SOLID MOLECULAR DISPERSION OF FESOTERODINE

The present invention relates to a solid dispersion comprising from 3:97 to 12:88 weight % ratio of fesoterodine hydrogen fumarate: an alkyl hydroxyalkylcellulose ether or a hydroxyalkylcellulose ether, or an ester of either thereof, or a mixture of any two or more thereof, in which the fesoterodine hydrogen fumarate is stabilised in the dispersion in a form not corresponding to its crystalline or amorphous form.

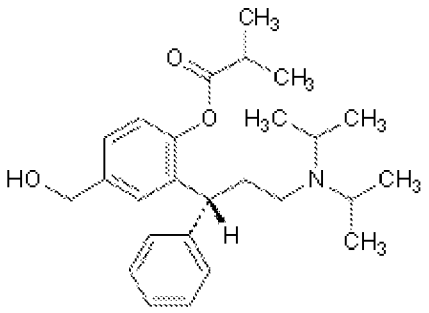
The present dispersion achieves comparable or improved chemical stability in respect of the fesoterodine hydrogen fumarate component to that observed for the commercial xylitol-based tablet formulation, in particular by minimising the levels of the two primary degradation products SPM7605 and SPM7675. The present dispersion is believed to achieve this stabilising effect as it displays the characteristics of a solid molecular dispersion.

Preferably, the present invention relates to a solid molecular dispersion comprising from 3:97 to 12:88 weight % ratio of fesoterodine hydrogen fumarate: an alkyl hydroxyalkylcellulose ether or a hydroxyalkylcellulose ether, or an ester of either thereof, or a mixture of any two or more thereof.

The invention also relates to an inert core bead or particle which is coated with said dispersion, to modified-release coating of such a bead or particle, and to a pharmaceutical capsule formulation comprising such coated beads or particles.

The invention further relates to an inert core bead or particle which is coated with said dispersion and to the manufacture of pharmaceutical tablets comprising such beads or particles.

Fesoterodine, that is 2-[(1*R*)-3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl isobutyrate, R-(+)-2-(3-(diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl isobutyrate or *R*-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, has the following chemical structure:



Fesoterodine and its physiologically acceptable acid salts are disclosed in WO99/58478 for use as antimuscarinic agents that are useful for the treatment of, inter alia, urinary incontinence.

Fesoterodine hydrogen fumarate is disclosed in WO01/35957A1 and US 6858650B1 as a preferred crystalline, physiologically compatible, acid addition salt form of fesoterodine.

Fesoterodine *per se* has only been previously prepared as an unstable oil which presents difficulty for pharmaceutical formulation, processing and use.

Fesoterodine hydrogen fumarate *per se* is crystalline and is suitable for pharmaceutical formulation and processing but it requires refrigeration in order to maintain adequate stability on storage for pharmaceutical use.

WO2007/141298A1 discloses pharmaceutical compositions comprising fesoterodine, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable stabiliser selected from xylitol, sorbitol, polydextrose, isomalt, dextrose, and combinations thereof. Such compositions are suitable for the manufacture of tablets and preferred tablet compositions described include those comprising fesoterodine hydrogen fumarate, hydroxypropyl methyl cellulose (HPMC) and xylitol which have shown excellent stability on tablet storage under ambient conditions for over 2 years. Indeed, a tablet composition comprising fesoterodine hydrogen fumarate, hydroxypropyl methyl cellulose (HPMC) and xylitol is the drug formulation that is used commercially in view of its acceptable shelf-life. The commercial 4mg dose formulation is described in WO2007/141298A1 on page 44, Table 1, Example

C, and the commercial 8mg dose formulation on page 45, Table 2, Example H. Studies have shown that the presence of a stabiliser such as xylitol is essential to achieve a pharmaceutically acceptable stability profile.

WO2010/043408 describes microencapsulated fesoterodine formulations but does not disclose formulations containing fesoterodine or a salt thereof, in combination with a polymeric binder, or a solid molecular dispersion thereof.

There is a need for further stable pharmaceutically acceptable formulations comprising fesoterodine hydrogen fumarate. More particularly, there is a need for a further stable formulation comprising fesoterodine hydrogen fumarate that has comparable, or improved, stability on storage than the current xylitol-based tablet formulation that is sold commercially in which the fesoterodine hydrogen fumarate exists in a crystalline form.

It has now been found that a pharmaceutical formulation comprising a solid dispersion comprising from 3:97 to 12:88 weight % ratio of fesoterodine hydrogen fumarate: an alkyl hydroxyalkylcellulose ether or a hydroxyalkylcellulose ether, or an ester of either thereof, or a mixture of any two or more thereof, in which the fesoterodine hydrogen fumarate is not in crystalline or amorphous form in said dispersion, has comparable or improved stability on storage to the commercial xylitol-based tablet formulation described above. Without wishing to be bound by theory, it is believed that there exists a solid molecular dispersion of fesoterodine hydrogen fumarate in an alkyl hydroxyalkylcellulose ether or a hydroxyalkylcellulose ether, or an ester of either thereof, or a mixture of any two or more thereof, in said dispersion.

As such, it has now been found that a pharmaceutical formulation comprising a solid molecular dispersion comprising from 3:97 to 12:88 weight % ratio of fesoterodine hydrogen fumarate: an alkyl hydroxyalkylcellulose ether or a hydroxyalkylcellulose ether, or an ester of either thereof, or a mixture of any two or more thereof, has comparable or improved stability on storage to the commercial xylitol-based tablet formulation. The observed stability is directly attributable to the solid molecular dispersion present in the formulation. This finding is unexpected in

that it has been surprisingly found that fesoterodine hydrogen fumarate can be stabilised in the presence of a polymeric binder (e.g. HPMC) but in the absence of a stabiliser such as xylitol. Such a pharmaceutical formulation is particularly suitable for development as a modified release, bead-in-capsule formulation of the drug for paediatric use, or for the manufacture of pharmaceutical tablets.

The term "solid dispersion" refers to a group of solid materials comprising at least two different components, generally a polymeric matrix and a drug. The matrix can be either crystalline or amorphous. The drug molecules can be dispersed throughout the matrix as particles composed of amorphous molecular clusters, or as crystals (highly ordered 3D-molecular arrangement), of the drug. Alternatively, if the drug is dispersed within the matrix at the molecular level then this is termed a "solid molecular dispersion". In a solid molecular dispersion the predominant intermolecular interaction is defined as being between each drug molecule and each polymer molecule, even if the drug molecules are present as (e.g.) molecular dimers in the solid molecular dispersion. What is essential is that each drug molecule predominantly interacts with a polymeric matrix environment. For a summary of the characteristics of solid dispersion systems see "*Pharmaceutical applications of solid dispersion systems*", Chiou W L, Riegelman S, Journal of Pharmaceutical Sciences (1971), 60(9), 1281-1302.

The present invention relates to a solid molecular dispersion comprising from 3:97 to 12:88 weight % ratio of fesoterodine hydrogen fumarate: an alkyl hydroxyalkylcellulose ether or a hydroxyalkylcellulose ether, or an ester of either thereof, or a mixture of any two or more thereof.

More preferably, the solid molecular dispersion comprises about either a 1:9 or 1:19 weight % ratio of fesoterodine hydrogen fumarate: an alkyl hydroxyalkylcellulose ether or a hydroxyalkylcellulose ether, or an ester of either thereof, or a mixture of any two or more thereof.

Most preferably, the solid molecular dispersion consists essentially of about a 1:9 or 1:19 weight % ratio of fesoterodine hydrogen fumarate: an alkyl

hydroxyalkylcellulose ether or a hydroxyalkylcellulose ether, or an ester of either thereof, or a mixture of any two or more thereof.

The alkyl hydroxyalkylcellulose ether or the hydroxyalkylcellulose ether, or an ester of either thereof, that is used as a component of the dispersion is classified as a polymeric binder. A polymeric binder is defined as a pharmaceutically acceptable material consisting of a polymeric material that is generally used to promote adhesion of a drug to itself or to another formulation component, such as the surface of an inert core bead or particle. Typical polymeric binders used in drug layering operations are water soluble to allow application of the mixture of drug and polymeric binder in an aqueous solution, although water insoluble binders can also be used, as appropriate.

The polymeric binder used in the present invention is an alkyl hydroxyalkylcellulose ether or a hydroxyalkylcellulose ether, or an ester of either thereof, or a mixture of any two or more thereof (referred to herein as the "cellulose ether component") (see Encyclopaedia of Polymer Science and Technology, John Wiley & Sons, Inc., Vol. 5, 507-532, "Cellulose Ethers"(2002) for general information on cellulose ethers).

Examples of an alkyl hydroxyalkylcellulose ether are hydroxypropyl methyl cellulose (HPMC, compendium name = hypromellose, e.g., Methocel E3 or E5 – trade marks), hydroxyethyl methyl cellulose (HEMC) and hydroxybutyl methyl cellulose (HBMC).

Examples of a hydroxyalkylcellulose ether are hydroxyethylcellulose (HEC) and hydroxypropylcellulose (HPC).

