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RESEARCH ARTICLE

Formulation and Evaluation of Darifenacin Hydrobromide Extended Release Matrix Tablets

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ABSTRACT

Darifenacin hydrobromide is a highly selective muscarinic (M3) receptor blocker that has been widely used for the treatment of overactive bladder syndrome. The bioavailability of darifenacin hydrobromide is 15–19% due to extensive first pass metabolism. Hence oral administration of darifenacin hydrobromide as extended tablets is a possible solution to overcome this problem. So the aim of the study was to formulate and evaluate Darifenacin hydrobromide extended release matrix tablets using extended release polymers like HPMC K4M, HPMC K15M and HPMC K100M, Metalose 60 SH-50 and Xanthum gum in different concentrations. Formulated tablets were characterized for different parameters like hardness, thickness, weight variation, friability, % Cumulative drug release etc. Nine formulations (F1 – F9) were formulated using direct compression technique. From the results obtained, it was concluded that the optimized formulation containing HPMC K15 M and K100M (1:2) showed better release up to 24hrs.The dissolution profiles and kinetic studies indicate that the release of Darifenacin Hydrobromide can be effectively controlled by the use of hydrophilic matrix systems. Different kinetic models were applied to the optimized formulation and observed that formulation (F9) followed first order kinetic model and Non-Fickian diffusion (or) Anomalous transport as mechanism of drug release.

KEYWORDS

Darifenacin Hydrobromide, Extended Release Matrix Tablets, Bioavailability, HPMC K15M and HPMC K100M

INTRODUCTION

Oral route is the most oldest and convenient route for the administration of therapeutic agents because of low cost of therapy and ease of administration which leads to higher level of patient compliance[1]. Approximately 50% of the drug delivery systems available in the market are oral drug delivery systems and historically too, oral drug administration has been the predominant route for drug delivery[2,3].

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It does not pose the sterility problem and minimal risk of damage at the site of administration[4].

During the past three decades, numerous oral delivery systems have been developed which act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate.[5]

The oral controlled release formulations have been developed for those drugs that are easily absorbed from the gastrointestinal tract (GIT) and have a short half-life and eliminated quickly from the blood circulation.[6] As these will release the drug slowly into the GIT and maintain a

constant drug concentration in the plasma for a longer period of time.[7] In oral controlled drug delivery the amount of drug release is constantly predetermined and these constant releases of drug provide a constant blood plasma level of the drug for optimal therapeutic response[8].

Why Darifenacin Hydrobromide as Extended Release Tablets?

Darifenacin hydrobromide is a highly selective muscarinic (M3) receptor blocker that has been widely used for the treatment of overactive bladder syndrome. Darifenacin hydrobromide is an Anticholinergic which inhibits the binding of acetylcholine to the muscarinic receptor in the detrusor muscle, thereby suppressing involuntary bladder contractions and increases bladder void volume, as well as decrease in micturition frequency and sensation of urgency.

Treatment of OAB is aimed at reducing the debilitating symptoms in order to improve the overall quality of life in affected patients and Anticholinergic agents that target the muscarinic receptors in the bladder (antimuscarinic agents) as the medical treatment of choice because they reduce the contractility of the detrusor muscle. The bioavailability of darifenacin hydrobromide is 15–19% due to extensive first pass metabolism. So the oral administration of darifenacin hydrobromide as extended release tablets is a possible solution to overcome this problem.

MATERIAL AND METHODS

Darifenacin Hydrobromide Gifted by Shasun Chemicals and Drugs Ltd, Chennai, Tamil Nadu. Dibasic Calcium phosphate, Metalose 60 SH-50, Xanthan gum and magnesium stearate gifted by Signet chemical Ltd. Mumbai. HPMC K4M, K15M and K100M, gifted by Colorcon, Mumbai. All other chemicals and reagents used were of A.R. grade.

