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*Research Article*

# FORMULATION AND EVALUATION OF EXTENDED RELEASE TABLETS OF DARIFENACIN HYDROBROMIDE

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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. The compatibility between drug and excipients were determined by using DSC. Eight formulations (F1 to F8) of darifenacin hydrobromide extended release tablets were developed by direct compression method using HPMC K4M CR and HPMC K 100M CR, as polymers at different ratios. Formulation F-6 containing 45 % of HPMC K4M CR & 5 % of HPMC K100M CR was found to be the optimized formulation based on *in- vitro* release of drug i.e. 82 % of drug release was observed in 16 hrs & up to 98 % in 24 hours. Kinetics to the *in-vitro* release of drug for the formulation, F-6 showed that it followed first order release (*R2* = 0.9686) and release mechanism followed was Hixson Crowell cube root law (*R2* =0.9816). Further, *in-vitro* release pattern of F-6 was found to be super imposable (i.e. the similarity factor *f2* was found to be 81.90) with the marketed product ENABLEX. F-6 formulation was found to be stable during accelerated stability studies conducted at 40 °C / 75% RH for three months as per ICH guidelines.

**Keywords:** Darifenacin hydrobromide, overactive bladder syndrome, extended release.

## INTRODUCTION

Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate and necessarily reduce the dosage frequency by two folds are known as extended release dosage forms. In Diffusion systems, the release rate of a drug being dependent on its diffusion through an inert membrane barrier[1, 2]. Usually, this barrier is an insoluble polymer. It may be a) Reservoir devices, b) Matrix devices. Darifenacin was found to have a short terminal elimination half-life after administration as intravenous and immediate-release oral dosage forms i.e. 3-4 hours, but this can be increased with an extended release formulation i.e. 14-16 hours. Darifenacin ER tablets are developed to overcome the inconvenience of multiple dosing per day that is necessary with the immediate release formulation[3, 4]. There is therefore a need of administering darifenacin in an oral dosage form once or twice daily in the form of extended release tablets for the treatment of overactive bladder in humans[5, 6].

## MATERIALS AND METHODS

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)

**Drug-Excipient Compatibility studies**

Compatibility studies are carried out to study the possible interactions between Darifenacin HBr and other inactive ingredients.

**Procedure**

The compatibility studies were carried out by taking a mixture of drug and excipients at the ratio 1:1 or in which they are expected to be present in the innovator product (Table: 1). Such samples are placed in previously labeled glass vials and properly closed using strips of aluminum foil. These samples are exposed to pre-determined storage conditions like 40 °C/75 %RH, 30 °C/60 %RH, etc. In the present study room conditions (25 °C/60 %RH) were selected. They were tested using DSC (differential scanning calorimeter) with respect to their physical and chemical aspects[7].

**METHOD FOR PREPARATION OF FILM COATED TABLETS**

**Direct compression method**

All the ingredients were weighed accurately as per the manufacturing formula. Darifenacin HBr was passed through # 30 mesh sieve and collected properly in a labeled polybag. Lactose anhydrous, Dicalcium phosphate, Methocel K4M CR, Methocel K100M CR were individually passed through # 40 mesh sieves & collected in labeled polybags. Magnesium stearate was passed through # 60 mesh sieves & collected in a polybag. The above sifted materials were loaded into an octagonal blender and blended at slow speed for about 15 min. Magnesium stearate which was passed through # 60 mesh was added to the contents of octagonal blender and mixed for 5 min. Blended material was loaded into a hopper and compresses the powder into tablets by using (Cad mach) compression machine with (8.0) mm SC plain 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 [8, 9].

**Evaluations:**

**Average Weight:[10]**

Weighed accurately 20 tablets and calculate the average weight.

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

**Uniformity of weight[11]**

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.

**Dissolution**

Dissolution test was carried out by using Dissolution test apparatus (Electrolab USP XXII-TDT-08L) with type USP-I apparatus (basket)and the medium was 900 ml of 0.01M HCl Comparative data should be provided in the following media: pH 4.5 buffer, pH 6.8 buffer and water at 100 rpm for 24 hrs (time intervals 1, 4, 8,12,16,20 & 24 hrs)[12].

**Accelerated Stability Studies**

Darifenacin extended release tablets 15 mg were evaluated for accelerated stability studies at 40°C / 75% RH condition HDPE Container, Storage Period: 2 and 3 months [13, 14].

**RESULTS AND DISCUSSIONS**

Pre-formulation studies on the active powder blend was evaluated for physical characteristics like bulk density, tap density, compressibility index, and Hausner's ratio before being compressed into tablets. Hausner's ratio of all the formulations was less than 1.25 indicating excellent flow properties. The compatibility between the drug and excipients were conducted by using DSC analysis. The compatible excipients with the drug were taken for the optimization of the formulation. Eight formulations of darifenacin hydrobromide granules were prepared by using different grades (HPMC K4M CR & HPMC K4M CR) and varying compositions of HPMC by direct compression method. The punched tablets were film-coated using opadry white coating material and the coated tablets were evaluated. Suitable analytical method, HPLC was developed for determination of the drug content. The average retention time is 6.234 min and the analytical wavelength is 220 nm. The method gave reproducibility. The darifenacin hydrobromide ER tablets of formulation F-6 containing 45 % of HPMC K4M CR & 5 % of HPMC K100M CR was found to be best formulation based on *in-vitro* drug dissolution studies determined using four different media as specified by CDER/FDA.

