WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 6.647
Volume 6, Issue 8, 897-910 Research Article ISSN 2278 – 4357

FORMULATION AND EVALUATION OF DARIFENACIN HYDROBROMIDE EXTENDED RELEASE MATRIX TABLETS

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Article Received on
30 May 2017,

Revised on 20 June 2017,
Accepted on 11 July 2017

DOI:10.20959/wjpps20178-9593

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ABSTRACT

Darifenacin is a muscarinic M3 selective receptor antagonist, which is intended for symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder syndrome. Therefore the present investigation concerned with the development of once-a-day darifenacin hydrobromide extended release tablets to extend the duration of action up to 24 hrs by controlling the dissolution rate using different viscosity grades of HPMC. Main aim and object of my present work is to formulate darifenacin hydrobromide extended release film coated tablets and compared with the innovator product enablex, marketed by novartis. Darifenacin extended release tablets were developed to overcome the inconvenience of multiple dosing per day that is necessary with the immediate release formulation. There is therefore a need of administrating darifenacin in an oral dosage form once or twice daily in the form of extended release tablets provide therapeutically effective plasma concentrations of darifenacin for the treatment of overactive bladder in humans.

KEYWORDS: extended release, HPMC, sympathomimetic, Darifenacin.

INTRODUCTION

Darifenacin- A Muscarinic M3 selective receptor antagonist

Darifenacin is a muscarinic M3 selective receptor antagonist, which is intended for symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder syndrome.[1-5] Anti-muscarinic agents work

on the principle of blocking the binding of acetylcholine to muscarinic receptors. Parasympathetic muscarinic activity results in a coordinated detrusor contraction and relaxation of the bladder outlet. The symptoms of OAB have been attributed to involuntary contractions of the bladder detrusor muscle during the filling phase of the micturition cycle.[6-10] This supports the rationale for using a drug that antagonizes the M3-mediated parasympathetic excitation of the detrusor smooth muscle contraction.

MATERIALS

Darifenacin Hydrobromide (MSN Laboratories, Hyderabad), Lactose anhydrous (DC grade) (SD Fine Chemicals Ltd, Mumbai), Dicalcium phosphate (DC grade) (SD Fine Chemicals Ltd, Mumbai), Methocel K4M CR (Signet Chemicals, Mumbai), Methocel K100M CR (Signet Chemicals, Mumbai), Magnesium Stearate (SD Fine Chemicals Ltd, Mumbai), Opadry White (Colorcon, Mumbai).

EXPERIMENTAL WORK AND RESULTS

Preformulation studies[10-13]

Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms.

Determination of Bulk density and Tapped density

Bulk density is the ratio of the weight of a powder to the volume it occupies. It is expressed as gm/ml. Volume occupied by powder includes volume of the solid portion of the particle and voids between the particles. Bulk density is important in determining the size of the containers needed for handling and processing.

An accurately weighed quantity of the powder (W), was carefully poured into the graduated cylinder and the volume (V_o) was measured, then the graduated cylinder was closed with lid, set into the density determination apparatus. The density apparatus was set for 500 taps and after that, the volume (V_f) was measured and continued operation till the two consecutive readings were equal.

The bulk density, and tapped density were calculated using the following formulas.

Bulk density $= W / V_o$

Tapped density$= W / V_F$

Where,

W = weight of the powder

V_O = initial volume

V_F = final volume

Flow Properties

Irregular flow of powders from the hopper produces tablets with non uniform weights. As respects content uniformity and dose precision can not be achieved in a production of tablets & capsules. Flow properties depend on particle size shape porosity and density of bulk powder. The flow characteristics are measured by angle of repose: Improper flow of powder is due to frictional forces between the particles. These frictional forces are quantified by angle of repose.

Angle of repose is defined as the maximum angle possible between the height of a pile of the powder and the horizontal plane.

$$\tan Q = \frac{H}{R}$$

Where, H = Height of pile.

