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(54) **Title:** STABILIZATION OF MOISTURE-SENSITIVE DRUGS

(57) **Abstract:** Described are stability-enhancing formulations of drugs that are sensitive to moisture. The formulations comprise co-granulates containing a moisture-sensitive drug and an excipient selected from fructose, xylitol, maltitol, and mixtures thereof. Also described are methods of producing a pharmaceutical tablet. The method comprises forming a blend of a moisture-sensitive drug and a first excipient selected from fructose, xylitol, maltitol, and mixtures thereof; spraying the blend with water to produce granules; drying and milling the granules; mixing a second excipient with the granules; and compressing into tablets.



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STABILIZATION OF MOISTURE-SENSITIVE DRUGS

The present disclosure relates generally to stability-enhancing formulations of drugs that are sensitive to moisture.

5 There are many drug substances that exhibit undesirable changes when exposed to a moist environment, prior to administration. Depending on the particular drug, the changes can result from internal molecular changes such as hydrolysis, or from reactions with other components of the drug product formulation or with the atmosphere. Since drug product manufacturing cannot always be conducted in an environment having a low humidity, there
10 can be significant drug degradation during the various production operations, prior to packaging a product. After packaging, stability of the products can be affected by moisture transfer through packaging components, as well as reactions involving components of the package atmosphere. Also, repeatedly opening and closing a package during normal use can expose the contents to atmospheric moisture. Due to normal fluctuations in the moisture
15 content of the atmosphere, undesired changes that will be experienced with a moisture-sensitive drug are not predictable.

A frequent result of contact between a sensitive drug compound and moisture is a reaction that results in formation of one or more different chemical species. This can be simply a hydration of the drug molecule that results in different dissolution or other physical
20 properties, or it can involve a reaction that produces a different compound having a diminished intended pharmacological activity. In some instances, a new molecular entity that is produced can have a radically different pharmacological activity that is harmful when administered.

Regulatory agencies require demonstration of drug stability, before marketing approval can be given. This requirement includes maintenance of at least a minimum drug content
25 during the expected shelf-life of the formulated product, while the unopened package is stored in a specified temperature and humidity environment. Where the drug is particularly sensitive to moisture, sometimes the packaging will incorporate a desiccant component to absorb moisture entering through the packaging materials and/or during repeated brief openings of the package.

30 There have been some approaches developed for reducing the effects of moisture on sensitive drugs. Sometimes the drug substance can be combined with a protective hydrophobic material, such as an oil or polymer. However, this frequently leads to other undesired effects,

such as altering the drug solubility parameters, and can create difficulties in processing to manufacture a formulated product.

According to U.S. Patent No. 7,807,715 it is necessary to enhance the chemical stability of fesoterodine and its salts in formulations, and this can be accomplished by granulating a mixture of the drug and a stabilizer selected from the group consisting of sorbitol, xylitol, polydextrose, isomalt, dextrose, and combinations thereof. The granulate is combined with excipient materials and compressed into tablet products. This patent, in its examples, teaches that mannitol, maltitol, and lactose act to increase the degradation of fesoterodine hydrogen fumarate, during storage of their granulates under various temperature and humidity conditions, so would not be desirable in granulation mixtures.

The drug fesoterodine fumarate is the active ingredient in a product being sold as TOVIAZ® tablets to treat urinary incontinence and frequency problems. Inactive ingredients are glyceryl behenate, hypromellose, indigo carmine aluminum lake, lactose monohydrate, soya lecithin, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and xylitol. The xylitol apparently is used as a drug stabilizer in the TOVIAZ product.

International Patent Application Publication No. WO 2012/098499 describes stabilizing fesoterodine fumarate by forming a molecular dispersion of the drug with an alkyl hydroxyalkylcellulose ether, a hydroxyalkylcellulose ether, an ester of either, or a mixture of any two or more thereof. The dispersion is said to not contain the drug in its crystalline or amorphous form, but has suitable stability.

European Patent Application Publication No. 2 508 173 describes stabilizing fesoterodine, or a salt or solvate thereof, by granulating with sucrose, polyethylene glycol, cyclodextrin, maltodextrin, or combinations thereof.

Considering all of these teachings, it becomes apparent that predicting the stability of a drug, when it is to be combined with various excipient substances, is not possible. Considerable effort is required to find suitable combinations that will deliver a moisture-sensitive drug in a desired, reproducible manner, facilitate pharmaceutical dosage form preparation, and provide the required drug stability during manufacturing, storage, and use.