Drug and Excipients Compatibility Study by FTIR spectroscopy

FTIR spectroscopy was mainly done for the identification of drug compound and also for the determination of whether any reaction occurs between drug, polymer mixer along with excipients or during the shelf life of product or any other unwanted effects on the formulation. Spectroscopy of pure drug (Darifenacin hydrobromide), dibasic calcium phosphate, HPMC K4M, K15M and K100M, Metalose 60 SH 50, Xanthum gum and Magnesium stearate were carried out on Bruker FT-IR model and spectrum was scanned in the wavelength range of 400-4000cm^{-1} to investigate any possible interaction between drug and its physical mixture with polymers and different excipients. Excipients are mixed with the Darifenacin Hydrobromide (API) in following ratios shown in Table 1.

Table 1: Ratios of drug and excipients

Sr. No	Composition	Ratio
1	API + Di basic calcium phosphate	1:10
2	API + Methocel K 4 M	1:5
3	API + Methocel K 15 M	1:5
4	API + Methocel K 100 M	1:5
5	API + Metalose 60 SH 50	1:5
6	API + Xanthum gum	1:5
7	API + Magnesium stearate	1:0.5

Preparation of Extended Release Tablets

The composition of Darifenacin Hydrobromide extended release matrix tablets formulations shown in Table 2. Drug, dibasic calcium phosphate and different grades of HPMC sifted through 30# mesh and magnesium stearate was weighed, passed through 80# mesh separately and collected. All the ingredients were weighed and mixed. Required quantity of powder blend was compressed using 8.0mm round shaped standard concave punches using 16 station compression machine.

Table 2: Composition of Darifenacin Hydrobromide Extended Release Matrix Tablets Formulations (F1 – F9)

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
API									
Darifenacin Hydrobromide	15	15	15	15	15	15	15	15	15
Excipients									
Dibasic calcium phosphate	122	122	122	122	122	122	122	122	122
Methocel K 4 M	60.00	0.00	0.00	0.00	0.00	30.00	0.00	20.00	0.00
Methocel K 15 M	0.00	60.00	0.00	0.00	0.00	30.00	30.00	40.00	20.00
Methocel K 100 M	0.00	0.00	60.00	0.00	0.00	0.00	30.00	0.00	40.00
Metalose 60 SH 50	0.00	0.00	0.00	60.00	0.00	0.00	0.00	0.00	0.00
Xanthan Gum	0.00	0.00	0.00	0.00	60.00	0.00	0.00	0.00	0.00
Magnesium Stearate	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Total	200.00	200.00	200.00	200.00	200.00	200.00	200.00	200.00	200.00

Evaluation Parameters[9-11]

Pre-compression Evaluations

A. Bulk Density

An accurately weighed quantity of powder, which was previously passed through 18# sieve [USP] was carefully poured into graduated cylinder. After pouring the powder into the graduated cylinder the powder bed was made uniform without disturbing. The volume was measured directly from the graduation marks on the cylinder as ml. The volume measured was called as the bulk volume and the bulk density is calculated by the following formula:

$$\text{Bulk density} = \frac{\text{Weight of the powder (w)}}{\text{Bulk volume } (v_o)}$$

B. Tapped Density

After measuring the bulk volume the same measuring cylinder was set into tap density apparatus. The tap density apparatus was set to 100 taps and operated for 500 taps. Volume measured was noted as (V_f). The tapped density is calculated by the following formula:

$$\text{Tapped Density} = \frac{\text{Weight of the powder (w)}}{\text{Tapped volume } (v_f)}$$

C. Angle of Repose

Angle of repose is the tan inverse of angle between height of the pile of powder and the radius of the base of conical pile.

$$\Theta = \tan^{-1} h/r$$

Where, h = height

r = radius

Values for angle of repose less than or equal to 30^o suggest a free flowing material and angles greater than or equal to 40^o suggest a poorly flowing material.

D. Compressibility Index (CI)

Compressibility is indirectly related to the relative flow rate, cohesiveness and particle size distribution of the powder. Powders with compressibility values lesser than about 20% have been found to exhibit good flow properties.

