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ORIGINAL RESEARCH ARTICLE

Formulation and Evaluation of Darifenacin Hydrobromide Extended Release Dosage Form using Multiparticulate Drug Delivery System

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ABSTRACT

Darifenacin Hydrobromide is a muscarinic M3 selective receptor antagonist. It is used in the treatment of urge incontinence or increased urinary frequency and urgency as may occur in patients with overactive bladder syndrome. The present work focused on developing an extended release dosage form using multiparticulate drug delivery system to offer benefits such as less inter and intra-subject variability in gastrointestinal transit time and show better reproducible pharmacokinetic behavior than conventional (monolithic) formulations which is equivalent to the marketed product Enablex. To design the dosage form, suitable cell spheres were selected for drug layering, followed by coating with ethyl cellulose polymer to obtain a drug reservoir system. Compatibility of Darifenacin Hydrobromide has been established with the proposed ingredients and preceded with the formulation optimization. F1 formulation has 5% ethyl cellulose coating, which was optimized to 14% in F8 formulation to obtain the required release pattern and complete release at 24 hr time point with similar profile as of Reference product with satisfactory similarity values (F2). Stability studies have been conducted as per ICH guidelines and the product was found stable till 3 months.

Key words: Darifenacin Hydrobromide, Extended release, Multiparticulate, Dissolution, Overactive bladder syndrome.

INTRODUCTION

Muscarinic receptors [1] are characterized through their interaction with muscarine, a water-soluble toxin derived from the mushroom *Amanita muscaria* that causes substantial activation of the peripheral sympathetic nervous system through its binding to muscarinic acetylcholine receptors (AChRs), resulting in convulsions and even death. The muscarinic AChRs occur primarily in the CNS, and are part of a large family of G-protein-coupled receptors ('G-proteins'), which use an intracellular secondary messenger system involving an increase of intracellular calcium to transmit signals inside cells. Binding of acetylcholine to a muscarinic AChR causes a conformational change in the receptor that is responsible for its association with and activation of an intracellular G protein, the latter converting GTP to GDP in order to become activated and dissociate from the receptor. The activated G-protein can then act as an enzyme to catalyse downstream intracellular events.

Multiparticulate [2] drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05-2.00mm [3]. Thus multiparticulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet and encapsulated or compressed into a tablet. Multiparticulate are discrete particles that make up a multiple unit system. They provide many advantages over single-unit systems because of their small size. Multi particulates are less dependent on gastric empty ting, resulting in less inter and intra-subject variability in gastrointestinal transit time [4]. They are also

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better distributed and less likely to cause local irritation. Recently much emphasis is being laid on the development of multiparticulate dosage forms in preference to single unit systems because of their potential benefits such as increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying. There are many reasons for formulating a drug as a multiparticulate system for example, to facilitate disintegration in the stomach, or to provide a convenient, fast disintegrating tablet that dissolves in water before swallowing which can aid compliance in older patients and children. Multiparticulate systems show better reproducible pharmacokinetic behavior than conventional (monolithic) formulations. After disintegration which occurs within a few minutes often even within seconds, the individual subunit particles pass rapidly through the GI tract. If these subunits have diameters of less than 2mm, they are able to leave the stomach continuously, even if the pylorus is closed. These results in lower intra and inter individual variability in plasma levels and bioavailability. Drug safety may also be increased by using multiparticulate dosage forms, particularly for modified release systems. For example, if the film coat of a single-unit (monolithic) enteric coated tablet is damaged, the complete dose will be released into the stomach where it may cause pain or ulceration or reduced efficacy, depending on the reason for choosing the protection of the enteric coating. Equally, if there is damage to the film coating of a monolithic tablet with a sustained release formulation, this can lead to "dose dumping" and result in dramatic side effects. The oral multi-unit particulate drug delivery systems (MDDS), have gained immense importance, not only because of their ability to control drug release, but also for the modified drug-release profiles they facilitate oral multiparticulate drug delivery systems (e.g. pellets, granules) offer biopharmaceutical advantages in terms of a more even and predictable distribution and transportation through the GI tract, which is fairly independent of the nutritional state [5]. By contrast, in multiparticulate formulation, the release characteristics are incorporated into every single subunit and any damage only affects the release behavior of the subunit involved, which represents a small part of the total dose, reducing the likelihood of safety problems [6].

