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FORMULATION & EVALUATION OF *DARIFENACIN HBR* EXTENDED RELEASE FILM COATED TABLETS AND COMPARED WITH THE INNOVATOR PRODUCT ENABLEX

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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 to offer benefits such as less inter and intra-subject variability in gastrointestinal transit time and show better reproducible pharmacokinetic behavior than conventional formulations which is equivalent to the marketed product Enablex. Formulation F3 gave a release profile similar to that of innovator product (Enablex). 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. Stability studies have been conducted as per ICH guidelines and the product was found stable till 3 months.

KEYWORDS: Darifenacin Hydrobromide, Extended release, Dissolution, Overactive bladder syndrome.

INTRODUCTION

Controlled release (CR) / Sustained release (SR) technology has rapidly emerged over the past three decades as a new interdisciplinary science that offers novel approaches to the delivery of bioactive agents into the systemic circulation for a prolonged period at a predetermined rate. The choice of drug to be delivered, clinical needs and drug pharmacokinetics are some of the important considerations in the development of CR / SR

formulations, in addition to the relationship between the rates of drug release from the delivery system to the maximum achievable rate of drug absorption in to the systemic circulation. By achieving a predictable and reproducible bioactive agent release rate for and extended period of time, CR / SR formulations can achieve optimum therapeutic responses, prolonged efficacy and also decreased toxicity.

Release Rate and Dose Consideration

As already mentioned, conventional dosage forms include solutions, capsules, tablets, emulsions, etc. These dosage forms can be considered to release their active ingredients into an absorption pool immediately.

$$\text{Dosage form} \xrightarrow[\text{Drug Release}]{K_r} \text{Absorption pool} \xrightarrow[\text{Absorption}]{K_a} \text{Target area} \xrightarrow[\text{Elimination}]{K_e}$$

The absorption pool represents a solution of the drug at the site of absorption.

Where

K_r= First order rate constant for drug release.

K_a=First order rate constant for drug absorption.

K_e=First order rate constant for overall drug elimination.

For immediate release dosage forms $K_r >>> K_a$ or alternatively absorption of drug across a biological membrane is the rate-limiting step in delivery of the drug to its target area.

For non-immediate release dosage forms, $K_r <<< K_a$, that is, release of drug from the dosage form is the rate limiting step. This cause the above kinetics scheme to reduce to

$$\text{Dosage form} \xrightarrow[\text{Release}]{K_r} \text{Target area} \xrightarrow[\text{Elimination}]{K_e}$$

Thus, the effort to develop a delivery system that releases drug slowly must be directed primarily at altering the release rate by affecting the value of K_r.

The ideal goal in designing a controlled-release system is to deliver drug to the desired site at a rate according to needs of the body, i.e. a self-regulated system based on feedback control but this is a difficult assignment.

In Film coating tablets are coated by a single or mixture of film forming polymers, such as HPMC, Carbowax, Polyethylene glycol l400 and Hydroxyl ethyl cellulose etc. The polymer is dissolved in some volatile solvents and is sprayed over the tablets in rotating pan. This process is continued till a uniform good film is formed over the tablets.

Materials, Methods and Excipients Profile Table: 1.

S.NO	INGREDIENTS	SPECIFICATIONS	CATEGORY
1	Darifenacin Hydrobromide	IH	Active
2	Lactose anhydrous (DC grade)	*USP*	Diluent & general binder
3	Dicalcium phosphate (DC grade)	USP	Diluent & general binder
4	Methocel K4M CR	USP	Polymer
5	Methocel K100M CR	USP	Polymer
7	Magnesium Stearate	USP	Lubricant
8	Opadry White	IH	Coating Agent

LIST OF EQUIPMENTS Table: 2.

S.NO	EQUIPMENT	MANUFACTURER	MODEL NO
1	Electronic Single Pan Balance	Sartorius	LA120S
2	Mesh #40 & 60	Retsec	ASL00
3	Tapped density tester	Electrolab	ETD-1020
4	Analytical Sieve Shaker	Retsec	ASL00
5	Blender	Saral Engg.	410AG
6	Mechanical stirrer	Remi motors	RQG-129D
7	Coating pan	Saral Engg.	GAC-275
10	pH meter	Digisum Electronics	707
11	Dissolution test apparatus	Electrolab USP XXII	TDT-08L
12	Stability chambers	Thermolab	M-722
13	D.T	Electro lab	ED-2AL
14	Hardness tester	Pharmatest	PTB-311E
15	Friabilator (USP)	Electro lab	EF-2
16	Compression machine	Cadmach	CMP210

BRIEF MANUFACTURING PROCEDURE OF FILM COATED TABLETS

Step1: Weighing

- All the ingredients were weighed accurately as per the manufacturing formula.