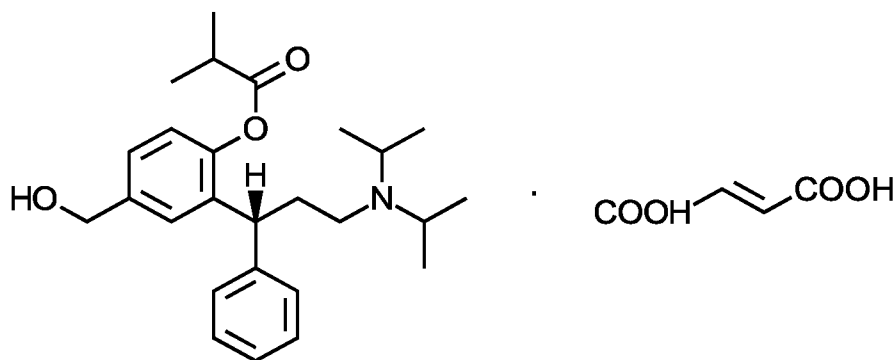
DETAILED DESCRIPTION

Numerous moisture-sensitive drugs are known, such as amlodipine, felodipine, fesoterodine, isradipine, nifedipine, nimodipine, nisoldipine, etc. Mention of any drug compound is intended to include the base drug as well as any of its salts, esters, solvates, etc. that will be useful for delivering the drug. In the following discussion, fesoterodine is used as a representative for moisture-sensitive drugs, for purposes of brevity. However, the scope of the present disclosure is not to be limited to this particular drug.

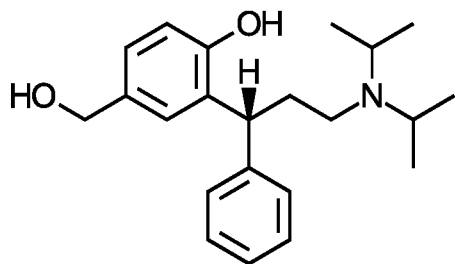
Moisture sensitivity is intended to encompass any undesired changes in a drug substance that occur as a result of exposure to moisture, such as atmospheric humidity. Such changes can involve drug compound degradation that forms one or more impurities, changes in physical characteristics, morphological changes, etc.

In some instances, drug stability is evidenced by a slow rate of degradant compound formation, over time. The period of time, during which a drug must remain stable, i.e., maintain its potency and/or impurity content in a formulation, varies according to commercial specifications set by the manufacturer. For example, a particular product might be required to maintain certain potency specifications for a period of six months, one year, two years, or some other time following manufacturing. The established shelf life of a product presumes maintenance in the original packaging, in specified temperature and humidity environments.

Fesoterodine fumarate is used to treat urinary incontinence and has the structural formula shown below. A chemical name for the drug is isobutyric acid 2-[(R)-3-diisopropylammonium-1-phenylpropyl]-4-(hydroxymethyl) phenyl ester hydrogen fumarate.



When exposed to moisture, fesoterodine tends to degrade, forming *inter alia* a deacylated molecule having the structural formula shown below, or a salt thereof. This degradant can be used as a marker for fesoterodine degradation.



Products containing fesoterodine can be analyzed for their fesoterodine content and the contents of the various degradant impurities, using high performance liquid chromatography (HPLC) methods.

5 Degradation of fesoterodine and other moisture-sensitive drugs can be inhibited by co-granulation of the drug with certain excipients, and use of the granulates to prepare the desired solid dosage forms such as tablets and capsules. Particularly useful excipients for co-granulation are fructose and mixtures of xylitol and maltitol.

Several sugars and sugar alcohols have been tested to determine their suitability for co-granulation with fesoterodine. The experiments involved wet granulating the drug with
10 varying proportions of excipient, using small amounts of water. In the cases of xylitol and maltitol, respectively having mean particle sizes of 300 μm and 200 μm , it was found that simply mixing the drug and excipient powders formed hard agglomerated particles that would not pass easily through a 40 mesh sieve (having 0.42 mm openings), indicating that further
15 processing the mixtures into formulated products might involve some difficulties. Several other excipients were found to not stabilize the drug, some of them even appearing to promote degradation of the drug.

It has now been determined that fructose, and mixtures of xylitol and maltitol, can advantageously be used in co-granulations with moisture-sensitive drugs to promote stability
20 of the drugs in their pharmaceutical formulations.