MATERIALS AND METHODS

Darifenacin Hydrobromide (Megafine Laboratories, Mumbai), Celpheres: CP 507 (Asahi kesai) Hypromellose: Methocel E3 (Dow Chemicals), Dimethyl Sulfoxide (Merck), Surelease coating system (Colorcon), Microcrystalline cellulose: Avicel PH 200 (FMC Biopolymer) and Magnesium stearate: Ligamed MF-2-V and Purified water.

Drug-Excipient Compatibility studies [7]

Procedure:

The compatibility studies were carried out by taking a mixture of drug and excipients at the ratio 1:1 or the probable ratio of usage in the current formulation. Individual excipients and API-Excipient mixtures were filled into labeled glass vials and these samples were exposed to pre-determined storage conditions like 40°C/75 %RH, and 60°C. Samples were analyzed at 15 days and 30days time periods for physical description as well as related substances using HPLC technique to evaluate possible interaction between drug and excipients.

Manufacturing process of tablets:

Preparation of Drug solution:

1. Darifenacin Hydrobromide was dissolved in Dimethyl Sulfoxide (DMSO) and Hypromellose (Methocel E3) in Purified water.
2. Both the mixtures were stirred for 20 min.

Drug loading:

1. Core pellets were loaded in to Fluid bed processor and run till up to product temp reached 40 $\pm$ 5°C.
2. The drug solution was sprayed on to the fluidized bed with optimum fluidization.
3. The following are the parameters followed and recorded during the process.

Table 1: Parameters considered for the tablet formulation

S No	Parameters	Set Values
1	Inlet temp(^{0}C)	45 - 53°C
2	Product temp (^{0}C)	36 - 42°C
3	Exhaust temp (^{0}C)	30 - 34°C
4	Pump (rpm)	10 – 18
5	Spray rate (g/min)	4 – 8
6	Atomization (bar)	1.0
7	Air flow (m^3/hr.)	50 - 70
8	% RH	8 - 12

The yield was calculated and drug loaded pellets were taken to next step of manufacturing.

Preparation of Ethyl cellulose Coating Solution

1. Surelease 25% was dispersed in sufficient amount of purified water to make a dispersion of 15% w/w solids.

Functional coating of the polymer solution on the drug loaded pellets:

1. Drug loaded pellets were loaded in to FBP and dried up to product temp 40 ± 5°C.
2. The polymer solution was sprayed on to the fluidized bed with optimum fluidization with the following parameters.

Table 2: Parameters considered for the coating solution

S No	Parameters	Set Values
1	Inlet temp(^{0}C)	48 - 56°C
2	Product temp (^{0}C)	38 - 43°C
3	Exhaust temp (^{0}C)	33 - 37°C
4	Pump (rpm)	10-20
5	Spray rate (g/min)	4 - 10
6	Atomization(bar)	1.0
7	Air flow (m^3/hr.)	50 - 70
8	% RH	8 - 12

Blending of the coated pellets with extra-granular ingredients

The coated pellets were blended with Avicel PH200 and lubricated with Magnesium stearate using bin blender.

Tablet compression:

The blend was compressed in to tablets by using suitable tooling.

Evaluation of blend parameters [8]**:**

1. Tapped & Bulk density

Tapped density is calculated using following formula.

Bulk density = weight of sample in g /volume occupied by the sample in mL

Tapped density = Wt. of sample in g / Tapped volume in mL

2. Compressibility Index and Hausner's ratio:

$$\text{Carr's index} = \frac{\text{Tapped Density - Bulk Density}}{\text{Tapped Density}} \times 100$$

$$\text{Hauser's ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

3. Angle of Repose

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to inter particulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and the horizontal plane.

$$\text{Tan } \theta = h / r$$

$$\text{Angle of repose } \theta = \text{Tan}^{-1} h / r$$

Where h = height; r = radius.

Evaluation of Tablets

1.0 Thickness:

Place a tablet in between the jaws of hardness tester and run the test with an already set program for determining thickness. Note down the result and continue the test for 9 such tablets. Record the value displayed in Hardness tester.

2.0 Hardness:

Place a tablet in between the jaws of hardness tester and run the test with an already set program for determining hardness. Note down the result and continue the test for 9 such tablets. Record the value displayed in kp for Hardness.

3.0 Friability:

Weigh accurately not less than 6.5g of tablets (W1). The tablets should be carefully dedusted prior to testing and place the tablets in the drum of the friability apparatus. Rotate the drum 100 times and remove the tablets. Remove any loose dust from the tablets as before, and accurately weigh (W2). If cracked, cleaved, or broken tablets are present after tumbling, the sample fails the test.