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

E. Hausner's Ratio

It is the ratio of bulk volume to tapped volume or tapped density to bulk density. Hausner's ratio is an important character to determine the flow property of powder and granules. This can be calculated by the following formula:

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Value < 1.25 indicate good flow (=20% Carr's index)

While > 1.50 indicate poor flow (=35% Carr's index)

Between 1.25 and 1.5, adding glidant will improve flow.

Post-compression Evaluations

A. Weight Variation Test

Twenty tablets were accurately weighed using an electronic balance and average weight was calculated by using the following formula:

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

The tablets passes the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double the percentage limit.

IP/BP	Limit	USP
80 mg or less	± 10%	130mg or less
More than 80mg or Less than 250mg	± 7.5%	130mg to 324mg
250mg or more	± 5%	More than 324mg

B. Hardness

Monsanto hardness tester was used to evaluate the hardness of tablets. Five tablets of each formulation were evaluated and average values were calculated.

C. Thickness

The thickness and diameter of the tablets was determined by using vernier calipers. Five tablets were used, and average values were calculated.

D. Friability

The friability of tablets was measured by Roche friabilator for 4min at 25rpm i.e.100 revolutions. Accurately weighed twenty tablets, placed into Roche friabilator and tablets were collected after 4min and observed for possible capping / breaking as none of these should be observed for the test to be valid. Tablets were weighed after dusting excess powder from their surface.

$$\text{Friability} = \frac{W_1 - W_2}{W_1} \times 100$$

Where, W_1 = Initial weight of tablets taken

W_2= Final weight of the tablets after testing

E. Assay[12]

Five tablets were randomly chosen from each formulation and powdered in a mortar and a portion of the resulting powder equal to the weight of the respective tablet was solubilized in 0.1N HCl. Several aliquots were then filtered using a sintered glass filter and assayed spectrophotometrically at 215nm.

F. In-vitro Drug Release Study[13]

In-vitro drug release studies were conducted using USP – Type 1 (basket) dissolution apparatus at a rotational speed of 100 rpm at 37±0.5°C and 900 ml of 0.1N HCl used as dissolution medium. Dissolution was carried out in 0.1N HCl for first 2hrs followed by pH 6.8 phosphate buffer up to 24hrs. Sink conditions were maintained for the whole experiment.

Samples (5 ml) were withdrawn at regular intervals and the same volume of fresh dissolution medium was replaced to maintain the volume constant. The samples withdrawn were filtered through a 0.45µ membrane filter and the drug content in each sample was analyzed after suitable dilution with a UV spectrophotometer at 215nm.

Kinetic Data Analysis[14]

To analyze the *in-vitro* release data various kinetic models were used to describe the release kinetics. The zero order Eq. (1) describes the systems where drug release rate is independent of its concentration. The first order Eq. (2) describes the release from system where drug release rate is concentration dependent. Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3).

$$C = k_0 t \ldots\ldots\ldots\ldots (1)$$

Where, k_0 is zero-order rate constant expressed in units of concentration/time and t is time.

$$\text{Log } C = \text{Log}C_0 - kt/2.303 \ldots\ldots (2)$$

Where, C_0 is the initial concentration of drug and K is first order constant.

$$Q = Kt_{1/2} \ldots\ldots\ldots (3)$$

Where, K is the constant reflecting the design variables of the system.

The following plots were made: *cumulative % drug release vs. time* (zero order kinetic models); *log cumulative of % drug remaining vs. time* (first order kinetic model); *cumulative % drug release vs. square root of time* (higuchi model) and *log cumulative % drug release vs. log time* (korsmeyer model).

RESULTS AND DISCUSSION

Drug-Excipient Compatibility Study

Drug and Excipients compatibility study was performed by using Bruker FT-IR spectrophotometer. From the spectra, it would be concluded that, there was no interaction between drug and different polymer mixtures and the drug was compatible with all the excipients used in the formulation shown in figure 1 and 2. Hence these release retarding materials were selected for formulation of extended release tablets.