Co-granulation can be conducted as a wet process or a dry process. In a wet process, a moving bed of a mixture of powdered ingredients, including a drug substance, is sprayed with a small quantity of a liquid to form granules. The liquid can be aqueous or non-aqueous, and can optionally contain one or more dissolved or dispersed excipients, such as a binder or
25 antioxidant. In some instances, the liquid will be a neat liquid ingredient, such as water, an alcohol, a substituted or unsubstituted hydrocarbon, etc. It is not necessary that the liquid ingredient is capable of dissolving some portion of a drug or solid excipient in the powder mixture, as typically it is only required to wet the particles. However, liquids having a degree

of solvent properties frequently are used. After the spraying is completed, the granules may be sized by passing through a sieve and are dried. Dry granules can further be subjected to a size reduction procedure, if desired.

Dry granulation may include passing a powder mixture through a roller compactor, then crushing and sizing the compacted material. Alternatively, a powder mixture can be compacted by a compression process called “slugging,” producing large (e.g., about 25 mm) flat tablets or plates, which are then crushed and sized.

Following the granulation procedure, drug-containing granules can be mixed with desired excipients and the mixture can be compressed into tablets or filled into capsules.

Solid pharmaceutical dosage units contain one or more drug substances, together with any desired number of excipients, such as, but not limited to, one or more of diluents, binders, drug stabilizers, disintegrants, glidants, lubricants, release rate modifiers, preservatives, antioxidants, coatings, colorants, flavoring agents, etc.

Various useful fillers or diluents according to the present application include, but are not limited to, starches, cellulose derivatives, sugars, and the like. Various grades of lactose include, but are not limited to, lactose monohydrate, lactose DT, lactose anhydrous, and others. Different starches include, but are not limited to, maize starch, potato starch, rice starch, wheat starch, pregelatinized starch, and others. Different cellulose compounds that can be used include crystalline cellulose and powdered cellulose. Other useful diluents include, but are not limited to, carmellose, sugar alcohols such as mannitol, sorbitol, and xylitol, calcium carbonate, magnesium carbonate, dibasic calcium phosphate, and tribasic calcium phosphate.

Various useful binders according to the present application include, but are not limited to, hydroxypropyl celluloses in various grades, hydroxypropyl methylcelluloses (e.g., Methocel™ products) and useful in various grades, polyvinylpyrrolidones (such as grades K25, K29, K30, and K90), copovidones (e.g., Plasdone™ S 630), powdered acacia, gelatin, guar gum, carbomers (e.g., Carbopol™ products), methylcelluloses, polymethacrylates, and starches. A binder may optionally be included in a granulating fluid.

Modification of drug release into fluids of the gastrointestinal tract sometimes is desirable. For example, a very soluble drug that is rapidly metabolized by the body can desirably be released from a pharmaceutical dosage form over a period of hours, following oral administration. This can be accomplished by including polymeric substances in the body of a

tablet. Suitable polymeric substances for this purpose include the “binder” materials described above, as well as polymers described below as being useful for forming coatings.

Various useful disintegrants include, but are not limited to, carmellose calcium, carboxymethylstarch sodium, croscarmellose sodium, crospovidones, examples of commercially available crospovidone products including but not limited to crosslinked povidones, Kollidon™ CL from BASF (Germany), Polyplasdone™ XL, XI-10, and INF-10 from ISP Inc. (USA), and low-substituted hydroxypropyl celluloses. Examples of low-substituted hydroxypropyl celluloses include, but are not limited to, low-substituted hydroxypropylcellulose LH11, LH21, LH31, LH22, LH32, LH20, LH30, LH32 and LH33 (all supplied by Shin-Etsu Chemical Co., Ltd.). Some other useful disintegrants include sodium starch glycolate, colloidal silicon dioxide, and various starches.

In embodiments, formulations of the present application contain at least one antioxidant, for enhancing the stability of a drug. The antioxidant may be present either as a part of the composition or a packaging component. The antioxidant is present in amounts effective to retard decomposition of the drug that is susceptible to oxidation. In embodiments, the content of an antioxidant in the formulations ranges from about 0.001 to 10 weight percent, with respect to the active agent content. Non-limiting examples of antioxidants include one or more of ascorbic acid and its salts, tocopherols, sulfite salts such as sodium metabisulfite or sodium sulfite, sodium sulfide, butylated hydroxyanisole, butylated hydroxytoluene, ascorbyl palmitate, and propyl gallate. Other suitable antioxidants will be readily recognized by those skilled in the art.