An example of an ester of an alkyl hydroxyalkylcellulose ether is hydroxypropyl methyl cellulose acetate succinate (HPMCAS) (see Pharmaceutical Research, 26(6), 1419-1431 (2009).

Most preferably, hydroxypropyl methyl cellulose (e.g. Methocel E5 LV – trade mark) is used as the sole cellulose ether component.

The present solid dispersion/solid molecular dispersion may be prepared by first preparing a solution of fesoterodine hydrogen fumarate and the alkyl

hydroxyalkylcellulose ether or hydroxyalkylcellulose ether, or an ester of either thereof, or a mixture of any two or more thereof, e.g. hydroxypropyl methyl cellulose alone, in a suitable solvent, e.g. water. This solution may be applied to inert core beads or particles and then the coated inert core beads or particles dried to form immediate-release (IR) beads or particles/granules. Fluid bed coating of the spouted fluid bed type assisted with a draft tube (such as fluid bed Wurster coating) or tumbling fluid bed coating (such as rotary or tangential granulation) can be used for the coating process (see, e.g., Fukumori, Yoshinobu and Ichikawa, Hideki (2006) 'Fluid Bed Processes for Forming Functional Particles', Encyclopedia of Pharmaceutical Technology, 1: 1, 1773 — 1778). Preferably, the fluid-bed coating is conducted using a fluid-bed coater in Wurster configuration.

Such inert core beads or particles are preferably comprised of a water-soluble or -swellable material and may be any such material that is conventionally used as inert core beads or particles or any other pharmaceutically acceptable water-soluble or water-swellable material that can be made into core beads, particles or pellets. Preferably, the inert core beads or particles are spheres of sucrose/starch (Sugar Spheres NF – trade mark) or sucrose crystals, or are extruded and dried spheres comprised of excipients such as microcrystalline cellulose or lactose. Preferably, the inert core beads or particles are comprised of microcrystalline cellulose alone or in combination with one or more sugars, or are comprised of lactose. Yet more preferably, the inert core beads or particles are comprised of microcrystalline cellulose or lactose alone. Most preferably, the inert core beads or particles are Celphere (trade mark – Asahi Kasei) microcrystalline cellulose spheres of CP-507 grade with a 500-710 micron diameter, or lactose, e.g. Pharmatose 110M (trade mark).

The immediate-release (IR) beads or particles/granules obtained may be coated with a modified-release (MR) layer that provides acceptable control of the release rate of fesoterodine in a patient.

The modified-release layer may be a sustained-release (SR) coating which is designed to release the drug at a steady rate. The sustained-release coating may be

a polymer coating such as a cellulose ester, a cellulose ether or an acrylic polymer, or a mixture of any thereof. Preferred coatings include ethyl cellulose, cellulose acetate or cellulose acetate butyrate, or a mixture of any thereof. The coating may be applied as a solution in an organic solvent or as an aqueous dispersion or latex. The coating may be applied using a fluid bed coater, a Wurster coater or a rotary bed coater. If desired the permeability of the coating may be adjusted by blending 2 or more of such coating materials. The porosity of the coating may be tailored by adding a pre-determined amount of a finely-divided, water-soluble material, such as a sugar, salt or water-soluble polymer (e.g. hydroxypropyl cellulose, hydroxypropyl methyl cellulose), to a solution or dispersion of the membrane-forming polymer to be used. When the dosage form resulting is ingested into the aqueous medium of the gastro-intestinal tract, these water-soluble additives are leached out of the membrane, leaving pores which facilitate release of the drug. The membrane coating can also be modified by the addition of a plasticiser such as diethyl phthalate, polyethyleneglycol-400, triacetin, triacetin citrate or propylene glycol. Most preferably, the sustained release coating comprises ethyl cellulose (e.g. Ethocel Standard 10 Premium – trade mark) in combination with hydroxypropylcellulose (e.g. Klucel EF – trade mark) as a pore former.

In a preferred embodiment of the invention, the modified/sustained-release coating is achieved by first preparing a solution of the selected MR/SR components (e.g. ethylcellulose and hydroxypropylcellulose) in a suitable solvent, e.g. aqueous isopropanol, and, secondly, by applying this solution to the IR beads or particles/granules, e.g. using a fluid bed coater as described above (e.g. using a fluid-bed coater in Wurster configuration), and drying the resulting MR/SR-coated beads or particles/granules. The composition and thickness of the MR/SR coating may be varied to achieve the desired drug release profile.

The modified-release layer may be a delayed-release coating which is designed, on dosage form ingestion, to incorporate a delay in time before the onset of drug release. The delayed-release coating may be a pH-sensitive polymer such as cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methyl

cellulose phthalate, polyvinyl acetate phthalate, or may be an anionic acrylic copolymer of methacrylic acid and methyl methacrylate such as those available from RohmPharma, e.g. EUDRAGIT L-100 (trade mark), EUDRAGIT L-30 D-55 (trade mark), EUDRAGIT S-100 (trade mark) or EUDRAGIT FS 30D (trade mark), or a mixture of any thereof. The thickness and composition of the delayed-release coating may be adjusted to give the desired delayed-release properties. In general, thicker coatings are more resistant to erosion and, consequently, provide a longer delay in the release of the drug, as do coatings which are designed to dissolve above ph7.

Typical IR and MR layer coating thicknesses used for the purposes of the present invention are as follows:

- IR layer – 10-100 micrometres, preferably 25-30 micrometres
- MR layer – 10-100 micrometres, preferably 10-15, 15-20 or 20-25 micrometres.

The IR or MR beads or particles/granules according to the invention may be filled into drug capsules by conventional techniques. Preferably, gelatin or hydroxypropyl methyl cellulose capsules are used for pharmaceutical formulation purposes.

Alternatively, the immediate-release beads or particles/granules obtained may be formed into pharmaceutical tablet formulations by conventional techniques.

The solid dispersion, the solid molecular dispersion, the IR/MR beads or particles/granules coated therewith, and the pharmaceutical formulations of the invention, may be used as medicaments. In particular, they may be used for the treatment of incontinence, preferably urinary incontinence. Most preferably, they may used for the treatment of urge urinary incontinence or mixed urinary incontinence.

The invention also provides a solid molecular dispersion obtainable by (a) achieving a solution of fesoterodine hydrogen fumarate and an alkyl hydroxyalkylcellulose ether or a hydroxyalkylcellulose ether, or an ester of either

thereof, or a mixture of any two or more thereof, in from 3:97 to 12:88 weight % ratio, and (b) by drying to form said dispersion.

The following Examples illustrate the invention:

EXAMPLE 1

Preparation of a solution of fesoterodine hydrogen fumarate and HPMC (hypromellose)

Component	Quantity/unit; (g/kg)
Fesoterodine hydrogen fumarate	30.069*
Hypromellose (Methocel E5 LV)	270.630*
Sterile water for irrigation (to be removed in manufacturing process and does not appear in final product)	3995.000*

(*quantities based on dry finished product with no overage. Can incorporate 10% overage of the quantities of the coating materials to allow for in-process loss due to tubing volumes, coating of containers, etc.)

- Set-up an overhead stirrer and impeller.
- Weigh out 90 % of water into an appropriate sized vessel.
- Set the agitator speed to produce a suitable vortex and gradually add the hypromellose to the water and mix for at least 4 hours, preferably overnight, ensuring the solution does not foam. Cover to prevent evaporation while stirring (ensure there are no lumps after stirring).
- Set-up an overhead stirrer and impeller .Weigh out the remaining 10% water into an appropriately sized vessel and add fesoterodine hydrogen fumarate under agitation. Mix for 10 minutes or until the fesoterodine hydrogen fumarate is fully dissolved. Cover to prevent evaporation while stirring.
- Add the fesoterodine hydrogen fumarate solution to the hypromellose solution under agitation.

- Mix for a minimum of 10 minutes or until all lumps have dissolved.
- Determine the quantity of liquid lost due to evaporation. Replace lost liquid with water, rinsing out the fesoterodine hydrogen fumarate solution-containing vessel.
- Ensure that the solution prepared is protected from sunlight at all times.

