 wherein the active ingredient is montelukast or a pharmaceutically acceptable salt thereof.

9. The formulation according to any one of claims 1 to 5 wherein the active ingredient is silodosin or a pharmaceutically acceptable salt thereof.

10. The formulation according to any one of claims 1 to 5 wherein the active ingredient is sildenafil or a pharmaceutically acceptable salt thereof.

11. The formulation according to any one of claims 1 to 8 wherein the active ingredient is solifenacin or a pharmaceutically acceptable salt thereof.

12. The formulation according to any one of claims 1 to 5 wherein the active ingredient is desmopressin or desmopressin acetate.

13. A package containing the formulation according to any one of the preceding claims.

14. The package according to claim 13 selected from the group consisting of a sachet and a stick pack.

15. A process for the manufacture of a pharmaceutical formulation as defined in any one of claims 1 to 12 comprising:

(a) forming a lyophilized powder by subliming the solvent from a preparation comprising one or more active ingredients and a solvent;

(b) forming a blend composition comprising or consisting of sorbitol, liquid paraffin and optionally citric acid;

(c) mixing the blend composition obtained in step (b) with the lyophilized powder obtained in step (a), wherein the blend composition comprises or

consists of 95% to 99.9% by weight of sorbitol, 0.1% to 5% by weight of liquid paraffin, and 0% to 4% by weight of citric acid, and the formulation comprises 0.01% to 30% by weight of active ingredient(s), 70% to 99.99% by weight of the blend composition, and 0% to 30% by weight of other pharmaceutically acceptable excipients.