Useful lubricants include magnesium stearate, glyceryl monostearate, palmitic acid, talc, carnauba wax, calcium stearate sodium, sodium or magnesium lauryl sulfate, calcium soaps, zinc stearate, polyoxyethylene monostearates, calcium silicate, silicon dioxide, hydrogenated vegetable oils and fats, stearic acid, and any combinations thereof.

One or more glidant materials, which improve the flow of powder blends, pellets, etc. and help to minimize dosage form weight variations, can be used. Useful glidants include, but are not limited to, silicon dioxide, talc, kaolin, and any combinations thereof.

Coloring agents can be used to color code compositions, for example, to indicate the type and dosage of the therapeutic agent therein. Suitable coloring agents include, without limitation, natural and/or artificial compounds such as FD&C coloring agents, natural juice

concentrates, pigments such as titanium oxide, silicon dioxide, iron oxides, zinc oxide, any combinations of two or more thereof, and the like.

Solid pharmaceutical dosage forms may be provided with outer coatings that modify the release characteristics of the contained drug or drugs, after administration. Other types of coatings are merely esthetic, or serve to protect the dosage forms against physical damage, moisture ingress, etc. during packaging, shipping, and use. The coatings typically comprise at least one pH-independent or pH-dependent polymer as the major ingredient, frequently also including any one or more of various additives.

Suitable pH-independent polymers that are considered to be water-soluble include both solution formers and polymeric substances that do not form true solutions, but swell upon contact with water to form colloidal dispersions having the appearance of solutions. Representative members include, but are not limited to: polyvinyl alcohols; cellulose ethers, such as methylcelluloses having nominal viscosities in the range of about 3 to about 5000 mPa•s, hydroxyethyl celluloses having nominal viscosities in the range of about 3 to about 5000 mPa•s, hydroxyethylmethyl celluloses having nominal viscosities in the range of about 100 to 70000 mPa•s, hydroxypropyl celluloses ("HPC") having nominal viscosities in the range of about 10 to about 5000 mPa•s, and hydroxypropyl methylcelluloses (hypromelloses or "HPMC"), of various grades such as "E", "F", and "K," having nominal viscosities in the range of about 1 to about 20000 mPa•s; polyvinylpyrrolidones (povidones or "PVP") having nominal molecular weights in the range of about 4000 to about 1,300,000; copovidone; macrogols having molecular weights in the range of about 400 to about 8000; graft copolymers of polyvinyl alcohols and macrogols; polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymers; and polymethacrylates. The viscosities are usually measured using a 2% by weight aqueous solution, at 20° C.

Water-insoluble pH-independent polymers include substances such as methylcelluloses, ethylcelluloses, cellulose acetates, and others. As is known in the art, some polymers have an aqueous solubility that depends on their molecular weights.

Various pH-dependent polymers for use in the present application include, but are not limited to, polymers and copolymers of acrylic and methacrylic acids, cellulose acetate butyrates, cellulose acetate phthalates, hydroxypropyl methylcellulose phthalates and succinates, poly(methyl methacrylate), poly(ethylmethacrylate), poly(butylmethacrylate), poly(isobutylmethacrylate), poly(hexylmethacrylate), poly(isodecylmethacrylate), poly(lauryl

methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), and any mixtures of two or more thereof.

Useful additives for coatings include, but are not limited to, plasticizers, antiadherents, opacifiers, solvents, and optionally colorants, lubricants, pigments, antifoam agents, and
5 polishing agents.

Various useful plasticizers include, but are not limited to, substances such as castor oil, diacetylated monoglycerides, dibutyl sebacate, diethyl phthalate, glycerin, polyethylene glycol, propylene glycol, triacetin, and triethyl citrate, and mixtures thereof. The type of plasticizer depends upon the type of coating agent. An opacifier such as titanium dioxide may also be
10 present in amounts ranging from about 0.5-20%, based on the total weight of the coating.

Anti-adhesives are frequently used in film coating processes to avoid sticking effects during film formation and drying. An example of a useful anti-adhesive for this purpose is talc. An anti-adhesive is frequently present in the film coating in amounts about 0.5-15%, based upon the total weight of the coating.

Various solvents that can be used in processes of preparing pharmaceutical formulations of the present application include, but are not limited to, water, methanol, ethanol, acetone, diacetone, polyols, polyethers, oils, esters, alkyl ketones, methylene chloride, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol
20 monoethyl ether, dimethylsulfoxide, N,N-dimethylformamide, tetrahydrofuran, and any mixtures of two or more thereof.