EXAMPLE 2

Preparation of a solid molecular dispersion of fesoterodine hydrogen fumarate and HPMC (hypromellose) on microcrystalline cellulose beads using Glatt GPCG 1.1 coater (fesoterodine hydrogen fumarate immediate release (IR) beads)

- Heat Glatt GPCG 1.1 in 6" Wurster configuration to a product temp of ~ 56 ºC.
- Quickly charge the microcrystalline cellulose spheres (500 – 710µm) (Celphere CP-507) (699.301 g/kg - quantity based on dry finished product with no overage. Can incorporate 10% overage of the quantity to allow for in-process loss due to tubing volumes, coating of containers, etc.) into the fluidising chamber of the Glatt GPCG 1.1 coater.
- Once the beads are fully fluidised commence spraying within 1 minute.
- Example target coating conditions for the Glatt GPCG 1.1:

Airflow: 80 m^3/hr (Set)
Inlet Air Temperature: 80ºC (Set)
Atomisation Pressure: 2.0 Bar (Set)
Maximum Spray rate: 12 g/min
Nozzle diameter: 1.2mm
Wurster Gap: 20mm
Filters: Socks (20µm mesh)
Filter shake: 15 secs every 5 mins
Tubing: Silicon, 0.125" ID x 0.062" wall
Pump: Watson Marlow 505Du peristaltic

- Commence spraying at ~7 g/min (3.9 rpm), after 10 minutes increase the spray rate to ~10g/min (5.6 rpm). After an additional 10 minutes ramp up the spray rate to ~12 g/min (6.9 rpm).
- The product temperature during coating (at/near maximum spray rate in steady state) should be approximately 50 ºC.
- Continue spraying until all the theoretical quantity of coating solution has been sprayed onto the beads.
- Cover the solution to prevent evaporation while coating.
- After coating, dry the beads by allowing the product temperature to rise by 2 ºC before shutting down the fluidisation air & heat.
- The beads should be sieved through an 850 µm sieve to screen out agglomerates.

EXAMPLE 3

Preparation of a solid molecular dispersion of fesoterodine hydrogen fumarate and HPMC (hypromellose) on microcrystalline cellulose beads using Glatt GPCG 3.1 coater (fesoterodine hydrogen fumarate immediate release (IR) beads)

- Heat Glatt GPCG 3.1 in 6" Wurster configuration to a product temp of ~ 56 ºC.
- Quickly charge the microcrystalline cellulose spheres (500 – 710µm) (Celphere CP-507) (699.301 g/kg - quantity based on dry finished product with no overage. Can incorporate 10% overage of the quantity to allow for in-process loss due to tubing volumes, coating of containers, etc.) into the fluidising chamber of Glatt GPCG 3.1 coater.
- Example target coating conditions for the Glatt GPCG 3.1:

Airflow: 50 CFM

Inlet Air Temperature: 75 ºC (Set)

Atomisation Pressure: 2.0 Bar (Set)

Maximum Spray rate: ~13.5 g/min

Inlet Air Dew Point: 15 ºC
Nozzle diameter: 1.2 mm
Wurster Gap/Partition Height: 30 mm
Filters: Socks (20µm mesh)
Filter shake: 15 secs every 5 mins
Tubing: Silicon, 0.125" ID x 0.062" wall
Pump: Peristaltic

- Commence spraying at ~8 g/min, after 10 minutes increase the spray rate to ~10g/min. After an additional 10 minutes ramp up the spray rate to ~12 g/min.
- After 1 hour the spray rate can be increased to ~13.5 g/min if the process appears stable with low agglomeration levels.
- The product temperature during coating (at/near maximum spray rate in steady state) should be approximately 50 ºC.
- Continue spraying until all the theoretical quantity of coating solution has been sprayed onto the beads.
- Cover the solution to prevent evaporation while coating.
- After coating, dry the beads by allowing the product temperature to rise by 2 ºC before shutting down the fluidisation air & heat.
- The beads should be sieved through an 850 µm (20 Mesh) sieve to screen out agglomerates.

EXAMPLE 4

Preparation of 10% (w/w of final bead) modified release (MR) fesoterodine hydrogen fumarate beads

Component	Quantity/unit: (g/kg) (Quantities based on dry finished product and do not include overages)
Fesoterodine hydrogen fumarate immediate release (IR) beads (Example	900.000

2 or Example 3)	
Ethylcellulose (Ethocel Standard 10 Premium)	80.000
Hydroxypropylcellulose (Klucel EF)	20.000
Isopropyl alcohol (to be removed in manufacturing process and does not appear in final product)	1327.474
Sterile water for irrigation (to be removed in manufacturing process and does not appear in final product)	181.019
TOTAL	1000.000

(a) Modified release solution preparation

- Calculate MR solution components with 10% overage (all components except fesoterodine hydrogen fumarate immediate release beads).

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	Overall solution - theoretical	Overall solution – 10% overage	Ethylcellulose solution	Hydroxypropylcellulose solution
Ethylcellulose	a	A	A	
Hydroxypropylcellulose	b	B		B
Isopropyl alcohol	c	C	F-A-G	F-B-G
Water	d	D	G	G
Total	a+b+c+d = e	E	F	F
Half total		E/2 = F		
Half water		D/2 = G		

- Set-up an overhead stirrer and impeller.

- Weigh out the required quantity of isopropyl alcohol and 50% of the water into an appropriate sized vessel.
- Set the agitator speed to produce a suitable vortex and gradually add the ethylcellulose to the water and mix for at least 4 hours, ensuring the mixture does not foam.
- Cover to prevent evaporation while stirring (ensure there are no lumps once stirring has finished).
- Set-up an overhead stirrer and impeller.
- Weigh out the remaining quantity of isopropyl alcohol and 50% of the water into an appropriate sized vessel.
- Set the agitator speed to produce a suitable vortex and gradually add the hydroxypropylcellulose to the water and mix for at least 4 hours.
- Cover to prevent evaporation while stirring.
- Add the hydroxypropylcellulose solution to the ethylcellulose solution under agitation. Mix for 10 minutes.
- Determine the quantity of liquid lost due to evaporation. Replace lost liquid with an isopropyl alcohol /water (88:12) solution, rinsing out the hydroxypropylcellulose-containing vessel, and mix for 10 mins.
- Cover to prevent evaporation.

<u>(b) Coating of IR beads with modified release layer coating using Glatt GPCG 1.1 fluid bed coater</u>

- Heat Glatt GPCG 1.1 in 6" Wurster configuration to a product temperature of ~ 40 ºC.
- Quickly charge the fesoterodine hydrogen fumarate immediate release beads into the fluidising chamber of the Glatt GPCG 1.1 fluid bed coater.
- Pre-heat the spheres to ~ 46ºC.
- Coat the spheres with the modified release solution (Step (a)) under the following target conditions:

Airflow: 80 m^3/hr (Set)
Inlet Air Temperature: 50ºC (Set)
Atomisation Pressure: 2.0 Bar (Set)
Maximum Spray rate: 13.5 g/min
Nozzle diameter: 1.2mm
Wurster Gap: 20mm
Filters: Bonnets (0.4 mm mesh)
Filter shake: 15 secs every 5 mins
Tubing: Silicon, 0.125" ID x 0.062" wall
Pump: Watson Marlow 505Du peristaltic

- Commence spraying at ~ 9.5 g/min (approximately 6 rpm), after 5 minutes increase the spray rate to ~11.5g/min (approximately 7 rpm). After an additional 5 minutes ramp up the spray rate to ~13.5 g/min (approximately 8 rpm).
- The pump rate can be adjusted as necessary to achieve the required spray rates.
- The product temperature during coating (at/near maximum spray rate in steady state) should be approximately 39 ºC.
- Continue spraying until all the theoretical quantity of modified release solution has been sprayed onto the beads.
- Cover the solution to prevent evaporation during spraying.
- After coating, dry the beads by allowing the product temperature to rise by 2 ºC before shutting down the fluidisation air & heat.
- The beads should be sieved through a 1000 µm sieve (or US Standard 18 Mesh) to screen out agglomerates.

<u>(c) Coating of IR beads with modified release layer coating using Glatt GPCG 3.1 fluid bed coater</u>

- Heat Glatt GPCG 3.1 in 6" Wurster configuration to a product temperature of ~ 40 ºC
- Quickly charge the fesoterodine hydrogen fumarate immediate release beads into the fluidising chamber of the Glatt GPCG 3.1 fluid bed coater.
- Coat the spheres with the modified release solution (Step (a)) under the following target conditions:

Airflow: 50 CFM
Inlet Air Temperature: 50 ºC (Set)
Atomisation Pressure: 2.0 Bar (Set)
Maximum Spray rate: 16 g/min
Inlet Air Dew Point: 15 ºC
Nozzle diameter: 1.2 mm
Wurster Gap/Partition height: 30 mm
Filters: Bonnets (0.4 mm mesh)
Filter shake: 15 secs every 5 mins
Tubing: Silicon, 0.125" ID x 0.062" wall
Pump: Peristaltic

- Commence spraying at ~ 11.0 g/min, after 5 minutes increase the spray rate to ~14.0 g/min. After an additional 5 minutes ramp up the spray rate to ~16.0 g/min.
- The product temperature during coating (at/near maximum spray rate in steady state) should be approximately 39 ºC.
- Continue spraying until all the theoretical quantity of coating solution has been sprayed onto the beads.
- Cover the solution to prevent evaporation during spraying.
- After coating, dry the beads by allowing the product temperature to rise by 2 ºC before shutting down the fluidisation air & heat.
- The beads should be sieved through a 1000 µm sieve (or US Standard 18 Mesh) to screen out agglomerates.

EXAMPLE 5

Preparation of 15% (w/w of final bead) modified release (MR) fesoterodine hydrogen fumarate beads

These are prepared by a similar process to that of Example 4 using the following components.