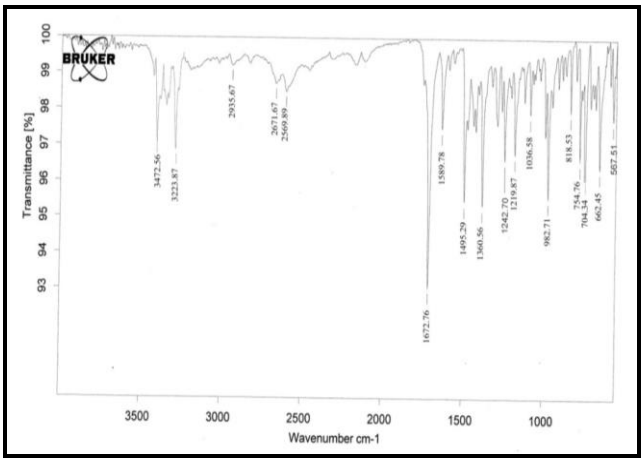

Figure 1: FT-IR spectra of Darifenacin Hydrobromide

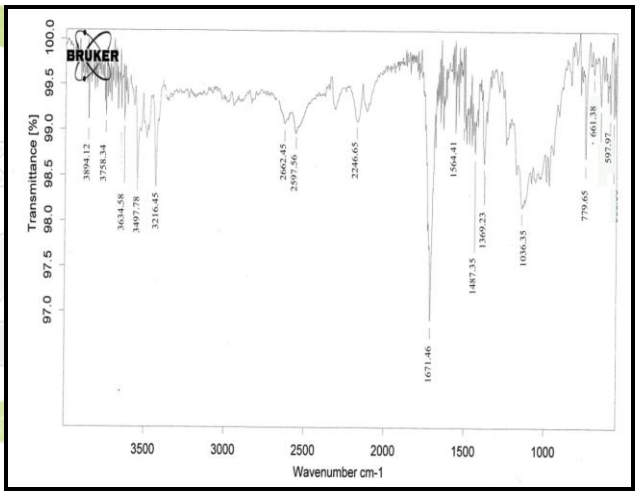

Figure 2: FT-IR Spectra of physical mixtures of Darifenacin hydrobromide, HPMC K4M, K15M, K100M, Metalose 60 SH 50, Xanthum gum and Magnesium stearate

Evaluation Parameters

Pre-compression Evaluations for Batches F1 to F9

The powder blend for formulation batches of API were evaluated for Bulk density, Tapped density, Angle of repose, Carr's index and Hausner's ratio and the results were shown in Table 3. The bulk densities of blends were in the range of 0.412g/cc to 0.482 g/cc. Tapped density was found between 0.467 g/cc to 0.553 g/cc. These values indicate that the blends had good flow

Table 3: Characterization of Darifenacin Hydrobromide extended release matrix blend

Formulation code	Bulk Density (g/cc)	Tapped Density (g/cc)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (º)
F1	0.426	0.485	12.1	1.14	27.23
F2	0.412	0.467	11.7	1.13	26.45
F3	0.436	0.502	13.1	1.15	23.56
F4	0.443	0.509	12.9	1.15	28.97
F5	0.423	0.478	11.5	1.13	23.26
F6	0.453	0.517	12.3	1.14	28.20
F7	0.457	0.512	11.5	1.12	29.04
F8	0.482	0.553	12.8	1.14	26.86
F9	0.424	0.475	10.9	1.12	27.61

Table 4: Characterization of Darifenacin Hydrobromide extended release matrix tablets

Formulation	Hardness (kg/cm^2)	Thickness (mm)	Weight variation (mg)	Friability (%w/w)	Content Uniformity (%)
F1	9.5	3.56	200	0.18	99.17
F2	8.2	3.49	202	0.22	99.44
F3	8.5	3.53	205	0.43	98.64
F4	9.1	3.61	201	0.20	100.2
F5	9.6	3.62	204	0.24	99.24
F6	8.5	3.63	201	0.53	99.19
F7	9.5	3.55	203	0.29	99.73
F8	9.4	3.71	201	0.17	99.69
F9	9.8	3.59	202	0.19	99.82

property. The angles of repose of different formulations were in the range of 23.26º to 29.04º, which indicates that the material had excellent flow property.