The foregoing lists of excipient substances are not exhaustive, but are representative of members of the various categories. Those skilled in the art will be aware of many other useful substances, and their use is specifically contemplated herein. Also, it is well-known that many
25 excipients can serve more than one purpose in pharmaceutical formulations. Co-processed excipients, such as combinations of lactose and starch, microcrystalline cellulose and colloidal silica, etc. can sometimes have advantages over using the individual components.

Particle sizes of powders and suspended powders may be determined using any of conventional technologies, including sieve sizing, optical microscopy, Coulter Counter™
30 electrical zone sensing methods, laser light diffraction (such as with equipment sold by Malvern Instruments Ltd. and Horiba Instruments, Inc.), etc. Particle size distributions frequently are represented by terms such as D₁₀, D₅₀, D₉₀, and the like, where the numerical

portion is the percentage of measured particles having a dimension that does not exceed the given size. For example, $D_{90}=10\text{ }\mu\text{m}$ means that 90 percent of the particles have sizes that do not exceed $10\text{ }\mu\text{m}$ in any dimension. Suspended particle sizes optionally can be measured using various physiological media to form the suspensions, e.g., simulated gastric fluid (pH 1.2), acetate buffer (pH 4.5) and simulated intestinal fluid (pH 5.5-7.5), or using water or a buffered or unbuffered aqueous medium.

Pharmaceutical products can be tested for their drug dissolution characteristics, such as using test 711 "Dissolution" in *United States Pharmacopeia 24*, United States Pharmacopeial Convention, Inc., Rockville, Maryland, 1999 ("USP"). Various fluids can be used as the dissolution media, including acids, buffers, simulated digestive tract fluids, etc., and many of these are defined in various monographs of the USP. An example of a procedure uses "Apparatus 2," which has a vessel containing a medium that is stirred with a rotating paddle. Typically, a dosage unit is immersed into the medium and samples of the medium are withdrawn at intervals for drug content analysis, frequently using HPLC techniques.

An example of a HPLC method for analyzing fesoterodine fumarate and its degradants was described by B. V. R. Reddy et al., "A Validated Stability-Indicating HPLC Assay Method for Determination of Fesoterodine Fumarate," *RASĀYAN Journal of Chemistry*, Vol. 5(2), pages 239-245, 2012.

The following examples describe certain specific aspects and embodiments in greater detail, are provided solely for purposes of illustration, and should not be construed as limiting the scope of the disclosure in any manner.

EXAMPLE 1

The effects of excipient substances on the stability of fesoterodine hydrogen fumarate are studied by mixing powders of the drug and excipients, then storing samples of the mixtures open to the atmosphere at 40°C and 75% relative humidity, for 2 days or 5 days. Xylitol alone and maltitol alone are used as comparator excipients. The amounts of drug-related degradant impurities are determined in the prepared mixtures and stored samples, using a HPLC procedure. Results are shown in the following table, where amounts of drug degradants are expressed as percentages of the initial drug concentration. In the table, "DF" is deacyl fesoterodine and drug:excipient proportions are by weight.

Mixture	Degradant Content					
	DF			Total		
	Initial	2 Days	5 Days	Initial	2 Days	5 Days
Drug + xylitol (1:2)	0.116	0.126	0.137	0.324	0.321	0.370
Drug + xylitol (1:6)	0.102	0.128	0.119	0.283	0.309	0.406
Drug + xylitol (1:9)	0.108	0.139	0.136	0.314	0.406	0.403
Drug + fructose (1:9)	0.104	0.384	--	0.365	0.866	--
Drug + maltitol (1:3)	0.110	0.335	0.478	0.383	0.540	0.816
Drug + maltitol (1:6)	0.112	0.358	0.515	0.315	0.582	0.868
Drug + maltitol (1:9)	0.116	0.433	0.549	0.310	0.625	0.893
Drug + maltitol (1:12)	0.108	0.586	0.796	0.297	0.831	1.236
Drug + xylitol + maltitol (1:2:2)	0.108	0.120	0.124	0.320	0.295	0.329
Drug + xylitol + maltitol (1:2:4)	0.111	0.132	0.131	0.345	0.335	0.339
Drug + xylitol + maltitol (1:2:7)	0.120	0.127	0.128	0.396	0.303	0.372

EXAMPLE 2

An extended release tablet formulation is prepared, using the ingredients in the table below.