Component	Quantity/unit: (g/kg) (Quantities based on dry finished product and does not include overages)
Fesoterodine hydrogen fumarate immediate release (IR) beads (Example 2 or Example 3)	850.000
Ethylcellulose (Ethocel Standard 10 Premium)	120.000
Hydroxypropylcellulose (Klucel EF)	30.000
Isopropyl alcohol (to be removed in manufacturing process and does not appear in final product)	1991.211
Sterile water for irrigation (to be removed in manufacturing process and does not appear in final product)	271.529
TOTAL	1000.000

EXAMPLE 6

Preparation of 20% (w/w of final bead) modified release (MR) fesoterodine hydrogen fumarate beads

These are prepared by a similar process to that of Example 4 using the following components.

Component	Quantity/unit: (g/kg) (Quantities based on dry finished product and does not include overages)
Fesoterodine hydrogen fumarate immediate release (IR) beads (Example 2 or Example 3)	800.000
Ethyl cellulose (Ethocel Standard 10 Premium)	160.000
Hydroxypropylcellulose (Klucel EF)	40.000
Isopropyl alcohol (to be removed in manufacturing process and does not appear in final product)	2654.942
Sterile water for irrigation (to be removed in manufacturing process and does not appear in final product)	362.038
TOTAL	1000.000

EXAMPLE 7

Preparation of capsules containing modified release fesoterodine hydrogen fumarate beads

- Charge beads into a suitable encapsulator (e.g. Bosch GKF 400)
- Charge suitable capsules into the encapsulator (e.g., gelatine size 3)

- Encapsulate the beads by filling an appropriate amount of MR beads into each capsule using the bead filling station of the encapsulator and ensuring the capsules are closed properly
- Clean or polish the capsules as appropriate using a standard capsule polisher

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EXAMPLE 8

Chemical stability studies for IR beads coated with a solid molecular dispersion of fesoterodine hydrogen fumarate and hypromellose (hydroxypropyl methylcellulose – Methocel E5 LV (trade mark))

Solutions of 90:10, 85:15 and 80:20 weight % hydroxypropyl methylcellulose – Methocel E5 LV (trade mark): fesoterodine hydrogen fumarate (equivalent to 1:9, 1:5.7 and 1:4 weight % fesoterodine hydrogen fumarate : hydroxypropyl methylcellulose – Methocel E5 LV (trade mark), respectively) were prepared and coated onto microcrystalline cellulose (MCC) beads at potencies of approximately 3.0, 3.6 and 4.2% weight% (based on final IR bead) in the following manner.

Solution Preparation and Coating Process Conditions

All solutions were prepared in the same manner following a dedicated solution preparation sheet by a similar method to that of Example 1. A hydroxypropyl methylcellulose – Methocel E5 LV (trade mark) and water solution was prepared at least 4 hours in advance of coating (normally the afternoon prior to commencement of coating), with the fesoterodine hydrogen fumarate portion of the solution in water being prepared on the day of coating then mixed with the hydroxypropyl methylcellulose – Methocel E5 LV (trade mark) solution, prior to coating. The coating conditions are summarised in Table 1.

Table 1. Coating Conditions

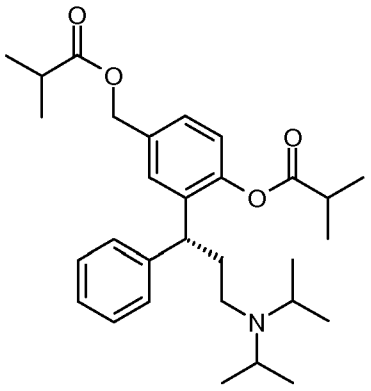
Equipment Parameter:	1 kg starting batch scale
Fluidised bed equipment	Glatt GPCG 1.1
Product container diameter (inch)	6
Spray nozzle	Schlick, 970 series, form S4
Liquid insert diameter (mm)	1.2
Atomizing air annulus position	1 mm below annulus
Air distribution plate type	C
Product filter	Woven silk filter sock
Silicone tubing internal diameter	0.125 inch (3.17 mm)
Fixed parameters:	

Spray rate acceleration	Start at ~8g/min & ramp up at 10 minute intervals
Target steady state spray rate (g min^{-1})	~13g/min
Atomising air pressure (Bar g)	2.0
Wurster gap (mm)	20
Target product temperature (^{o}C)	50 ± 3 ºC
Target fluidization air flow (m^3 h^{-1})	80 ± 10 %

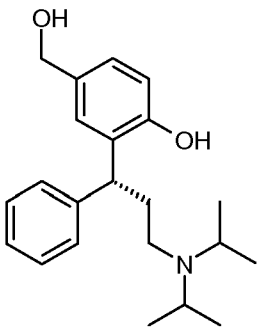
Stability Studies

In order to assess the chemical stability of the fesoterodine hydrogen fumarate IR beads (prepared as above at ratios of 90:10, 85:15 and 80:20 weight % hydroxypropyl methylcellulose – Methocel E5 LV (trade mark): fesoterodine hydrogen fumarate) batches of each were subdivided into approximately 5g lots, transferred to 60cc HDPE (high density polyethylene) bottles and then stored at the accelerated storage conditions of 40°C/75%RH (RH=relative humidity).

Samples were withdrawn after 4, 8 and 12 weeks storage and analysed by HPLC (using similar conditions to those shown in Table 2 with the difference that 75 microlitre injection volumes were used) with focus on the two key degradation products SPM 7675 and SPM 7605 (the chemical structures of which are shown below) and the total level of degradation products observed.



SPM 7675



SPM 7605

Results

Summary plots showing the levels of SPM 7675, SPM 7605 and the total degradation products observed in the IR beads (90:10, 85:15 and 80:20 weight % hydroxypropyl methylcellulose – Methocel E5 LV (trade mark): fesoterodine hydrogen fumarate) when stored at 40°C/75%RH are shown in Figures 1(a)-(c).

For comparative purposes, Figures 1(a)-(c) also include data on the levels of SPM 7675, SPM 7605 and total degradation products present in the fesoterodine hydrogen fumarate commercial xylitol-based tablet formulation (Xylitol 1* and Xylitol 2**) stored under similar accelerated stability conditions.

In summary, it can be seen that the fesoterodine hydrogen fumarate IR beads prepared with a ratio of 90:10 weight % hydroxypropyl methylcellulose – Methocel E5 LV (trade mark): fesoterodine hydrogen fumarate have a comparable chemical stability to the commercial xylitol tablet formulation.

(*Xylitol 1 – sample of 4mg fesoterodine commercial tablets (see WO2007/141298A1 on page 44, Table 1, Example C) packaged in blisters in accordance with European Union regulatory requirements . The packaging material is a laminated aluminium foil, mouldable for bottoms of push-through packages. The composite film consists of the following materials:

- Oriented polyamide (oPA), thickness of about 25 µm
- Aluminium, thickness of about 45 µm
- PVC, thickness of about 60 µm)

(**Xylitol 2 – sample of 4mg fesoterodine commercial tablets (see WO2007/141298A1 on page 44, Table 1, Example C) from a package containing 90 tablets per bottle each with a desiccant canister filled with 3 g of silica gel.)

EXAMPLE 9

Chemical stability and dissolution studies for IR beads coated with a solid molecular dispersion of 1:9 weight% fesoterodine hydrogen fumarate:hypromellose (hydroxypropyl methylcellulose – Methocel E5 LV – trade mark) and for sustained release (SR, i.e. MR) coated bead formulations thereof

Process Description – Immediate Release (IR) Beads

These were prepared by a similar process to that described in Example 2.

Process Description – 10% and 20% Sustained Release (SR) Beads

These were prepared by a similar process to that described in Example 4 and 6, respectively, using a Glatt GPCG 1.1 fluid bed coater.

Stability Studies for fesoterodine hydrogen fumarate Immediate Release (IR) and Sustained Release (SR) beads

Stability studies were conducted on both fesoterodine hydrogen fumarate IR beads and fesoterodine hydrogen fumarate SR beads (10% and 20% w/w of final bead).

Fesoterodine hydrogen fumarate IR and SR beads (10% and 20% SR coat) were packaged in sealed double polyethylene bags with desiccant in between liners inside a fibreboard drum and stored at 5°C, 25°C / 60% relative humidity (RH) and 30°C / 75% RH.

Visual appearance, chemical stability (degradation products by HPLC) and dissolution were tested initially, after 3 and 6 months storage at 5°C, and after 6 weeks and 3 months storage at 25°C / 60% RH and 30°C / 75% RH.

Analytical Methods

(a) Degradation Products by HPLC

The method for the determination of the degradation products of fesoterodine hydrogen fumarate IR and SR beads was a reversed-phase HPLC method with conditions as described in Table 2. Identification was accomplished by comparing retention times of the impurity markers and samples. Quantification of specified and unspecified degradation products was achieved by the comparison of peak area response in a test sample with that of an external standard solution. Total degradation products is the sum of all specified and unspecified degradation products by HPLC, excluding Process Related Impurities, present above the reporting threshold of 0.05%.