R = Radius of the base of pile.

Q = Angle of repose.

Compressibility Index[13-14]

Compressibility is indirectly related to the relative flow rate, cohesiveness and particle size of a powder. The compressibility of a material can be estimated from the tap and bulk density measurements.

Compressibility index were calculated using the formula.

Compressibility index=T.D-B.D/T.D*100

Hausner ratio: It indicates the flow property of the powder and Measured by the ratio of tapped density to bulk density.

Hausner ratio=T.D\B.D

Where,

T.D= Tapped density, B.D= Bulk density

Pre-formulation Characteristics of Darifenacin.

S.No	Drug	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Compressibility Index (%)	Hausner Ratio
1	Darifenacin	0.520	0.650	20.0	1.25

Table 1: Compilation of Darifenacin Extended Release Tablets.

S.No	Materials	F-1 Mg/Tab	F-2 Mg/Tab	F-3 Mg/Tab
1	Darifenacin	8.98	8.98	8.98
2	Lactose Anhydrous (DC Grade)	50	49.02	49.02
3	Dicalcium Phosphate (DC Grade)	40	40	40
4	Methocel K4M CR	99.02	90	90
5	Methocel K100M CR	0	10	10
6	Magnesium Stearate	2	2	2
	Uncoated Tablet weight (mg)	200	200	200
7	Opadry white (mg)	6.00	6.00	6.00
	Total weight (mg)	**206.00**	**206.00**	**206.00**

In- Process specification

Table 2: In- Process specification of the tablets.

S. No.	Parameters	Specifications
1	Description	White colored round shaped uncoated extended release tablets
2	Uniformity of tablets	200mg ± 2%
3	Weight of 20 tablets	200mg ± 4%
4	Thickness	3.7mm ± 0.2 mm
5	Hardness	NLT 5kg/cm^2
6	Friability	NMT 1%
7	Drug release 1st hr 4th hr 16th hr 24th hr	 10-20% 30-50% 60-75% NLT 90%

Evaluation of Darifenacin Extended Release Tablets

1. Description: By physical observation.

2. Average Weight: Weighed accurately 20 tablets and calculate the average weight.

$$\textbf{Average Weight} = \frac{\text{Weight of 20 tablets}}{20}$$

3. Uniformity of weight

20 tablets were selected randomly from a particular batch and weighed individually and

average weight was determined. Not more than two of the individual weights (mass) deviate from the average weight by more than the percentage deviation shown below and none deviated by more than twice that percentage.

4. Thickness

Ten tablets were selected randomly and reported the minimum and maximum thickness.

5. Hardness

Ten tablets were selected randomly from a batch and reported the minimum and maximum hardness by using the calibrated pharmatest apparatus.

6. Content Uniformity

Twenty tablets were selected randomly from a batch and powdered and assayed, the average weight of the medicament present in each tablet is calculated which is then compared with the desired weight.

Table 3: Evaluation of Tablets.

S.No	TEST	F-1	F-2	F-3
1.	Weight of tablet (mg)	208.39	210.0	208.2
2.	Hardness (kg/cm^2)	8.0	9.0	9.0
3.	Thickness (mm)	3.7	3.8	3.8
4.	Friability (%)	0.1	0.27	0.1

Table 4: Comparison Between Innovator(Enablex) And Product.

S.No	Parameter	Innovator	Product
1	Tablet Weight (mg)	209.70	208.08
2	Thickness (mm)	3.82	3.95
3	Dimension (mm)	8.17	8.11
5	Shape	Round	Round
6	Colour	White	White

Preparation of dissolution medium 0.1 N HCL

85ml of Hydrochloric acid dissolve in 50ml of purified water and diluted into 10000ml with purified water.

Preparation of standard solution

Weigh accurately 23 mg of Darifenacin working standard in 20ml volumetric flask, add 10

ml of methanol and sonicate to dissolve for about 5mins, further make up the volume with methanol Further dilute 1 ml to 50 ml with the medium (0.01N Hcl).