Calculation: Calculate the Friability in %,

$$\text{Friability} = \frac{(W1 - W2) \times 100}{W1}$$

Where,

W1 = Initial weight of the tablets taken

W2 = Final weight of the tablets after testing.

4.0 *In-Vitro* Dissolution by HPLC

Chemicals/Reagents:

Table 3: List of chemicals used for dissolution test

S. No	Chemicals/Reagents	Make/Grade
1	Di-ammonium hydrogen orthophosphate	Merck (GR-Grade)
2	Acetonitrile	Merck (HPLC-Grade)
3	Methanol	Merck (HPLC grade)
4	Water	Purified water/TKA water

Dissolution parameters:

Table 4: Parameters used for dissolution test

Medium	0.1 N HCl ; 900 mL
Apparatus	Type-I (Basket)
RPM	100
Time point	4, 8 & 24 h
Temperature	37 °C ± 0.5 °C

Chromatographic conditions:

Table 5: Chromatographic parameters

Column	Kromasil 100- C8, 250 mm x 4.6 mm x 5 µm (Part No.: 83325)
Flow rate	1.0 mL / min
Detector wave length	215 nm
Oven temperature	30 °C
Injection volume	20 µL
Run time	10 min

The below procedure was followed to conduct dissolution testing.

Buffer:

Dissolve accurately 3.3 g of Di-ammonium hydrogen orthophosphate in 1000 mL of purified water, using magnetic stirrer. Filter through 0.45 µm Nylon membrane filter or suitable filter and degas by sonicating for 5 minutes.

Mobile Phase: Mix the buffer and Acetonitrile in the ratio 40:60 (v/v)

Dissolution media preparation (0.1N HCl):

Take 85mL of concentrated hydrochloric acid and dilute to 10000mL in suitable container and mix well.

Preparation of Standard stock solution:

Accurately weigh 40 mg of Darifenacin hydrobromide working standard into 200 mL volumetric flask, add 5 mL of methanol, dissolve and sonicate for 2 minutes. Make up the volume up to 200 mL with dissolution media.

Preparation of Standard solution for 15 mg:

Further dilute 5 mL of the standard stock solution to 50 mL with dissolution media.

Preparation of Sample solution: Place 6 Tablets individually in six dissolution vessels containing 900 mL of media that has been equilibrated to 37 °C ± 0.5 °C. Take care to exclude air bubbles from the surface of the tablet, start the apparatus immediately. Collect 10 mL of the sample after specified time, withdraw sample from a zone midway between the surface of the medium and top of the rotating basket and not less than 1 cm from the vessel wall and filter through 10.0 µm online filter or alternatively filter through 0.45 µm GHP membrane filter (Make: Pall life sciences). Replace the volume with 10 mL of the dissolution medium.

Procedure: Separately inject equal volumes (20 µL) of dissolution media, standard and sample solutions into the chromatograph. Record the chromatograms and measure the peak responses of the major peaks and check for the system suitability requirements.

Sequence of injections:

1 x Diluent (Dissolution medium)
5 x Standard solution
1 x Sample solution 1, 2, 3, 4, 5 and 6
1 x Control standard (standard preparation)

Note: End run with standard solution

Composition of the trials performed

Table 6: Composition of trials

S.No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
1	Darifenacin HBr	17.846	17.846	17.846	17.846	17.846	17.846	17.846	17.846
2	Microcrystalline cellulose pellets (Celpheres CP507)	104.154	104.154	104.154	104.154	94.154	94.154	90.154	87.154
3	Hydroxypropyl methyl cellulose (Methocel E3 Premium LV)	6	8	10	10	10	10	10	10
4	Dimethyl sulfoxide (DMSO)	75	75	75	75	75	75	75	75
5	Water (g)	425	425	425	425	425	425	425	425
6	Drug loaded pellets	128	130	132	132	122	122	118	115
7	Surelease coating system	10	10	10	14	16	20	24	28
8	Water	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
9	Surelease coated pellets	138	140	142	146	138	142	142	143
10	Microcrystalline cellulose (Avicel PH 200)	59	57	55	51	59	55	55	54
11	Magnesium stearate	3	3	3	3	3	3	3	3
12	**Uncoated tablet weight**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**
13	Opadry coating system	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
	Total tablet weight	**205.0**	**205.0**	**205.0**	**205.0**	**205.0**	**205.0**	**205.0**	**205.0**