Table 2. Chromatographic Conditions

Mobile phase A (MPA)	0.1 % trifluoroacetic acid (aq)						
Mobile phase B (MPB)	0.1% trifluoroacetic acid (far UV Acetonitrile)						
Detector	UV absorbance at 220nm						
Injection volumes	REF MIX	75 µL					
	LOQ	20 µL					
	TEST	20 µL					
Column temperature	35°C						
Auto sampler temperature	5°C						
Flow Rate	1.2 mL/min						
Run Time	23 minutes						
Elution Mode	Gradient						
	Time (min)	0.0	10.0	10.1	19.0	19.1	23.0
	MPA (%)	75	75	50	50	75	75
	MPB (%)	25	25	50	50	25	25
Column Stationary Phase	Spheribond CN 5 µm or Waters Spherisorb CN 5 µm or equivalent						

(b) Dissolution

The rate of dissolution of fesoterodine hydrogen fumarate IR and SR beads is determined using a rotating paddle procedure (USP Apparatus 2) in 900 mL of USP

phosphate buffer dissolution medium. The amount of fesoterodine hydrogen fumarate dissolved in the dissolution medium is determined by a reversed-phase HPLC method with conditions as described in Table 3.

Table 3. Chromatographic Conditions

Mobile phase A (MPA)	Potassium phosphate buffer @ pH ~6.5 + 5% far UV acetonitrile	
Mobile phase B (MPB)	Far UV acetonitrile	
Detector	UV absorbance at 220nm	
Injection volume	75 µL	
Column temperature	30°C	
Flow Rate	2.0 mL/min	
Run Time	2 minutes	
Elution Mode	Isocratic	
	MPA (%)	75
	MPB (%)	25
Column Stationary Phase	Water XBridge C18 5 µm or equivalent	

Results

Stability data for fesoterodine hydrogen fumarate IR beads are presented in Tables 4 to 6, for fesoterodine fumarate SR beads (10% SR coat) in Tables 7 to 9, and for fesoterodine fumarate SR beads (20% SR coat) in Tables 10 to 12.

The immediate release (IR) beads coated with a solid molecular dispersion of 1:9 weight% fesoterodine hydrogen fumarate:hypromellose (hydroxypropyl methyl cellulose – Methocel E5 LV – trade mark) showed no significant increase in the levels of degradation products after 6 months storage at 5°C and only small and acceptable increases after 3 months storage at 25°C / 60% RH and 30°C / 75% RH.

Similarly, the sustained release (SR) beads (at both 10 and 20% SR coating levels) showed no significant increase in the levels of degradation products after 6 months storage at 5°C and only small and acceptable increases after 3 months storage at 25°C / 60% RH and 30°C / 75% RH.

Dissolution profiles of both the IR and SR beads were satisfactory at all storage conditions.

Table 4. Stability of fesoterodine hydrogen fumarate IR Beads stored at 5ºC

Time Point		Initial	3 months	6 months
Test	**Acceptance Criteria**	**Results**		
Appearance	Off white free flowing beads. No evidence of visible foreign matter or contamination.	Meets Test	Meets Test	Meets Test
Degradation Products				
	SPM 7605	0.10%	0.13%	0.16%
	SPM 7675	0.19%	0.15%	0.16%
	Total	1.4% [a]	0.69%	0.69%
Dissolution	Report Result Time Point (minutes)			
	15	NT	107	106
	30	80	111	109
	45	NT	111	112
	60	82	111	111

Table 5. Stability of fesoterodine hydrogen fumarate IR Beads stored at 25ºC/60%RH

Time Point		Initial	6 weeks	3 months
Test	**Acceptance Criteria**	**Results**		
Appearance	Off white free flowing beads. No evidence of visible foreign matter or contamination.	Meets Test	Meets Test	Meets Test
Degradation Products				
	SPM 7605	0.10%	0.24%	0.32%
	SPM 7675	0.19%	0.08%	0.21%
	Total	1.4% [a]	0.71%	0.90%
Dissolution	Report Result Time Point (minutes)			
	15	NT	105	91
	30	80	106	94
	45	NT	108	98
	60	82	108	99

Table 6. Stability of fesoterodine hydrogen fumarate IR Beads stored at 30ºC/75%RH

Time Point		Initial	6 weeks	3 months
Test	**Acceptance Criteria**	**Results**		
Appearance	Off white free flowing beads. No evidence of visible foreign matter or contamination.	Meets Test	Meets Test	Meets Test
Degradation Products				
	SPM 7605	0.10%	0.48%	0.89%
	SPM 7675	0.19%	0.12%	0.29%
	Total	1.4% [a]	1.1%	1.6%
Dissolution	Report Result Time Point (minutes)			
	15	NT	103	98
	30	80	106	101
	45	NT	109	101

	60	82	109	102

Table 7. Stability of fesoterodine hydrogen fumarate SR Beads (10% SR Coat) stored at 5ºC

Time Point		Initial	3 months	6 months
Test	**Acceptance Criteria**	**Results**		
Appearance	Off white free flowing beads. No evidence of visible foreign matter or contamination.	Meets Test	Meets Test	Meets Test
Degradation Products				
	SPM 7605	0.11%	0.13%	0.16%
	SPM 7675	0.21%	0.14%	0.16%
	Total	1.2% [a]	0.60%	0.69%
Dissolution	Report Result Time Point (hours)			
	1	14	15	13
	2	39	40	37
	4	84	82	77
	16	108	105	102

Table 8. Stability of fesoterodine hydrogen fumarate SR Beads (10% SR Coat) stored at 25ºC/60%RH

Time Point		Initial	6 weeks	3 months
Test	**Acceptance Criteria**	**Results**		
Appearance	Off white free flowing beads. No evidence of visible foreign matter or contamination.	Meets Test	Meets Test	Meets test
Degradation Products				
	SPM 7605	0.11%	0.25%	0.34%
	SPM 7675	0.21%	0.12%	0.21%
	Total	1.2% [a]	0.56%	0.93%
Dissolution	Report Result Time Point (hours)			
	1	14	16	11
	2	39	42	35
	4	84	84	79
	16	108	NT	107

Table 9. Stability of fesoterodine hydrogen fumarate SR Beads (10% SR Coat) stored at 30ºC/75%RH

Time Point		Initial	6 weeks	3 months
Test	**Acceptance Criteria**	**Results**		
Appearance	Off white free flowing beads. No evidence of visible foreign matter or contamination.	Meets Test	Meets Test	Meets Test
Degradation Products				
	SPM 7605	0.11%	0.50%	0.96%
	SPM 7675	0.21%	0.16%	0.30%
	Total	1.2% [a]	0.90%	1.7%

Dissolution	Report Result Time Point (hours)			
	1	14	15	14
	2	39	35	35
	4	84	75	70
	16	108	NT	92

Table 10. Stability of fesoterodine hydrogen fumarate SR Beads (20% SR Coat) stored at 5ºC

Time Point		Initial	3 months	6 months
Test	**Acceptance Criteria**	**Results**		
Appearance	Off white free flowing beads. No evidence of visible foreign matter or contamination.	Meets Test	Meets Test	Meets Test
Degradation Products				
	SPM 7605	0.11%	0.14%	0.19%
	SPM 7675	0.23%	0.15%	0.16%
	Total	1.1%	0.64%	0.72%
Dissolution	Report Result Time Point (hours)			
	1	0	3	4
	2	0	9	11
	4	28	28	31
	16	93	83	93

Table 11. Stability of fesoterodine hydrogen fumarate SR Beads (20% SR Coat) stored at 25ºC/60%RH

Time Point		Initial	6 weeks	3 months
Test	**Acceptance Criteria**	**Results**		
Appearance	Off white free flowing beads. No evidence of visible foreign matter or contamination.	Meets Test	Meets Test	Meets Test
Degradation Products				
	SPM 7605	0.11%	0.29%	0.35%
	SPM 7675	0.23%	0.12%	0.21%
	Total	1.1%	0.89%	0.95%
Dissolution	Report Result Time Point (hours)			
	1	0	7	2
	2	0	13	9
	4	28	32	28
	16	93	NT	106

Table 12. Stability of fesoterodine hydrogen fumarate SR Beads (20% SR Coat) stored at 30ºC/75%RH

Time Point		Initial	6 weeks	3 months
Test	**Acceptance Criteria**	**Results**		
Appearance	Off white free flowing beads. No evidence of visible foreign matter or contamination.	Meets Test	Meets Test	Meets Test
Degradation Products				
	SPM 7605	0.11%	0.50%	0.94%
	SPM 7675	0.23%	0.16%	0.30%
	Total	1.1%	0.93%	1.7%
Dissolution	Report Result Time Point (hours)			
	1	0	7	3
	2	0	NT	9
	4	28	29	26
	16	93	NT	95
NT= Not tested a) Isopropyl alcohol (IPA) used in the sample dilution solvent was found to enhance the level of an unspecified impurity. IPA was replaced by methanol as the dilution solvent from the 3M time point				

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EXAMPLE 10

Preparation of tablets containing a solid molecular dispersion of 1:19 or 1:9 weight % fesoterodine hydrogen fumarate: HPMC (hypromellose) on lactose particles using a Glatt GPCG 1.1 coater

a) Preparation of a solution of fesoterodine hydrogen fumarate and HPMC (hypromellose)

	1:9 Formulation	**1:19 Formulation**
Component*	**Quantity per tablet (mg)**	**Quantity per tablet (mg)**
Fesoterodine hydrogen fumarate	8.0	8.0
Lactose (Pharmatose 110M)	65.853	65.853
Hypromellose (Methocel E5)	72.0	152.0
Isopropanol	1.064	2.128
Water	0.456	0.912

(*quantities based on dry finished product with no overage. Can incorporate 10% overage of the quantities of the coating materials to allow for in-process loss due to tubing volumes, coating of containers, etc.)