Preparation of sample solution

Transfer one tablet into 900ml of the dissolution medium and check the absorbance of the diluted samples at 220nm.

DISSOLUTION PROFILE

$$\text{Dissolution factor} = \frac{\text{Std. Wt.} * 1 * \text{volume of the medium} * \text{conversion factor} * \text{Std. Purity}}{20 * \text{Label claim} * 100}$$

$$= \frac{23.42 * 1 * 900 * 0.840 * 99.5}{20 * 7.5 * 100}$$

$$\% \text{ Dissolution} = \frac{\text{Sample. Abs} * \text{Dissolution factor}}{\text{Std. Abs}}$$

Chromatographic System[15-16]

Column	:	C-8, UG-5, Develosil
Wave length (λ)	:	UV, 220nm
Column temp	:	50º C
Flow	:	1.0 ml /min
Injection Volume	:	10µl
Run time	:	15min

Procedure

Inject one replicate of standard preparation for system suitability and five replicates of standard preparation and sample preparation in duplicate into the chromatographic system.

System suitability requirements

Theoretical plates should be not less than 3000, and asymmetry should be not more than 2.0. Standard area of % RSD should be not more than 2.o. Calculate the % of assay by using following formula.

Calculation

$$\% \text{ of Assay} = \frac{\text{Spl. Area x Std. Wt x Std.D.F x Avg.Wt x Potency of Std}}{\text{Std. Area x Std. Wt x Spl. D.F x Labeled Amount x 100}}$$

Table 5: Standard Peak Area in the HPLC Method for the Estimation of Darifenacin.

Vial	Injection volume(µl)	RT (MIN)	Peak Area	Area%
1	10	5.33	1652667	100
1	10	5.32	1652585	100
1	10	5.32	1667248	100
1	10	5.33	1653487	100
1	10	5.32	1654521	100
Average	10	5.32	1656101	100

Similarity Factor and Dissimilarity Factor calculation

The similarity factor (f2) was defined by CDER, FDA, and EMEA as the 'logarithmic reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and reference release profiles.[17-18]

Dissimilarity or difference factor (f1) describes the relative error between two dissolution profiles. It approximates the percent error between the curves. The percent error is zero when the test and reference release profiles are identical and increases proportionally with the dissimilarity between the two profiles.

There are several methods for dissolution profile comparison. f2 is the simplest among those method. Moore & Flanner proposed a model independent mathematical approach to compare the dissolution profile using two factors f1 & f2.[19]

$$f1 = \{ [\sum_{t=1}^{n} |R_t - T_t|] / [\sum_{t=1}^{n} R_t] \} . 100$$

$$f2 = 50 . \log \{ 1 + (1/n) \sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} . 100$$

Where 'R_t' "T_t' are the cumulative percentage dissolved at each of the selected n time point of the reference & test product respectively. The factor f1 is proportional to the average difference between the two profiles, where as factor f2 is inversely proportional to the averaged squared difference between the two profiles, with emphasis on the larger difference among all the time points. The factor f2 measures the closeness between the two profiles. Because of the nature of measurement, f1 was described as difference factor, & f2 as similarity factor. The similarity factor f2 and its significance is shown in Table.

Table 6: The similarity factor F2 and its significance.

S. No.	Similarity Factor (F2)	Significance
1.	<50	Test and reference profiles are dissimilar.
2.	50 -100	Test and reference profiles are similar.
3.	100	Test and reference profiles are identical.
4.	>100	The equation yields a negative value.

When the two profile are identical, f2 = 100. An average difference of 10% at all measured time point's results in a f2 value of 50. FDA has set a public standard of f2 value 50-100 to indicate similarity between two dissolution profiles.