RESULTS

Blend Parameters:

Table 7: Parameters of blended material

Formulation	Bulk density	Tapped density	Angle of repose	Carr's index	Hausner's ratio
F1	0.51	0.61	27.25	16.39	1.20
F2	0.50	0.62	26.25	19.35	1.24
F3	0.51	0.59	26.45	13.56	1.16

F4	0.52	0.62	23.56	16.13	1.19
F5	0.51	0.62	27.54	17.74	1.22
F6	0.50	0.60	28.97	16.67	1.20
F7	0.52	0.61	25.56	14.75	1.17
F8	0.51	0.63	27.23	19.05	1.24

Compression Parameters:

Table 8: Compression parameters

Formulation	Hardness (kp)	Thickness (mm)	Average weight (mg)	Friability (%w/w)	% of Drug
F1	6.1	3.51	200	0.53	98.9
F2	7.3	3.52	201	0.41	99.6
F3	8.0	3.49	201	0.10	99.3
F4	8.1	3.52	199	0.13	100.2
F5	8.4	3.48	202	0.09	100.1
F6	8.0	3.56	202	0.13	99.8
F7	8.3	3.53	200	0.15	99.7
F8	8.2	3.54	201	0.14	100.3

Note: *Values furnished are average values of 10 units except for friability test.*

In-Vitro Dissolution profiles:

Table 9: *In-vitro* dissolution studies

Time (hrs)	Enablex	% RSD	F1	% RSD	F2	% RSD	F3	% RSD	F4	% RSD	F5	% RSD	F6	% RSD	F7	% RSD	F8	% RSD
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	10	17	27	16	28	19	26	15	23	17	18	16	13	15	9	14	7	15
4	32	9	61	8	59	9	58	7	57	9	48	8	43	9	39	8	30	8
8	56	8	78	8	79	9	78	7	79	6	78	4	75	8	65	7	52	7
12	73	5	96	7	96	5	97	4	94	5	92	4	88	6	82	6	72	5
16	84	6	99	6	98	2	99	3	98	3	97	2	97	3	91	4	85	4
20	93	4	100	1	101	1	100	2	100	1	100	1	103	2	96	3	96	3
24	96	2	101	1	101	1	101	2	101	1	102	2	104	3	98	1	98	1
***f*2 Value**			**35**		**35**		**36**		**37**		**41**		**45**		**58**		**78**	

Drug release kinetics:

Zero order release rate kinetics: To study the zero order release kinetics the release rate data are fitted to the following equation

$F=K_0t$

Where; F is the fraction of drug release; K_0 is the rate constant; T is the release time

First order model: This model has also been used to describe absorption and/elimination of drug, the release of the drug which followed first order kinetic can be expressed by the equation

$\text{Log } C=\log c_0-kt/2.303$

Where; C_o is the initial concentration of drug; K is the first order rate constant; t = is the time

Korsmeyer and peppas model:

The release rate data were fitted to the following equation:

$Mt / M\infty = Kt_n$

Where; Mt / M∞ is the fraction of drug release ; KM is the release constant; t is the release time

Graphical representations of Drug Release Kinetics [9,10]**:**

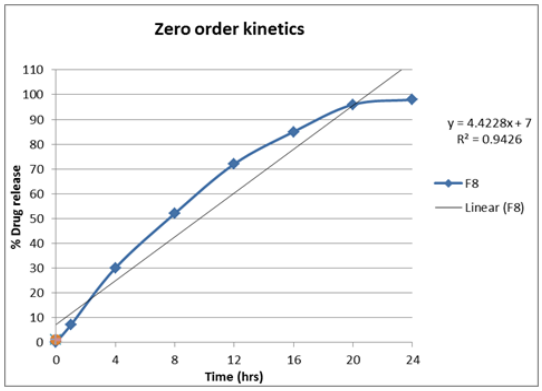

Fig 1: Zero Order Plot for Optimized formulation (F8)

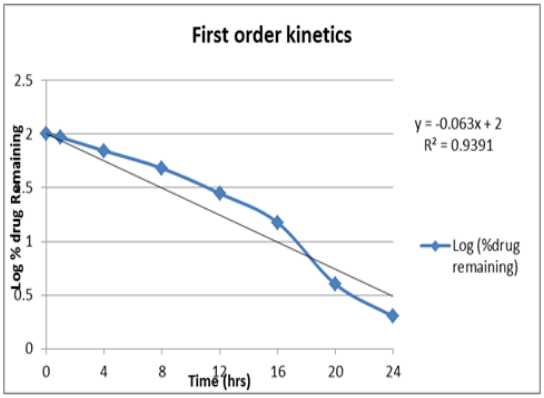

Fig 2: First Order Plot for Optimized formulation (F8)