- Calculate amounts of materials to use based on a 300g starting charge of lactose in the coater.
- Set-up an overhead stirrer and impeller.
- Weigh out 50 % of water into an appropriate sized vessel.
- Dissolve fesoterodine hydrogen fumarate in water
- Mix remainder of water with isopropanol (IPA)

- Set the agitator speed to produce a suitable vortex and gradually add the HPMC to the IPA/water and mix for a suitable time ensuring that the solution does not foam. Cover to prevent evaporation while stirring (ensure there are no lumps after stirring).
- Add the remaining water/API solution to the HPMC solution with agitation

b) Preparation of a solid molecular dispersion of fesoterodine hydrogen fumarate and hypromellose on lactose powder using Glatt GPCG 1.1 coater

- Heat Glatt GPCG 1.1 in 6" Wurster configuration to a product temp of ~ 30 ºC.
- Charge the lactose powder (300 g) into the coater
- Once the powder is fully fluidised commence spraying within 1 minute.
- The product temperature during coating (at/near maximum spray rate in steady state) should be approximately 30 ºC.
- Continue spraying until all the theoretical quantity of coating solution has been sprayed onto the powder.
- Cover the solution to prevent evaporation while coating.
- After coating, dry the granules by allowing the product temperature to rise by 2ºC before shutting down the fluidisation air & heat.

c) Preparation of tablets containing the granules from step (b)

	1:9 Formulation	**1:19 Formulation**
Component*	**Quantity per tablet (mg)**	**Quantity per tablet (mg)**
Fesoterodine Granules	145.853	225.853
Hypromellose (Methocel K100M)	78.137	120.995
Glyceryl Behenate (Compritol 888	6.512	10.084

ATO)		
Talc	5.535	8.571
Total	236.0	365.5

- Blend fesoterodine granules and hypromellose in a suitable blender.
- Add Compritol and talc to the blender and blend.
- Compress tablets using a suitable tablet press and appropriately sized tooling.

EXAMPLE 11

Determination of the comparative chemical stability of samples of fesoterodine hydrogen fumarate with HPMC and other polymeric binders on lactose particles

a) Sample preparation

The 1:19 and 1:9 HPMC samples were prepared as described in Example 10, steps (a) and (b).

The non-HPMC samples were prepared by a similar method to that described in Example 10, steps (a) and (b), using the specified non-HPMC polymeric binder. All non-HPMC samples contained 1:9 weight % of fesoterodine hydrogen fumarate: polymeric binder.

b) Stability data

The analytical methodology employed for the determination of the degradation products SPM-7605 and SPM 7675 (see chemical structures in Example 8) in samples of fesoterodine hydrogen fumarate and HPMC/other polymeric binder on

lactose was similar to that described in Example 9 with minor modifications to the HPLC conditions as described in Table 13.

Table 13.

Mobile phase A (MPA)	0.1 % trifluoroacetic acid (aqueous)				
Mobile phase B (MPB)	0.1% trifluoroacetic acid (far UV acetonitrile)				
Detector	UV absorbance at 220nm				
Injection volumes	Test	75 µL			
Flow Rate	1.2 mL/min				
Run Time	45 minutes				
Elution Mode	Gradient				
	Time (min)	0.0	35.0	35.1	45.0
	MPA (%)	72	72	50	50
	MPB (%)	28	28	50	50
Column Stationary Phase	Waters Spherisorb CN 5 µm or equivalent				

12 week chemical stability data were generated on the samples after storage at 40C/75% RH under closed conditions using induction sealed HDPE bottles and using a 1g desiccant cartridge. The results obtained are summarised in Table 14.

TABLE 14:

Polymeric binder used in sample[1,2] (on lactose particles)	**SPM 7605 %**	**SPM 7675 %**	**Fesoterodine %**
EC 10 cP	12.88	1.27	84.93
Eudragit L	4.87	-	95.02
Eudragit NE 30D	11.37	4.74	80.54
Eudragit RS 30D	11.83	4.74	79.41

Eudragit RS PO	18.50	3.33	73.50
HPMC (1:19)	0.97	0.18	98.36
HPMC (1:9)	1.68	0.40	97.53
Kollicoat SR 30D	9.47	1.09	86.05
Kollidon SR	8.42	0.75	88.02
PVA	1.82	1.03	96.62
PVP	7.11	0.29	90.77
Xylitol (reference)[3]	4.37	0.51	92.77

[1] All formulations were in a 1:9 wt % ratio of fesoterodine hydrogen fumarate:polymeric binder except where noted

[2] See Table 15 for specific details of the polymeric binders used.

[3] 1:9 weight % of fesoterodine hydrogen fumarate:xylitol.

TABLE 15:

Polymeric binder	Compendial Name	Trade Name	Supplier
EC 10 cP	Ethylcellulose USP	Ethocel Std 10	Dow
Eudragit L	Methacrylic Acid Copolymer, Type A NF	Eudragit L	Evonik
Eudragit NE 30D	Polyacrylate dispersion 30%	Eudragit NE 30D	Evonik

Eudragit RS 30D	Ammonio Methacrylate Copolymer Dispersion Type B	Eudragit RS 30D	Evonik
Eudragit RS PO	Ammonio Methacrylate Copolymer Type B NF	Eudragit RS PO	Evonik
HPMC (1:19)	Hypromellose USP	Methocel E5	Dow
HPMC (1:9)	Hypromellose USP	Methocel E5	Dow
Kollicoat SR 30D	Polyvinyl acetate dispersion USP	Kollicoat SR 30D	BASF
Kollidon SR	Polyvinyl acetate/ polyvinylpyrrolidone	Kollidon SR	BASF
PVA	Polyvinyl alcohol USP	Mowiol 4-88	Polysciences
PVP	Povidone USP	Kollidon 30	BASF
Xylitol	Xylitol USP	Xylisorb 90	Roquette

c) Results

It is clearly evident from Table 14 that of the polymeric binder samples analysed, only fesoterodine and HPMC samples (in ratios of either 1:19 or 1:9 wt. %) provided acceptable chemical stability as judged by the levels observed for the key SPM 7605and SPM 7675 degradants when the samples as described were stored for 12weeks at 40°C/75% R.H.

EXAMPLE 12

Comparative chemical stability of tablets containing solid molecular dispersions of 1:19 or 1:9 weight % fesoterodine hydrogen fumarate: HPMC (hypromellose) on lactose particles versus the commercial xylitol-based tablet

a) Sample preparation

The tablets containing the 1:19 and 1:9 HPMC dispersions on lactose were prepared as described in Example 10, steps (a), (b) and (c)

b) Stability data

The analytical methodology employed for the determination of the degradation products SPM7605 and SPM7675 (see chemical structures in Example 8) in samples of fesoterodine hydrogen fumarate in HPMC dispersions on lactose was similar to that described in Example 9 with minor modifications to the HPLC conditions as described in Table 16.

Table 16:

Mobile phase A (MPA)	0.1 % trifluoroacetic acid (aq)					
Mobile phase B (MPB)	0.1% trifluoroacetic acid (far UV Acetonitrile)					
Detector	UV absorbance at 220nm					
Injection Volume	TEST	75 µL				
Column temperature	35°C					
Auto sampler temperature	10°C					
Flow Rate	1.2 mL/min					
Run Time	45 minutes					
Elution Mode	Gradient					
	Time (min)	0.0	39	39.1	41.0	45.0
	MPA (%)	74	74	50	50	74
	MPB (%)	26	26	50	50	26
Column Stationary Phase	Spheribond CN 5 µm or Waters Spherisorb CN 5 µm or equivalent					

The comparative stability of tablets containing 1:19 or 1:9 HPMC dispersions on lactose versus the commercial xylitol-based tablet (8mg strength) was assessed by

storage of samples for 10 days at the purposefully selected, stressed (high temperature), storage conditions of 60°C/30% RH, 50°C/50%RH and 50°C/30%RH. The results are summarised in Tables 17, 18 and 19.