For dissolution comparison: At least 12 units should be used for each profile determination. Mean dissolution values can be used to estimate the similarity factor, f2. To use mean data, the % coefficient of variation at the earlier point should not be more than 20% & at other time points should not be more than 10%. The dissolution measurements of the two products (test & reference) should be made under same test condition. The dissolution time point for both the profiles should be the same.

Because f2 values are sensitive to the number of dissolution time points, only one Measurement should be considered after 85% dissolution of the product.

STABILITY STUDY

For all the pharmaceutical dosage forms it is important to determine the stability of the dosage form. This will include storage at both normal and exaggerated temperature conditions, with the necessary extrapolations to ensure the product will, over its designed shelf life, provide medication for absorption at the same rate as when originally formulated. The design of the formal stability studies for the drug product should be based on the knowledge of the behavior and properties of the drug substance and formal stability studies on the drug substance.

Selection of batches

Data from stability studies should be provided on at least three promptly batches of the drug product. The primary batches should be of the same formulation and packaged in a same type of package as proposed for marketing. The manufacturing process used for primary batches should simulate that, to be applied to production batches and should provide product of the same quality and making the same specification as that intended for marketing. Two of the three batches should be at least pilot scale batches and the third one can be smaller.

Testing Frequency

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the drug product. For a product with a prolonged shelf life of at least 12 months, the frequency of testing at long term storage condition should normally be 3 months over the first year, every 6 months over the second year and annually thereafter through the proposed shelf life.

At the accelerated storage condition, a minimum of three points, including the initial and final time point (e.g. 0, 3, and 6 months), from a 6 month study is recommended. When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage conditions, a minimum of four time points, including the initial and final points (e.g. 0, 6, 9, and 12) from a 12-month study is recommended.

Storage Conditions

In general, a drug product should be evaluated under storage condition that tests its stability and if applicable, its sensitivity to moisture or potential for solvent loss. The long term testing should cover a minimum of 12 months study or at least three batches at the time of submission and should be continued for a period of sufficient time cover the proposed shelf life. Long term, accelerated and where appropriate, intermediate storage conditions for drug products are detailed in Table.

Table 7: Stability storage conditions[20]

Study	Storage condition	Minimum time period covered by data at submission.
Long term	25ºC ± 2 ºC/ 60% RH ± 5% RH	12 months
Intermediate	30ºC ± 2 ºC/ 65% RH ± 5% RH	6 months
Accelerated	40ºC ± 2 ºC/ 75% RH ± 5% RH	6 months

When significant change occurs at any time during 6 months testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria.

In general significant change for a drug product is defined as.

- A 5% change in assay from its initial value; or failure to meet the acceptance criteria for when using biological or immunological procedures.
- Any degradation products exceeding its acceptance criterion.

- Failure to meet the acceptance criterion for appearance, physical attributes, and functionality test. E.g. Hardness, dose delivery per actuation; however some changes in physical attributes may be accepted under accelerated condition and as appropriate for the dosage form.
- Failure to meet the acceptance criterion for Ph; or.
- Failure to meet the acceptance criterion for dissolution for 12 dosage units.

Storage conditions are maintained as stated in ICH guidelines.[21] The globalization and increase in worldwide trade in recent years has led to the need for international drug approvals and unification of regulatory requirements and evaluation products. ICH has already a number of harmonized guidelines providing guidance on generation of data that would be acceptable in European Union, Japan, and USA.

Evaluation

A systematic approach should be adopted in the presentation and evaluation of the stability information, which should include as appropriate, results from the physical, chemical and microbiological tests, particular attributes of the dosage form. The purpose of the stability study is to establish based on testing a minimum of three batches of drug product, a shelf life and storage instruction applicable to all future batches of the drug product manufactured and packaged under similar circumstances.

Any evaluation should consider not only the assay but also the degradation products and other attributes, where appropriate attention should be paid to reviewing the adequacy of the mass balance and different stability and degradation performances.