Step 2: Sieving &mixing

- Darifenacin HBr, Lactose anhydrous, Dicalcium phosphate, Methocel K4M CR, Methocel K100M CR were passed through #40 mesh sieve & collected in a polybag.
- Magnesium stearate was passed through #60 mesh sieve & collected in a polybag.

Step 3: Blending

- The above sifted materials were loaded into an octagonal blender and blended at slow speed for about 15 min.
- Magnesium stearate was passed through #60 mesh and it was added to the contents of octagonal blender and mixed for 5 min.

Step 4: Compression

- Blended material was loaded into a hopper and compresses the powder into tablets by using (cad mach) compression machine with (8.0) mm SC punches.
- Check for weight variation, hardness, friability, thickness to meet the parameters.
- Collect the tablets in a cleaned double poly bag indicating the product and batch number.

In- Process specification

Table: 3 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%

Step 5: Film Coating

39 gm of Opadry White dispersed in 286.1 gm of purified water with electrical stirrer till the consistency has been reached.

SPECIFICATIONS

a) Pan size (capacity) : 265

b) Pan Speed : 12 RPM

c) In let temperature : 70 ^{0}C

d) Out let temperature : 45 ^{0}C

e) Bed temperature : 48 ^{0}C

f) Air pressure : 3Kg/cm^2

g) Peristaltic pump speed: 1.5 RPM

ANALYTICAL DATA

Darifenacin Extended Release Tablets Method of Analysis.

DISSOLUTION (BY UV)

Dissolution Parameters

Medium: 0.01 N Hcl

Volume: 900 ml

Apparatus: Basket

Temperature: 37.0 ± 0.5 °C

RPM: 100

Sampling Intervals: 1, 4, 8,12,16,20 & 24 hrs

Wavelength: λmax: 220nm.

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

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

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

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

Chromatographic System

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

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

RESULTS AND DISCUSSION

Pre-formulation Characteristics of Darifenacin

Table: 4.

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

Compilation of Darifenacin Extended Release Tablets

Table: 5.

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

7	Uncoated Tablet weight (mg)	200	200	200
8	Opadry white (mg)	6.00	6.00	6.00
	Total weight (mg)	**206.00**	**206.00**	**206.00**

EVALUATION OF TABLETS

Table: 6.

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

COMPARISON BETWEEN INNOVATOR AND PRODUCT

Table: 7.

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

Standard Peak Area in the HPLC Method for the Estimation of Darifenacin
Table: 8.

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

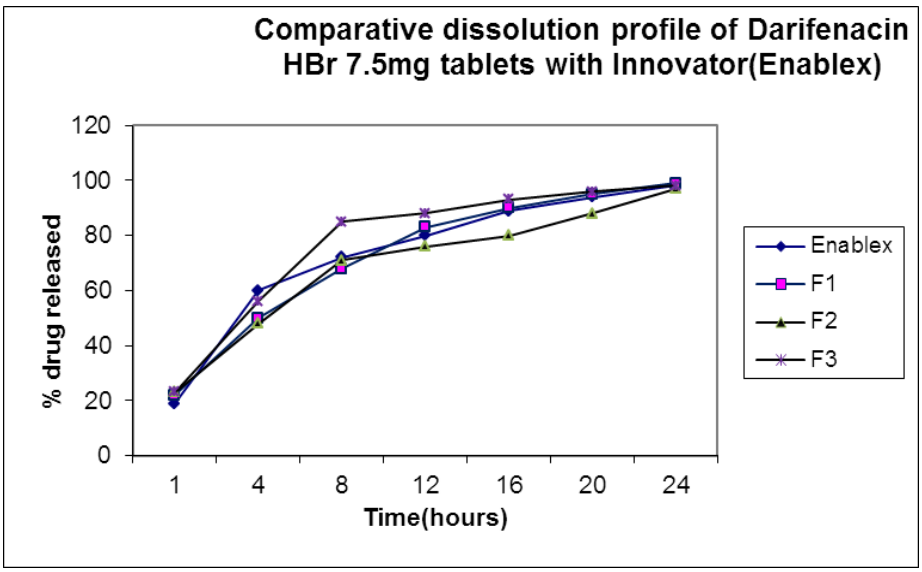
DISSOLUTION DATA

Formulation	AVG PEAK AREA				AREA%	AVG RETENTION TIME(MIN)			
	2^{nd}(hr)	4^{th}(hr)	12^{th}(hr)	24^{th}(hr)		2^{nd}(hr)	4^{th}(hr)	12^{th}(hr)	24^{th}(hr)
F-1	931899.6	1397849	1738351	1792114	100	5.31	5.31	5.30	5.31
F-2	878136.2	1254480	1587813	1792114	100	5.30	5.30	5.31	5.32
F-3	698924.7	913978	1444444	1790322	100	5.31	5.31	5.32	5.31
ENABLEX	764923	798653	1508258	1635821	100	5.33	5.31	5.31	5.31