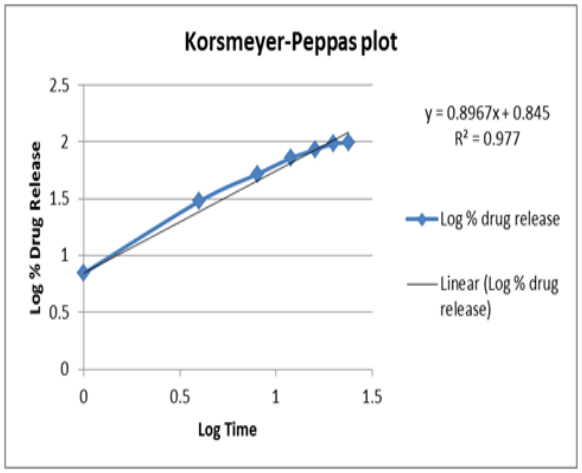

Fig 3: Korsmeyer-Peppas plot of Optimized formulation (F8)

DISCUSSION

Drug Excipient Compatibility Studies:

According to guidelines on impurity of drug product the drug product containing 15 mg dose /day acceptance criteria is 0.5%. Drug – excipient compatibility indicates that the all used excipients in the formulation are compatible with the drug by HPLC, impurities was less than 0.5%.

Blend parameters:

(Table 7) shows that the angle of repose of different formulations was found between 23.56 to 28.97 which indicates that material had excellent flow property. So it was confirmed that the flow property of blends were free flowing. The bulk density of blend was found between 0.50g/mL to 0.52 g/mL. Tapped density was found between 0.59g/mL to 0.63 g/mL. These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 13.56-19.35 and Hausner's ratio from 1.16-1.24 which reveals that the blends have fair flow character.

Compression parameters:

(Table 8) shows that the Hardness of the tablet was acceptable and uniform from batch to batch variation, which was found to be in between 5 - 9 kp. All the formulations passed the weight variation test as the % weight variation was within the acceptable limits. Friability values were found to be less than 1% in all the formulations F1 – F8 and considered to be satisfactory ensuring that all the formulations are mechanically stable. The % drug content for all the formulations were close to 100 and varied between 98.9 to 100.3%.

CONCLUSION

An optimized formulation was obtained with F8. Formulations F1 to F5 were releasing the drug more than 90% around 12 hr time point. Formulation F8 was satisfactory with respect to all parameters and the drug release profile was found to be similar to that of the marketed product with satisfactory f2 value.

REFERENCES

1. Karl Kreder, Roger Dmochowski; The Overactive Bladder: Evaluation and Management, Page No 204 to 207.
2. Hong Wen, Kinam Park; Oral Controlled Release Formulation Design and Drug Delivery: Theory to Practice, Page No 118-120.
3. Shaji J., Chadawar V.,Talwalkar P., Multiparticulate Drug Delivery System, The Indian Pharmacist, June 2007, 6(60): 21-28
4. Tang E. S.K., Chan L.W, Heng P.W.S, Coating of Multiparticulates for Sustained Release, Amer J Drug Delivery 2005: 3(1): 17-28
5. Bipin R G, Bhatu P B, Ankit V K. Development and in vitro evaluation of multiparticulate system using novel coating material for controlled drug delivery system. Int J pharm and pharm sci 2011; 3(3): 0975-1491.
6. Preparing Modified Release Multiparticulate Dosage Forms With Eudragit Polymers, Pharma Polymers, November 2002, 9:2-3.
7. Yihong Qiu, Yisheng Chen, Geoff G.Z. Zhang, Lirong Liu, William Porter, Developing Solid Oral Dosage Forms: Pharmaceutical Theory & Practice, Pharmaceutical Theory and Practice Series, Edition 2009, Page 125-127.
8. U.S.P. 36 – NF 31, General chapters.
9. Milo Gibaldi. "Biopharmaceutics and Clinical Pharmacokinetics", 4th Edn, 2001, Page 329 & 337.
10. D.M.Brahmankar and Sunil B.Jaiswal,Biopharmaceutics and Pharmacokinetics A Treatise", Page.335-350.