Hence it was confirmed that the flow property of blends were good. Carr's index for all the formulations was found to be in the range of 10.9 to 13.1 and Hausner's ratio ranges from 1.12 to 1.15, which reveals that the blends have good flow character. From the pre-compression studies it could be concluded that for all the formulations of API shows good flow properties and direct compression method was used for compression of tablets.

Post-compression Evaluations for Batches F1 to F9

Darifenacin Hydrobromide extended release matrix tablets were prepared by direct compression method by using different polymers like Metalose 60 SH 50, Xanthan gum and different grades of HPMC in different ratios and the formulations were evaluated for different parameter like hardness, friability, drug content, weight variation and the results are shown in Table 4. The hardness for tablets of different formulations was found to be in range of 8.2 to 9.8 kg/cm^2, indicates good mechanical strength of tablets. Further the strength of tablets was confirmed by conducting friability test and the values were found to be less than 1% for all the formulations and considered to be satisfactory. All the formulations passed the weight variation test as the % weight variation was within the

acceptable limits. The % drug content for all the formulations were in the range of 98.64% to 100.2% which indicates that the amount of drug in all the formulations was uniform.

In-vitro Dissolution Study

In-vitro drug release studies were carried out by using USP–Type1 (basket) dissolution apparatus at a rotational speed of 100 rpm at 37±0.5°C and 900 ml of 0.1N HCl used as dissolution medium for first 2hrs followed by pH 6.8 phosphate buffer up to 24hrs. Sink conditions were maintained for the whole experiment. Samples (5 ml) were withdrawn at regular intervals and the drug content in each sample was analyzed after suitable dilution by using UV spectrophotometer at 215nm. The data obtained from the *in-vitro* drug release was plotted between time vs % cumulative drug release. Drug release profiles for all the formulations were shown in figure 3&4.

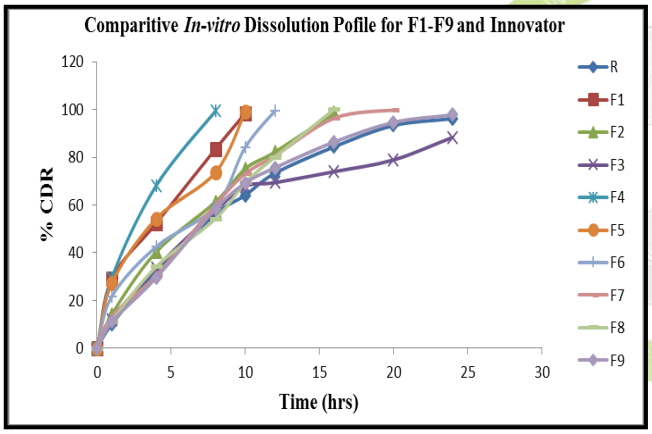

Figure 3: Comparative dissolution profile for formulation F1 to F9 and innovator (Enablex)

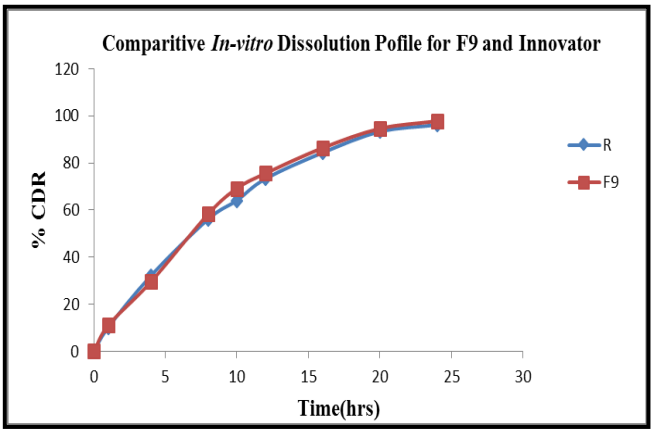

Figure 4: Comparative dissolution profile for formulation F9 and innovator (Enablex)

From the dissolution profiles it could be concluded that formulation F1 containing HPMC K4M (60mg) released the drug 98.4% at 10hrs time point due to less viscosity of polymer and F2 containing HPMC K15M (60mg) released the drug 98.6% at 16hrs due to less retarding nature of the polymer.