From the dissolution studies, it was found that 82 % of the drug was released in 16 hrs & up to 98 % in 24 hours. The dissolution profile of the optimized formulation F-6 was compared with

the marketed product ENABLEX. The similarity factor, *f2* is 81.90 indicating that the dissolution profile of optimized formulation was super-imposable with the dissolution profile of the marketed product. Application of kinetics to the *in-vitro* dissolution profile of the optimized formulation showed that the release of drug followed first order kinetics (R2 = 0.9686) and Hixson-Crowell cube root law (R2 = 0.9816)
Accelerated stability studies on all the formulations were conducted as per ICH guidelines (40±2 °C and 75±5 % RH) for 3 months and the optimized formulation was found to be stable. Further studies are needed to investigate the developed tablets for their performance *in-vivo* and it's equivalence with the marketed products.

**CONCLUSION**

The conclusions arrived in this thesis indicated that the darifenacin hydrobromide ER tablets developed in this research was found to be pharmaceutically equivalent to the marketed product ENABLEX based on *in-vitro* release studies. The drug release was extended for 24 hrs, thereby making it suitable for administration as a once-a-day formulation. Thus, the objectives of the thesis were arrived.

**Table 1: Ratios of drug and excipients taken for compatibility studies**

| S.No. | API & Excipient | Ratio |
|---|---|---|
| | **API + Diluent** | |
| 1 | API: Lactose Anhydrous | 1:1 |
| 2 | API: Lactose monohydrate | 1:1 |
| 3 | API: Calcium carbonate | 1:1 |
| 4 | API: Dicalcium phosphate | 1:1 |
| | **API + Polymers** | |
| 1 | API: HPMC K100M CR | 1:1 |
| 2 | API: HPMC K4M CR | 1:1 |
| 3 | API: HPMC E4M | 1:1 |
| 4 | API: Methocel E5 | 1:1 |
| 5 | API: HPMC K15M | 1:1 |
| | **API + Lubricant** | |
| 1 | API: Magnesium Stearate | 10:01 |
| 2 | API: Stearic acid | 10:01 |
| 3 | API: Hydrogenated Castor oil powder | 10:01 |
| | **API + Coating material** | |
| 1 | API: Opadry white | 1:1 |

**Table 2: Formulation of Darifenacin hydrobromide ER Tablets**

| FORMULATION MATERIAL(mg/tab) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|
| Darifenacin Hydrobromide | 17.96 | 17.96 | 17.96 | 17.96 | 17.96 | 17.96 | 17.96 | 17.96 |
| Anhydrous Lactose | 40.04 | 40.04 | 40.04 | 40.04 | 40.04 | 40.04 | 40.04 | 40.04 |
| Dicalcium phosphate | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Methocel K4M CR | 100 | 50 | 60 | 70 | 80 | 90 | 95 | 0 |
| Methocel K100M CR | 0 | 50 | 40 | 30 | 20 | 10 | 5 | 100 |
| Magnesium Stearate | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Uncoated Tablet Weight(mg) | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |
| Coating Material (Build up weight of tablet is 3% using coating suspension) | | | | | | | | |
| Opadry White | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Coated Tablet Weight (mg) | 206 | 206 | 206 | 206 | 206 | 206 | 206 | 206 |

**Table 3: Percentage deviation allowed for the tablets**

| Pharmaceutical Form | Avg. Weight | % Deviation |
|---|---|---|
| Tablets (Un coated and film coated) | Less than 80 mg | **10** |
| | More than 80 and less than 250 mg | **7.5** |
| | More than 250 mg | **5** |

**Table 4: DSC results of drug-excipient compatibility studies**

| Excipient | Category | Compatibility status with the drug |
|---|---|---|
| Lactose Anhydrous | Diluent | Compatible |
| Dicalcium phosphate | Diluent | Compatible |
| HPMC K4M CR | Polymer | Compatible |
| HPMC K100M CR | Polymer | Compatible |
| Magnesium Stearate | Lubricant | Compatible |
| Opadry white | Coating material | Compatible |

**Table 5: Dissolution studies of F-6 in 0.01M HCl**

| Time (hours) | Cum. % drug | Log cum.% undissolve | $\sqrt{t}$ | Cube root % drug undissolved |
|---|---|---|---|---|
| 0 | 0 | 2.0 | 0 | 4.6 |
| 1 | 20.8 | 1.89 | 1 | 4.2 |
| 4 | 55.5 | 1.64 | 2 | 3.5 |
| 8 | 69.6 | 1.42 | 2.828 | 3.1 |
| 12 | 81.1 | 1.27 | 3.464 | 2.6 |
| 16 | 89 | 1.04 | 4 | 2.2 |
| 20 | 95 | 0.69 | 4.472 | 1.7 |
| 24 | 98.6 | 0.14 | 4.898 | 1.1 |

**Table 6: Stability data for darifenacin hydrobromide ER tablets (F-6)**

| S.No | 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 corresponds to that of the standard preparation. | Complies | Complies | Complies | Complies |
| 3 | Hardness (kg/cm2) | NLT 5 | 10.31 ± 0.408 | 9.53 ± 1.212 | 8.5 ± 0.969 | 9.89 ± 1.959 |
| 4 | Thickness (mm) | 3.60 to 3.90 | 3.76 ± 0.102 | 3.67 ± 2.312 | 3.79 ± 0.225 | 3.82 ± 0.119 |
| 5 | Dissolution | | | | | |
| | 1st hr | 10-25% | 22% | 23% | 19% | 19% |
| | 4th hr | 30-50% | 50% | 48% | 34% | 42% |
| | 16th hr | 60-75% | 70% | 76% | 73% | 69% |
| | 24th hr | NLT 90% | 99% | 97% | 92% | 95% |
| 6 | Assay | NLT 90.0% and NMT 110% | 103.50% | 103.30% | 100.80% | 99.99% |

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