Ingredient	mg/Tablet
Fesoterodine fumarate	8
Fructose, granular	72
Water*	2
StarLac®†	77.5
Hypromellose (Methocel® K100M Premium)	120
Hypromellose (Methocel K4M Premium)	24
Talc (500 grade)	8.5
Glyceryl behenate (COMPRITOL® 888 ATO)	10
Coating	
OPADRY® AMB 80W105004 (dark blue)**	15
Water*	60

† A spray-dried composition containing 85% α -lactose monohydrate and 15% maize starch, from Meggle Group.

* Evaporates during processing, not present in the final product.

** OPADRY AMB products, from Colorcon, are formulated moisture barrier coating compositions containing a polyvinyl alcohol polymer.

Formulation process:

1. Fesoterodine fumarate and fructose are blended, then granulated by spraying with water. The granules are dried and milled to an average particle size not exceeding 1200 μm .

2. StarLac and the hypromellose ingredients are blended, then mixed with the granules. Talc and glyceryl behenate are sequentially added with blending.

3. The mixture is compressed into tablets, coated with the coating suspension, and dried.

Tablets prepared as above and commercial TOVIAZ fesoterodine tablets, 8 mg are tested for their drug dissolution characteristics using the USP dissolution method in apparatus 2 (paddle) with 900 mL of phosphate buffer (pH 6.8) and 75 rpm stirring. The results are shown in the following table, wherein the numeric values are cumulative percentages of the label drug content that dissolve.

Time (hours)	TOVIAZ (Lot No. V111327)	Example 2
0	0	0
1	14	11
2	24	22
4	40	41
6	52	56
8	62	69
12	76	83
16	85	93
20	89	98

Prepared tablets are analyzed for their drug degradant impurities, both as prepared and following four weeks of storage, open to the atmosphere at 40°C and 75% relative humidity.

Results obtained using a HPLC procedure are shown in the table below, where numeric values are percentages of the label drug content.

Impurity	Initial	Stored
Deacyl fesoterodine	0.053	0.146
Total	0.305	0.461

EXAMPLE 3

- 5 An extended release tablet formulation is prepared, using the ingredients in the table below.

Ingredient	mg/Tablet
Fesoterodine fumarate	8
Xylitol	16
Maltitol	32
Water*	1.5
StarLac	95.5
Hypromellose (Methocel K100M Premium)	120
Hypromellose (Methocel K4M Premium)	24
Talc (500 grade)	8.5
Glyceryl behenate (COMPRITOL 888 ATO)	10
Coating	
Opadry AMB 80W105004 (dark blue)	15
Water*	60

* Evaporates during processing, not present in the final product.

The formulation process is similar to that described in Example 2, except that a mixture of maltitol and xylitol is used for granulation with the drug, instead of fructose.

- 10 Tablets prepared as above and commercial TOVIAZ fesoterodine tablets, 8 mg are tested for their drug dissolution characteristics using the USP dissolution method in apparatus 2 (paddle) with 900 mL of phosphate buffer (pH 6.8) and 75 rpm stirring. The results are shown in the following table, wherein the numeric values are cumulative percentages of the label drug content that dissolve.

Time (hours)	TOVIAZ (Lot No. V111327)	Example 3
0	0	0
1	14	14
2	24	24
4	40	40
6	52	52
8	62	62
12	76	76
16	85	84
20	89	89

Prepared tablets are analyzed for their drug degradant impurities, both as prepared and following four weeks of storage, open to the atmosphere at 40°C and 75% relative humidity. Results obtained using a HPLC procedure are shown in the table below, where numeric values are percentages of the label drug content.

Impurity	Initial	Stored
Deacyl fesoterodine	0.052	0.200
Total	0.288	0.492

5

EXAMPLE 4

Tablets containing 4 mg (Formulation A) or 8 mg (Formulation B) of fesoterodine fumarate are prepared using the ingredients in the following table.

Ingredient	Kilograms	
	Formulation A	Formulation B
Fesoterodine fumarate	0.5	1
Fructose, granular	9	9
Water*	0.25	0.25
StarLac	10.187	9.687
Hypromellose (Methocel K100M Premium)	15	15
Hypromellose (Methocel K4M Premium)	3	3

Talc (500 grade)	1.063	1.063
Glyceryl behenate (COMPRITOL 888 ATO)	1.25	1.25
Coating		
OPADRY AMB 80W99006 (light blue)	1.875	--
OPADRY AMB 80W105004 (dark blue)	--	1.875
Water*	7.5	7.5

* Evaporates during processing, not present in the final product.