Table 17. Stability of fesoterodine hydrogen fumarate commercial xylitol-based 8mg tablets stored at stressed conditions

Condition		Initial	60ºC/30%RH		50ºC/50%RH		50ºC/30%RH
Degradation Products		**Results**					
Time point		Initial	3d	5d	5d	10d	10d
	SPM 7605 %	0.33	1.40	1.98	3.37	7.28	1.59
	SPM 7675 %	0.17	0.49	0.67	0.74	1.35	0.51
	Total %	0.93	2.7	4.2	5.2	12.4	3.0

Table 18. Stability of tablets containing 1:9 wt % fesoterodine hydrogen fumarate:HPMC on lactose particles stored at stressed conditions

Condition		Initial	60ºC/30%RH		50ºC/50%RH		50ºC/30%RH
Degradation Products		**Results**					
Time point		Initial	3d	5d	5d	10d	10d
	SPM 7605 %	0.22	1.22	1.69	1.45	2.37	1.48
	SPM 7675 %	0.10	0.26	0.35	0.29	0.29	0.34
	Total %	1.2	2.3	5.1	4.3	4.3	4.1

Table 19. Stability of tablets containing 1:19 wt % fesoterodine hydrogen fumarate:HPMC on lactose particles stored at stressed conditions

Condition		Initial	60ºC/30%RH		50ºC/50%RH		50ºC/30%RH
Degradation Products		**Results**					
Time point		Initial	3d	5d	5d	10d	10d
	SPM 7605 %	0.16%	0.66	0.92	0.77	1.28	0.82
	SPM 7675 %	0.12%	0.15	0.18	0.14	0.19	0.15
	Total %	1.4%	2.1	2.1	1.7	2.4	3.0

It is clearly evident from Tables 17, 18 and 19 that the levels of SPM 7605 and SPM 7675 in tablets containing 1:9 or 1:19 wt % fesoterodine hydrogen fumarate:HPMC on lactose particles were less than levels observed for the commercial xylitol-based tablet under all three storage conditions used.

ANALYSIS

1. **Analysis of IR layer of IR and MR beads comprising a solid molecular dispersion of fesoterodine hydrogen fumarate and HPMC (hypromellose) on microcrystalline cellulose beads by Fourier Transform Infrared (FTIR) spectroscopy**

IR and MR bead sample preparation

(a) IR beads (see Examples 2 and 3)
The beads were cut in half with a scalpel after which the IR layer was peeled off using a scalpel and tweezers. The peeled off IR layers were lightly pressed down onto a glass slide with a glass cover slip, after which they were transferred to the Attenuated Total Reflection (ATR) window for analysis. IR layers of five or six half beads were used for the collection of one spectrum.

(b) MR beads (see Examples 4 and 6)
The beads were cut in half with a scalpel after which the MR layer was peeled off using a scalpel and tweezers. Then the IR layer was peeled off. The peeled off IR layers were lightly pressed down onto a glass slide with a glass cover slip, after which they were transferred to the ATR window for analysis. For the 20% MR coated beads (see Example 6), IR layers of one or two half beads were used for the collection of one spectrum. For the 10% MR coated beads (see Example 4), IR layers of five half beads were used for the collection of one spectrum.

Crystalline fesoterodine hydrogen fumarate reference

This was obtained by the method described in US6858650B1, Preparation 6.

Preparation of amorphous fesoterodine hydrogen fumarate reference

Crystalline fesoterodine hydrogen fumarate (see above) was cryogenically ball milled using a Retsch MM301 mill and 1.5mL Retsch stainless steel mill chamber and ball. Each milling session lasted 10 minutes and the mill speed was set at 30Hz. The mill chamber with sample inside was cooled in liquid nitrogen for 5 minutes before milling, and between each subsequent milling session. The sample was milled for 50 minutes in total, after which a PXRD pattern was collected to confirm that the sample was amorphous fesoterodine hydrogen fumarate.

FTIR

The infrared spectra were acquired using a ThermoNicolet Nexus FTIR spectrometer equipped with a 'DurasamplIR' single reflection ATR accessory (diamond surface on zinc selenide substrate) and d-TGS KBr detector. The spectra were collected at $2cm^{-1}$ resolution and a co-addition of 512 scans. Happ-Genzel apodization was used. Using ATR FTIR will cause the relative intensities of infrared bands to differ from those seen in a transmission FTIR spectrum using KBr disc or nujol mull sample preparations. Due to the nature of ATR FTIR, the bands at lower wavenumber are more intense than those at higher wavenumber.

FTIR data treatment

Spectra were transferred into absorbance units within the ThermoNicolet Omnic 6.1a software

Results

Figures 2-5a inclusive show the FTIR ATR spectra obtained for

- crystalline fesoterodine hydrogen fumarate
- amorphous fesoterodine hydrogen fumarate

- IR layer of IR beads comprising a solid molecular dispersion of fesoterodine hydrogen fumarate and hypromellose (see Example 2 or 3)
- IR layer of 10% MR beads comprising a solid molecular dispersion of fesoterodine hydrogen fumarate and hypromellose (see Example 4)
- IR layer of 20% MR beads comprising a solid molecular dispersion of fesoterodine hydrogen fumarate and hypromellose (see Example 6)

The results show that

- when assessing infrared peak frequency positions and intensities obtained by analysis of the IR layers of IR and MR beads, there are peaks that overlap with the peaks seen for amorphous fesoterodine fumarate as well as those seen for crystalline fesoterodine hydrogen fumarate, and there are peaks with different frequency positions and intensities that can be used to characterise the IR layers of IR and MR beads, amorphous fesoterodine fumarate and crystalline fesoterodine hydrogen fumarate.

- in the spectra obtained from the samples of the IR layers of IR and MR beads, the absence of some of the more intense, characteristic peaks observed in the spectra obtained from samples of crystalline fesoterodine hydrogen fumarate and amorphous fesoterodine hydrogen fumarate.

- there are obvious changes in relative intensities of peaks in the spectra obtained from the samples of the IR layers of IR and MR beads in comparison to the peaks in the spectra obtained from samples of crystalline fesoterodine hydrogen fumarate and amorphous fesoterodine hydrogen fumarate.

Without being bound by theory, it is believed that these changes in peak frequency position and intensity observed show that there is a clear interaction of fesoterodine hydrogen fumarate with the HPMC polymeric binder in the IR layers of IR and MR beads. These effects are similar to those described by Konno and Taylor, J.Pharm.Sci (2006) 95, 12, 2692-2705. These effects are believed to be caused by

the presence of a solid molecular dispersion of fesoterodine hydrogen fumarate in the HPMC polymeric binder in the IR layers of the IR and MR beads analysed. In other words it is believed that neither amorphous molecular clusters, nor crystals, of fesoterodine hydrogen fumarate in the HPMC polymeric binder could be detected in the IR layers of the IR and MR beads analysed.

2. Analysis of IR granules comprising a solid molecular dispersion of fesoterodine hydrogen fumarate and HPMC (hypromellose) on lactose particles by Fourier Transform Infrared (FTIR) spectroscopy

The IR granules were prepared as described in Examples 10a and 10b.

Sample Preparation

No sample preparation was performed. The sample was placed onto the ATR crystal and pressure was applied.

FTIR

The infrared spectra were acquired using a ThermoNicolet Nexus FTIR spectrometer equipped with a 'DurasamplIR' single reflection ATR (attenuated total reflection) accessory (diamond surface on zinc selenide substrate) and d-TGS KBr detector. The reference spectra for crystalline and amorphous fesoterodine hydrogen fumarate, HPMC (Methocel E5LV) and lactose (Pharmatose – trade mark) were collected using the following experimental settings:

Sample	No scans	Resolution (cm^{-1})
Crystalline fesoterodine hydrogen fumarate	128	4
Amorphous fesoterodine hydrogen fumarate	256	4
HPMC (Methocel E5LV)	128	4

Lactose (Pharmatose 110 mesh)	64	4

For the sample containing a solid molecular dispersion of 1:9 weight % fesoterodine hydrogen fumarate/HPMC on lactose particles the spectra were collected at 4cm^{-1} resolution and a co-addition of 512 scans.

For the sample containing a solid molecular dispersion of 1:19 weight % fesoterodine hydrogen fumarate/HPMC on lactose particles the spectra were collected at 8cm^{-1} resolution and a co-addition of 512 scans.

Happ-Genzel apodization was used. Using ATR FT-IR will cause the relative intensities of infrared bands to differ from those seen in a transmission FT-IR spectrum using KBr disc or nujol mull sample preparations. Due to the nature of ATR FT-IR, the bands at lower wavenumber are more intense than those at higher wavenumber.

The FTIR spectra obtained are shown In Figures 6, 6a, 6b, 7, 7a, 8 and 8a.

FTIR data treatment

Spectra were transferred into absorbance units within ThermoNicolet Omnic 6.1a software and saved as .spc files. The spectra were then opened in Grams/AI 8.0 where a peak fit was performed using 4 peaks in the region 1792cm^{-1} to 1521cm^{-1}, using a mixture of Gaussian/Lorentzian peak shape and 50 iterations for the fit.

Evidence for the presence of a solid molecular dispersion rather than a physical mixture of amorphous or crystalline domains in a matrix.

When assessing infrared peak positions for the samples containing a solid dispersion of fesoterodine hydrogen fumarate/HPMC on lactose particles there are peaks that overlap with those for amorphous fesoterodine hydrogen fumarate as well as those for crystalline fesoterodine hydrogen fumarate.