Formulation F3 containing HPMC K100M (60mg) which retarded the drug release but only 88.4% of drug was released at 24hrs due to higher molecular weight of polymer.

Formulations F4 and F5 containing Metalose 60SH 50 (60mg) and Xanthan gum (60 mg) released the drug 99.4% and 99.2% at 8hrs and 10hrs respectively due to less retarding nature of polymers.

The drug release profiles for five formulations (F1 to F5) could not match with that of the drug release profiles of innovator product. Hence combinations of different grades of HPMC were tried for formulations F6 to F9 in 1:1 and 1:2 ratios.

The drug released from formulation F6 containing 1:1 ratio of HPMC K4M and K15M was found to be 99.4% at 12hrs, and the drug release was found to be extended when HPMC K4M was used alone.

The drug released from formulation F7 containing 1:1 ratio of HPMC K15M and K100M was found to be 99.8% at 20 hrs and the drug release was found to be extended when HPMC K15M was used alone.

The drug released from formulation F8 containing 1:2 ratio of HPMC K4M and K15M was found to be 100.1% at 16hrs and the drug release was found to be extended than formulation F6 but it could not effectively control the drug release up to 24hrs due to less viscosity of polymeric concentration.

The drug released from formulation F9 containing 1:2 ratio of HPMC K15M and K100M was found to be 97.8% at 24hrs and the drug release was retarded when HPMC K15M was used alone and extended when HPMC K100M was used alone.

Among all formulations, formulation F9 containing HPMC 15M and 100M (1:2) extended the drug release up to 24hrs and it was comparable with that of the innovator product (Figure 4).

Hence formulation F9 was considered as an optimized formulation.

Release Kinetics

The kinetic release data was computed from the drug release data obtained from the *in-vitro* dissolution study. Kinetic release data obtained for optimized formulation F9 and innovator product was fitted to the mathematical models; Zero order, First order, Higuchi and Korsmeyer-Peppas models. The R^2 values are shown in table 5 for optimized formulation.

The drug release was found to be first order as R^2 value of first order (0.974) (Table 5) was found to be more than R^2 value of zero order (0.906.)(Table 5), indicates that the drug release was concentration dependent.

To know the mechanism of drug release the data was fitted to higuchi model (R^2 value 0.989) (Table 5) and the drug release was found to be diffusion controlled. Further to know the exact mechanism of drug release the data was fitted to Koresmeyer-peppas model and based on the "n" value (n = 0.617) (Table 5), the mechanism of drug release was found to follow anomalous behavior or non – Fickian transport. (If n = 0.45 it is called Case I or Fickian diffusion, 0.45 < n < 0.89 is for anomalous behavior or non – Fickian transport, n = 0.89 for case II transport and n > 0.89 for Super case II transport).

Table 5: Release kinetics for optimized formulation F9

Zero order R^2	First order R^2	Higuchi R^2	Koresmeyer-peppas	
			R^2	n
0.906	0.974	0.989	0.798	0.617

CONCLUSION

The extended release matrix tablets of Darifenacin hydrobromide were formulated by direct compression method by using various polymers like HPMC K4M, HPMC K15M, and HPMC K100M in different ratios, Metalose 60 SH 50 and xanthan gum. The formulations were evaluated for various parameters like Hardness, Friability, Weight variation, *In-vitro* release study, Drug content, etc. From the results obtained, it was concluded that the optimized formulation F9 containing HPMC K15M and K100M (1:2) showed better release rate which extended the drug release up to 24hrs when compared with that of the innovator product.

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