Formulation process:

1. Milled fesoterodine fumarate ($D_{90} \leq 10 \mu\text{m}$) and fructose are passed through a 20 mesh sieve and blended in a high shear mixer, then water is sprayed onto the mixture. The formed granules are briefly kneaded, then dried at about 45° C until the loss on drying at 65° C is 0.5% or less. Granules are passed through a comminuting mill having a screen with 1.02 mm round holes and 30% open area.

2. StarLac and the hypromellose ingredients are passed through a 20 mesh sieve and blended with the granules, then talc (passing through a 30 mesh sieve) is added and blended. Glyceryl behenate is passed through a 30 mesh sieve, added to the blender, and blending is continued to achieve uniformity.

3. The blend is compressed to form tablets weighing 320 mg and having a hardness about 10 kiloponds.

4. The coating suspension is sprayed onto tablets in a coating pan, and the coated tablets are dried.

ADDITIONAL DISCLOSURE

Further specific aspects and embodiments are described in the following paragraphs A-F.

A. A pharmaceutical formulation comprising a co-granulate containing a moisture-sensitive drug and fructose.

B. The pharmaceutical formulation of paragraph A, wherein a weight ratio of drug to fructose is about 1:9.

C. A pharmaceutical formulation comprising a co-granulate containing a moisture-sensitive drug, xylitol, and maltitol.

D. The pharmaceutical formulation of paragraph C, wherein a weight ratio of drug to xylitol to maltitol is about 1:2:4.

E. The pharmaceutical formulation listed in any of paragraphs A-D, wherein a drug is fesoterodine fumarate.

5 F. Tablets prepared according to the procedure described in any of Examples 2-4.

What is claimed is:

1. A pharmaceutical formulation comprising a co-granulate comprising a moisture-sensitive drug and an excipient selected from the group consisting of fructose, xylitol, maltitol, and mixtures thereof.
- 5 2. The pharmaceutical formulation of claim 1, wherein the excipient comprises fructose.
3. The pharmaceutical formulation of claim 2, wherein the moisture-sensitive drug and fructose are present in a weight ratio of about 1:9.
4. The pharmaceutical formulation of claim 1, wherein the excipient comprises a mixture of xylitol and maltitol.
- 10 5. The pharmaceutical formulation of claim 4, wherein the moisture-sensitive drug, xylitol, and maltitol are present in a weight ratio in the range of about 1:2:2 to 1:2:7.
6. The pharmaceutical formulation of claims 4 and 5, wherein the moisture-sensitive drug, xylitol, and maltitol are present in a weight ratio of about 1:2:4.
7. The pharmaceutical formulation of any one of claims 1 to 6, wherein the moisture-sensitive drug comprises fesoterodine fumarate.
- 15 8. The pharmaceutical formulation of any one of claims 1 to 7, further comprising a diluent, a binder, a drug stabilizer, a disintegrant, a glidant, a lubricant, a release rate modifier, a preservative, an antioxidant, a coating, a colorant, a flavoring agent, or combinations thereof.
- 20 9. A method of producing a pharmaceutical tablet, the method comprising
forming a blend of a moisture-sensitive drug and a first excipient selected from
the group consisting of fructose, xylitol, maltitol, and mixtures thereof;
spraying the blend with water to produce granules;
drying and milling the granules;
25 mixing a second excipient with the granules; and
compressing into tablets.
10. The method of claim 9, wherein the first excipient comprises fructose.
11. The method of claim 9, wherein the first excipient comprises a mixture of xylitol and maltitol.
- 30 12. The method of any one of claims 9 to 11, wherein the second excipient is selected from the group consisting of diluent, binder, drug stabilizer, disintegrant, glidant, lubricant,

release rate modifier, preservative, antioxidant, coating, colorant, flavoring agent, or combinations thereof.

13. The method of any one of claims 9 to 12, wherein the moisture-sensitive drug comprises fesoterodine fumarate.
- 5 14. The method of any one of claims 9 to 13, wherein the granules are dried and milled to an average particle size of less than 1200 μm .
15. The method of any one of claims 9 to 14, further comprising coating the tablets with a coating suspension.