Comparative Dissolution profile of Darifenacin HBr Extended Release Tablet Formulations with Innovator (ENABLEX) Zero order

Table: 9.

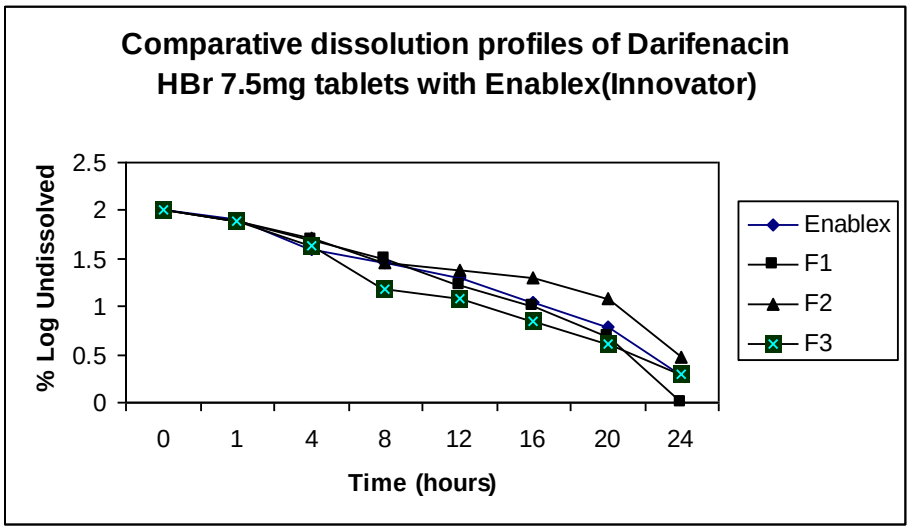
Time(hr)	% Dissolved			
	F-1	F-2	F-3	Innovator
0	0	0	0	0
1	22	23	23	19
4	50	48	56	60
8	68	71	85	72
12	83	76	88	80
16	90	80	93	89
20	95	88	96	94
24	99	97	98	98



Comparative Dissolution profile of Darifenacin Extended Release Tablet Formulations with Innovator (ENABLEX) First order

Table: 10.

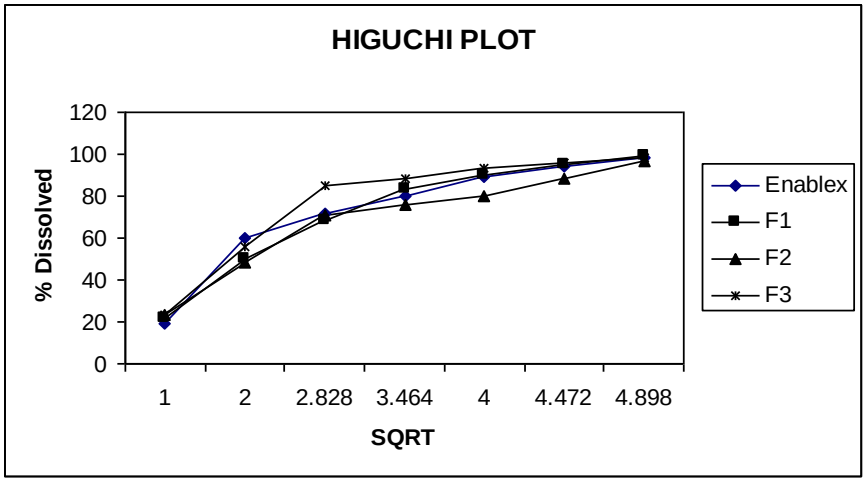
Time(hr)	Log % Undissolved			
	F-1	F-2	F-3	Innovator
0	2	2	2	2
1	1.892	1.886	1.886	1.908
4	1.698	1.716	1.643	1.602
8	1.505	1.462	1.176	1.447
12	1.23	1.38	1.079	1.301
16	1	1.301	0.845	1.041
20	0.698	1.079	0.602	0.778
24	0	0.477	0.301	0.301



Comparative Dissolution profile of Darifenacin Extended Release Tablet Formulations with Innovator (ENABLEX) Higuchi Plot

Table: 11.