Accelerated Stability Studies[22]

Darifenacin extended release Tablets 7.5 mg were evaluated for accelerated stability studies at 40^0C / 75 % RH condition. The stability details / results are presented as below.

Storage Condition: 40^0C / 75 % RH

Pack: HDPE Container.

Storage Period: 2 and 3 months.

DISSOLUTION DATA

Table 8: Comparative Dissolution profile of Darifenacin HBr Extended Release Tablet Formulations with Innovator (ENABLEX).

Time (hr)	% Dissolved			
	F-1	F-2	F-3	Innovator
0	0	0	0	0
1	22	23	23	19
4	50	48	56	60
8	68	71	85	72
12	83	76	88	80
16	90	80	93	89
20	95	88	96	94
24	99	97	98	98

Table 9: R Values.

Formulation	Zero order	First order	Higuchi	Peppas	"n" Value
F1	0.935	0.979	0.984	0.946	0.24
F2	0.933	0.962	0.980	0.975	0.37
F3	0.856	0.990	0.936	0.977	0.37
Rt	0.896	0.987	0.960	0.963	0.29

Table 10: pH Conditions of GIT (To match F2 value in biological fluid).

Region	pH (Fasted)	pH(Fed)	Resident time
Stomach	1.7 (1.4 - 2.1)	5	1– 5 hrs
Duodenum	4.6 (2.4 –6.8)	4.5 – 5.5	> 5 hrs
Jejunum	6.1 (6.0 – 7.0)	4.5 – 5.5	1 – 2 hrs
Ileum	6.5	6.5	2 – 3 hrs
Colon	8	8	15 – 48 hrs

F1 and F2 calculation,

DISSOLUTION PROFILE COMPARISON						
	Innovator	TEST				
Time(hrs)	Avg. Reference	Avg. Test	/R-T/	/R-T/^{2}	F_2 =65.96	
					F_1 = 5.84	
1.00	19	28	-9	81.00		
4.00	60	54	6	36.00		
8.00	72	76	-4	16.00		
12.00	80	83	-3	9.00		
16.00	89	87	2	4.00		
20.00	94	92	2	4.00		
24.00	98	96	2	4.00		

Table 11: Stability data for Darifenacin Extended Release Tablets 500mg (F3).

	Test	Specifications	Initial	Period in Months		
				1	2	3
1	Description	White colored, round shaped film coated tablets.	Complies	Complies	Complies	Complies
2	Identification	The retention time of major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation as obtained in the assay.	Complies	Complies	Complies	Complies
3	Hardness (kg/cm^2)	NLT 3	7	9.5	8	8
4	Related Substances (%)	Not more than 1.0	0.19	0.30	0.32	0.38
5	Thickness (mm)	3.5 ± 0.2	3.54	3.57	3.49	3.42
6	Dissolution (by HPLC) 1^{st} hr 4^{th} hr 16^{th} hr 24^{th} hr	 10-25% 30-50% 60-75% NLT 90%	 22% 50% 70% 99%	 23% 48% 76% 97%	 19% 34% 75% 92%	 19% 42% 69% 95%
7	Assay (By HPLC) content of Darifenacin	NLT 90.0% and NMT 110%	103.5%	100.3%	100.8%	99.99%

CONCLUSION

Formulation-F3 containing 7.5 mg of Darifenacin per tablet and developed employing Anhydrous Lactose (49.02 mg), Dibasic Calcium Phosphate (40 mg), Methocel K4M CR (90 mg), Methocel K100M CR (10 mg) in the core and by film coating with Opadry White, is similar and equal to the innovator product in respect of all tablets properties and dissolution rate.

No significant change was observed in the drug content, physical properties and dissolution rate of these tablets after the storage period of 3 months at 40^{o} C and 75%RH. Hence the study resulted in the development of Darifenacin extended release tablets comparable to the innovator product fulfilling the objective of the study.

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