AMENDED CLAIMS

received by the International Bureau on 22 August 2014 (22.08.2014)

What is claimed is:

1. A pharmaceutical formulation comprising a co-granulate comprising a moisture-sensitive drug and an excipient selected from the group consisting of fructose, a mixture of xylitol and maltitol, and combinations thereof.
2. The pharmaceutical formulation of claim 1, wherein the excipient is fructose.
3. The pharmaceutical formulation of claim 2, wherein the moisture-sensitive drug and fructose are present in a weight ratio of about 1:9.
4. The pharmaceutical formulation of claim 1, wherein the excipient is a mixture of xylitol and maltitol.
5. The pharmaceutical formulation of claim 4, wherein the moisture-sensitive drug, xylitol, and maltitol are present in a weight ratio in the range of about 1:2:2 to 1:2:7.
6. The pharmaceutical formulation of claim 5, wherein the moisture-sensitive drug, xylitol, and maltitol are present in a weight ratio of about 1:2:4.
7. The pharmaceutical formulation of any one of claims 1 to 6, wherein the moisture-sensitive drug comprises fesoterodine fumarate.
8. The pharmaceutical formulation of claim 1, further comprising a diluent, a binder, a drug stabilizer, a disintegrant, a glidant, a lubricant, a release rate modifier, a preservative, an antioxidant, a coating, a colorant, a flavoring agent, or combinations thereof.
9. A method of producing a pharmaceutical tablet, the method comprising
forming a blend of a moisture-sensitive drug and a first excipient selected from
the group consisting of fructose, a mixture of xylitol and maltitol, and combinations
thereof;
spraying the blend with water to produce granules;

drying and milling the granules;
mixing a second excipient with the granules; and
compressing into tablets.

- 5 10. The method of claim 9, wherein the first excipient is fructose.
11. The method of claim 9, wherein the first excipient is a mixture of xylitol and maltitol.
12. The method of claim 9, wherein the second excipient is selected from the group
10 consisting of diluent, binder, drug stabilizer, disintegrant, glidant, lubricant, release rate
modifier, preservative, antioxidant, coating, colorant, flavoring agent, or combinations
thereof.
13. The method of any one of claims 9 to 12, wherein the moisture-sensitive drug
15 comprises fesoterodine fumarate.
14. The method of any one of claims 9 to 12, wherein the granules are dried and milled to
an average particle size of less than 1200 μm .
- 20 15. The method of any one of claims 9 to 12, further comprising coating the tablets with a
coating suspension.
16. A tablet for oral administration comprising a co-granulate consisting of fesoterodine
fumarate and fructose in a ratio of about 1:9, and one or more additional
25 pharmaceutically acceptable excipients.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/021824**A. CLASSIFICATION OF SUBJECT MATTER****A61K 47/36(2006.01)i, A61K 9/20(2006.01)i, A61K 47/30(2006.01)i**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K 47/36; A61K 9/14; A61K 47/10; A61K 31/4422; A23L 1/00; A01N 37/02; A61K 31/22; A61K 31/198; B29C 1/04; A61K 9/20; A61K 47/30

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & keywords: moisture sensitive drug, fructose, xylitol, maltitol, granule, fesoterodine fumarate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 7807715 B2 (ARTH, C. et al.) 5 October 2010 See column 4, lines 2-3, column 23, lines 47-48, column 26, lines 3-6, column 32, lines 21-60; and claims 1, 6-9.	1-5, 9-12
X	WO 2008-062435 A2 (ALKEM LABORATORIES LTD.) 29 May 2008 See claims 1-3, 6.	1-5
A	US 6039813 A (PEPPER, T. et al.) 21 March 2000 See abstract; and claims 1, 13, 29.	1-5, 9-12
A	US 2007-0122476 A1 (HANSHEW, JR., D. D. et al.) 31 May 2007 See abstract; and claims 1-3, 7, 15-20.	1-5, 9-12
A	US 2011-0123692 A1 (EROMA, O.-P. et al.) 26 May 2011 See abstract; and claims 1, 33-37.	1-5, 9-12



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"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)

"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

"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

"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

"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

"&" document member of the same patent family

Date of the actual completion of the international search

23 June 2014 (23.06.2014)

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Name and mailing address of the ISA/KR

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INTERNATIONAL SEARCH REPORTInternational application No.
PCT/US2014/021824**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 6-8, 13-15
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2014/021824

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US 7807715 B2	05/10/2010	US 2008-0138421 A1 US 2009-0117159 A1 US 2010-0130606 A1 US 2013-0296423 A1 US 8088398 B2 US 8501723 B2	12/06/2008 07/05/2009 27/05/2010 07/11/2013 03/01/2012 06/08/2013
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