SQRT	% Dissolved			
	F-1	F-2	F-3	Innovator
1	22	23	23	19
2	50	48	56	60
2.828	68	71	85	72
3.464	83	76	88	80
4	90	80	93	89
4.472	95	88	96	94
4.898	99	97	98	98



Comparative Dissolution profile of Darifenacin Extended Release Tablet Formulations with Innovator (ENABLEX) Peppas Plot

Table: 12.

LOGT	Log% dissolved			
	F-1	F-2	F-3	Innovator
0.602	1.892	1.886	1.886	1.908
0.903	1.698	1.716	1.643	1.602
1.079	1.505	1.462	1.176	1.447
1.204	1.23	1.38	1.079	1.301
1.301	1	1.301	0.845	1.041
1.38	0.698	1.079	0.602	0.778

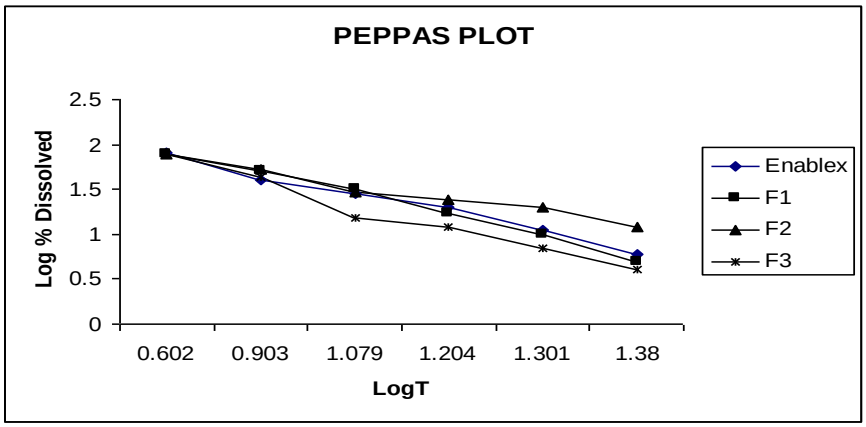


Table: 13. R Values

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: 14- 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.

Table 15 P^H 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

Table: 16 F1 and F2 calculation.

	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		

Stability storage conditions Table: 17.

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

Table: 18 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) 1st hr 4th hr 16th hr 24th 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%

RESULTS AND DISCUSSION

The objective of the study is to formulate Darifenacin Extended Release Film coated tablets. Four formulations of film coated tablets were developed employing different proportions of Anhydrous Lactose, Dibasic Calcium Phosphate, Methocel K4M CR, Methocel K100M CR in the core tablet and by film coating the cores with Opadry White. All the finished products were evaluated for uniformity of weight, thickness, hardness, drug content uniformity and dissolution rate. Based on the analysis of innovator product (ENABLEX), product specifications for various tablet properties are prescribed. Dissolution rate study was performed in 900ml of 0.1N HCl using USP-I (Basket) apparatus.

All the four tablet formulations are of good quality and fulfilled the pre-set specifications for various tablets properties.

Dissolution of Darifenacin from all the formulations developed was slow and spread over 24hrs.Release followed first order kinetics. Release data of the tablets were obeyed First order, Higuchi, Peppas equation models Higuchi plots were linear indicating that the drug release from these tablets was diffusion controlled. When the release data was analyzed as per Peppas equation model, the "n" value was in the range 0.24-0.37 with all the four formulations developed and innovator product (Enablex) indicating that the fickian diffusion was the release mechanism.

Among the four products developed formulation F3 gave a release profile similar to that of innovator product (Enablex). The dissolution profiles of formulation F3 and innovator product (Enablex) were compared by calculating difference factor (f1) and similarity factor (f2). The values of f1 and f2 were found to be 5.84 and 65.96 respectively for the comparison of dissolution profiles of formulation F3 and innovator product (Enablex). As such formulation-F3 developed is considered similar and equal to the innovator product.

Formulation F3 developed was subjected to stability testing by conducting accelerated stability study at 40^0 C/ 75%RH for 3 months .No significant change was observed in the percentage drug dissolved in 24 hrs after storage period of 3 months at 40^0 C and 75%RH.The other properties of formulation also remained unaltered. No significant change in drug content and other physical properties of tablets were observed.

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 film coated tablets comparable to the innovator product fulfilling the objective of the study.

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