However, the absence of some of the more intense, characteristic peaks seen for the amorphous and crystalline fesoterodine hydrogen fumarate samples in the

spectra for the fesoterodine hydrogen fumarate/HPMC on lactose particle samples analysed, as well as the obvious changes in relative intensities and shifts compared to the amorphous and crystalline fesoterodine hydrogen fumarate samples, allows a conclusion that there is a clear interaction of the fesoterodine hydrogen fumarate with the HPMC matrix in the fesoterodine hydrogen fumarate/HPMC on lactose particle samples. This interaction causes typical shifts in the infrared frequencies of certain functional groups, as described in the literature by Konno and Taylor, J.Pharm.Sci, 95, 12, 2692-2705 (2006). Therefore we can conclude that fesoterodine hydrogen fumarate is present in the fesoterodine hydrogen fumarate/HPMC on lactose particle samples as a solid molecular dispersion.

3. Analysis of IR granules comprising fesoterodine hydrogen fumarate and either PVA or methyl methacrylate (Eudragit) on lactose particles by Fourier Transform Infrared (FTIR) spectroscopy and PXRD

PXRD

Capillary PXRD data was collected on the samples of fesoterodine hydrogen fumarate and either PVA or methyl methacrylate (Eudragit NE 30D or Eudragit RS PO) on lactose particles prepared as in Example 11.

PXRD data was collected using a Bruker-AXS Ltd D8 Advance powder X-ray diffractometer fitted with a capillary stage, a theta-theta goniometer, a KA-1 (Cu) primary monochromator and a Braun position sensitive detector. The sample was mounted in a 1.0 or 1.5mm quartz capillary. The sample was rotated whilst being irradiated with copper K-alpha1 X-rays (wavelength = 1.5406 Ångstroms) with the X-ray tube operated at 40kV/40mA. The analysis was performed with the goniometer running in continuous mode set for a 6 second count per 0.011° step over a two theta range of 2 to 55°.

The patterns that were collected show no evidence for crystalline fesoterodine hydrogen fumarate in the samples. It would have been expected that PXRD would be capable of detecting crystalline fesoterodine hydrogen fumarate at the API concentration levels (ca. 5% w/w%) in these samples and hence it is concluded that the samples analysed did not contain crystalline fesoterodine hydrogen fumarate.

FTIR

FTIR ATR analysis was carried out on the above samples of fesoterodine hydrogen fumarate and either PVA or methyl methacrylate (Eudragit) on lactose particles in an attempt to determine if the fesoterodine hydrogen fumarate was present in either an amorphous state or as a solid molecular dispersion with the polymeric binder used.

The region of the spectra where important information on characteristic fesoterodine hydrogen fumarate functional groups is obtained spans from 1800-1500cm^{-1}.

Unfortunately methyl methacrylate (Eudragit) itself displays a very intense peak around 1724cm^{-1} that masks several characteristic fesoterodine hydrogen fumarate peaks leaving only one observable characteristic fesoterodine hydrogen fumarate peak around 1581cm^{-1}. Unfortunately this peak is not effective alone in distinguishing the existence of fesoterodine hydrogen fumarate in an amorphous state from the existence of fesoterodine hydrogen fumarate in solid molecular dispersion in the sample of fesoterodine hydrogen fumarate and methyl methacrylate (Eudragit) on lactose particles.

For the sample of fesoterodine hydrogen fumarate and PVA on lactose particles, FTIR ATR analysis showed that there are dominant PVA peaks ranging from 1731-1568cm^{-1} leaving no clear region to assess peaks characteristic of fesoterodine hydrogen fumarate and to distinguish the existence of fesoterodine hydrogen fumarate in an amorphous state from the existence of fesoterodine hydrogen

fumarate in solid molecular dispersion in the sample of fesoterodine hydrogen fumarate and PVA on lactose particles.

In summary, despite use of best efforts, it could not be determined if the samples of fesoterodine hydrogen fumarate and either PVA or methyl methacrylate (Eudragit) on lactose particles contained fesoterodine hydrogen fumarate in an amorphous state or fesoterodine hydrogen fumarate in a solid molecular dispersion.

CLAIMS

1. A solid molecular dispersion comprising from 3:97 to 12:88 weight % ratio of fesoterodine hydrogen fumarate: an alkyl hydroxyalkylcellulose ether or a hydroxyalkylcellulose ether, or an ester of either thereof, or a mixture of any two or more thereof.

2. A solid dispersion comprising from 3:97 to 12:88 weight % ratio of fesoterodine hydrogen fumarate: an alkyl hydroxyalkylcellulose ether or a hydroxyalkylcellulose ether, or an ester of either thereof, or a mixture of any two or more thereof, in which the fesoterodine hydrogen fumarate is stabilised in the dispersion in a form not corresponding to its crystalline or amorphous form.

3.A dispersion as claimed in claim 1 or 2 comprising about a 1:9 weight % ratio of fesoterodine hydrogen fumarate: an alkyl hydroxyalkylcellulose ether or a hydroxyalkylcellulose ether, or an ester of either thereof, or a mixture of any two or more thereof .

4.A dispersion as claimed in claim 3 consisting essentially of about a 1:9 weight % ratio of fesoterodine hydrogen fumarate: an alkyl hydroxyalkylcellulose ether or a hydroxyalkylcellulose ether, or an ester of either thereof, or a mixture of any two or more thereof.

5. A dispersion as claimed in claim 1 or 2 comprising about a 1:19 weight % ratio of fesoterodine hydrogen fumarate: an alkyl hydroxyalkylcellulose ether or a hydroxyalkylcellulose ether, or an ester of either thereof, or a mixture of any two or more thereof.

6. A dispersion as claimed in claim 5 consisting essentially of about a 1:19 weight % ratio of fesoterodine hydrogen fumarate: an alkyl hydroxyalkylcellulose ether or a

hydroxyalkylcellulose ether, or an ester of either thereof, or a mixture of any two or more thereof.

7. A dispersion as claimed in claim 1 or 2 consisting essentially of fesoterodine hydrogen fumarate, and an alkyl hydroxyalkylcellulose ether or a hydroxyalkylcellulose ether, or an ester of either thereof, or a mixture of any two or more thereof.

8. A dispersion as claimed in any one of claims1 to 7 wherein the cellulose ether component is selected from hydroxypropyl methyl cellulose (HPMC), hydroxyethyl methyl cellulose (HEMC), hydroxybutyl methyl cellulose (HBMC), hydroxyethylcellulose (HEC), hydroxypropyl cellulose (HPC) or hydroxypropyl methyl cellulose acetate succinate (HPMCAS): or is a mixture of any two or more thereof.

9. A dispersion as claimed in claim 8 wherein the cellulose ether component is hydroxypropyl methyl cellulose alone.

10. A dispersion as claimed in any one of claims 1 to 9 for use as a medicament.

11. A dispersion as claimed in any one of claims 1 to 9 for use in the treatment of urinary incontinence.

12. An inert core bead or particle which is coated with a dispersion as claimed in any one of claims 1 to 9.

13. An inert core bead or particle as claimed in claim 12 wherein the core bead or particle comprises microcrystalline cellulose

14. An inert core bead or particle as claimed in claim 12 wherein the core bead or particle comprises lactose.

15. An inert core bead or particle as claimed in claim 13 which is further coated with a modified-release layer.

16. An inert core bead or particle as claimed in claim 15 wherein the modified release layer comprises ethyl cellulose and hydroxypropyl cellulose.

17. An inert core bead or particle as claimed in any one of claims 12 to 16 for use as a medicament.

18. An inert core bead or particle as claimed in any one of claims 12 to 16 for use in the treatment of urinary incontinence.

19. A pharmaceutical formulation comprising modified-release beads as claimed in claim 15 or 16.

20. A formulation as claimed in claim 19 wherein the said modified-release beads are encapsulated.

21. A pharmaceutical tablet formulation comprising an inert core bead or particle as claimed in claim 14.

22. A formulation as claimed in any one of claim 19 to 21 for use as a medicament.

23. A formulation as claimed in any one of claims 19 to 21 for use in the treatment of urinary incontinence.

24. A solid dispersion comprising from 3:97 to 12:88 weight % ratio of fesoterodine hydrogen fumarate: an alkyl hydroxyalkylcellulose ether or a hydroxyalkylcellulose ether, or an ester of either thereof, or a mixture of any two or more thereof, in which the fesoterodine hydrogen fumarate is stabilised in the dispersion in a form not corresponding to its crystalline or amorphous form and which generally displays the FTIR characteristics shown in Figure 3, 3a, 4, 4a, 5, 5a, 7, 7a, 8 or 8a.

25. A solid molecular dispersion obtainable by (a) achieving a solution of fesoterodine hydrogen fumarate and an alkyl hydroxyalkylcellulose ether or a hydroxyalkylcellulose ether, or an ester of either thereof, or a mixture of any two or more thereof, in from 3:97 to 12:88 weight % ratio, and (b) by drying to form said dispersion.