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FORMULATION AND EVALUATION OF DARIFENACIN HYDROBROMIDE EXTENDED RELEASE FORMULATION USING RESERVOIR DRUG DELIVERY SYSTEM

G. Venkata Sudarsan[1], Prabhakar reddy veerareddy*[2] T.Vijaya Bhaskara Reddy[3]

[1]Department of Biotechnology, Acharya Nagarjuna University, Nagarjuna Nagar, Andhra Pradesh, India

*[*2]College of Pharmacy, Palamuru University, Mahabubnagar, Andhra Pradesh, India*

[3]Acharya Nagarjuna University, Nagarjuna Nagar, Andhra Pradesh, India

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 reservoir drug delivery system which is equivalent to the marketed product Enablex. To design the dosage form, suitable excipients were selected for formulating core tablets, 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 followed by the formulation optimization. F3 formulation has 3% ethyl cellulose coating on to the core tablets, which was optimized to 9% 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).

Keywords: Darifenacin Hydrobromide, Extended release, Reservoir drug delivery system, 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.

Address for correspondence

Prof. Dr. Prabhakar Reddy Veerareddy
College of Pharmacy, Palamuru University, Mahabubnagar, E-Mail: vpreddyindia@gmail.com
Contact: 09989804999

A typical reservoir system[2] consists of a core (the reservoir) and a coating membrane (the diffusion barrier). The core contains the active ingredients and excipients, whereas the membrane is made primarily of rate-controlling polymer(s). The governing release mechanism is diffusion from the reservoir across the membrane to the bulk solution. Osmotic pressure could be operative to obtain a reservoir release system in certain cases, especially for highly soluble drug molecules. Release profile from a reservoir system depends on both formulation and solubility of drug molecules. Similar to matrix systems, developing a reservoir system with pH-independent release is not straightforward unless the solubility of drug molecules is pH independent. A reservoir system normally contains many coated units (particulates) such as beads, pellets, and mini tablets and tablets.

MATERIALS AND METHODS

Darifenacin Hydrobromide (Megafine Laboratories, Mumbai), Povidone: Plasdone K 29/32 (ISP), Surelease coating system (Colorcon), Dicalcium Phosphate: A-Tab

(Innophos) and Magnesium stearate: Ligamed MF-2-V (Peter Greven) and Purified water.

Drug-Excipient Compatibility studies[3]

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:

Formulation of core tablets, rate controlling polymer coating:

All the ingredients were weighed as per the manufacturing formula. Darifenacin HBr was co-sifted along with equal quantity of Dicalcium phosphate, remaining Dicalcium phosphate, Povidone were sifted separately and all these sifted materials were blended together for 15 min followed by lubrication of the blend using Magnesium stearate. This lubricated blend was compressed into tablets. Surelease coating system was dispersed in required quantity of purified water for 20 minutes and the core tablets were coated using this rate controlling polymer dispersion till the required build-up is achieved and cured for required time using the following parameters.

Table 1

S. No	Parameters	Set Values
1	Inlet temp(^{0}C)	52 - 58°C
2	Exhaust temp (^{0}C)	39 - 43°C
3	Pump (rpm)	2 – 6
4	Spray rate (g/min)	4 – 8
5	Atomization (bar)	1.0

These polymer coated tablets were then film coated using Opadry coating system.

Evaluation of blend parameters[4]:

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:

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

$$\textit{Hausner's ratio} = \frac{\textit{Tapped Density}}{\textit{Bulk Density}}$$

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.

$\tan \theta = h / r$

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

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 2

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

Dissolution parameters:

Table 3

Medium	0.1 N HCl ; 900 mL
Apparatus	Type-I (Basket)
RPM	100
Time points	1, 2, 4, 8, 12, 16, 20, 24 hrs
Temperature	37 °C ± 0.5 °C

Chromatographic conditions:

Table 4

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.

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

Sequence of injections:

Compositions of the trials performed

Table 5

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	Dicalcium Phosphate	176.154	174.154	165.154	163.154	159.154	157.154	155.154	153.154
3	Povidone (Plasdone K 29/32)	3.00	5.00	8.00	8.00	8.00	8.00	8.00	8.00
4	Magnesium stearate	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Rate controlling polymer Coating									
5	Surelease coating system	--	--	6.0	8.0	12.0	14.0	16.0	18.0
6	Purified Water	--	--	Qs	Qs	Qs	Qs	Qs	Qs
	Coated tablet weight	--	--	**200**	**200**	**200**	**200**	**200**	**200**
7	Opadry coating system	--	--	5.0	5.0	5.0	5.0	5.0	5.0
8	Purified Water	--	--	Qs	Qs	Qs	Qs	Qs	Qs
	Film coated tablet weight	--	--	**205.0**	**205.0**	**205.0**	**205.0**	**205.0**	**205.0**

RESULTS

Blend Parameters:

Table 6

Formulation	Bulk density	Tapped density	Angle of repose	Carr's index	Hausner's ratio
F1	0.43	0.56	25.62	23.21	1.30
F2	0.44	0.55	26.25	20.00	1.25
F3	0.44	0.54	26.8	18.52	1.23
F4	0.45	0.55	27.26	18.18	1.22
F5	0.44	0.53	27.54	16.98	1.20
F6	0.45	0.56	28.42	19.64	1.24
F7	0.44	0.55	25.56	20.00	1.25
F8	0.45	0.57	25.21	21.05	1.27

Compression Parameters:

Table 7

Formulation	Hardness (kp)	Thickness (mm)	Average weight (mg)	Friability (%w/w)	% of Drug
F1	6.2	3.57	200	0.62	98.9
F2	7.2	3.52	201	0.41	99.5
F3	8.0	3.49	201	0.10	99.2
F4	8.1	3.51	199	0.11	100.4
F5	8.6	3.46	202	0.13	99.9
F6	8.5	3.46	202	0.12	99.8
F7	8.7	3.43	200	0.11	99.9
F8	8.4	3.44	201	0.08	100.2

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

In-Vitro Dissolution profiles:

Table 8

Time (hrs)	Enablex	% 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
1	10	17	27	22	19	19	10	17	8	14	9	14	8	15
4	32	9	61	9	57	10	46	8	42	9	35	7	29	7
8	56	8	89	8	80	8	71	8	69	7	66	7	51	7
12	73	5	97	2	90	7	87	4	83	4	82	5	76	5
16	84	6	98	3	100	3	94	4	92	3	90	4	88	3
20	93	4	98	2	102	2	97	2	99	1	96	2	97	2
24	96	2	97	2	102	2	99	1	100	1	98	1	99	1
*f*2 Value			32		37		48		52		60		71	

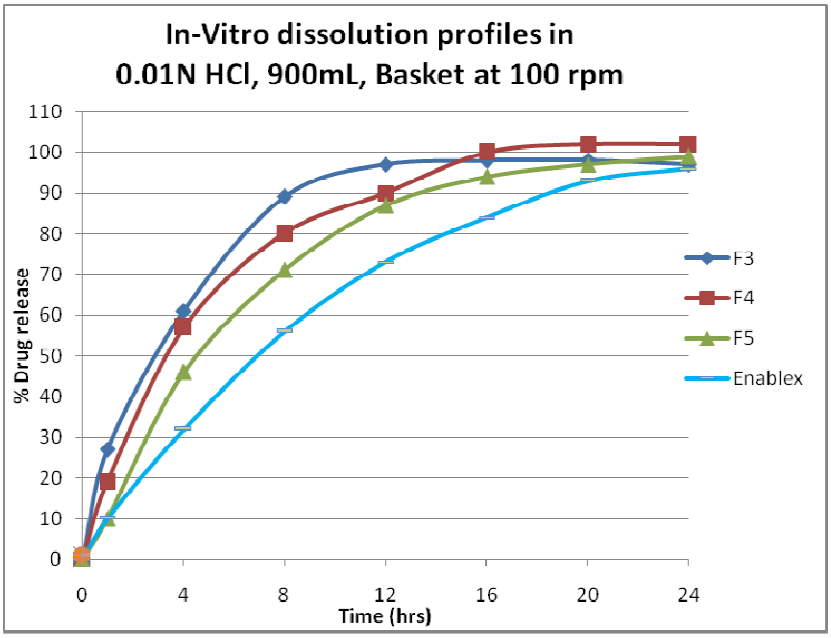

Fig 1: Graphical representation of In-vitro dissolution profiles (F3 to F5)

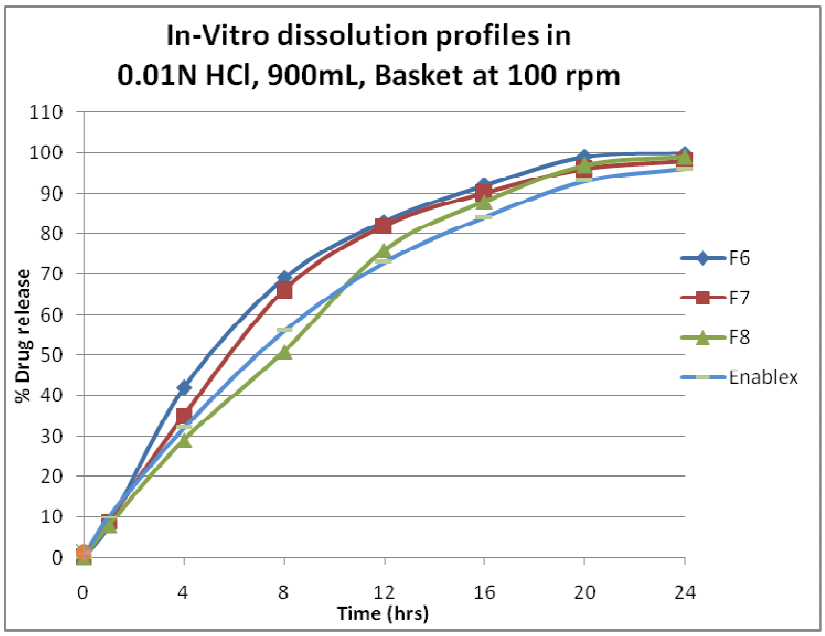

Fig 2: Graphical representation of In-vitro dissolution profiles (F6 to F8)

DRUG RELEASE KINETICS[5]:

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

$F=K_0t$

Here, 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[6, 7]:

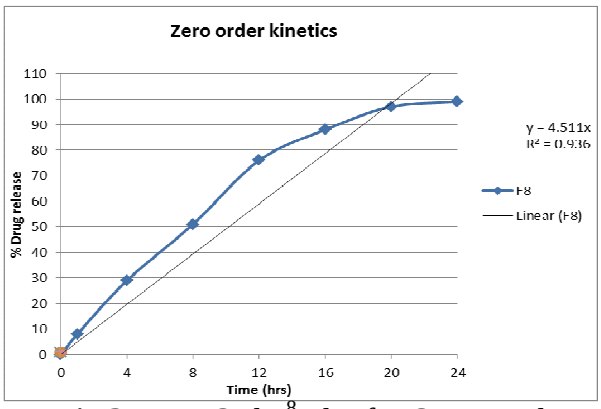

Fig 3: Zero Order[8] Plot for Optimized formulation (F8)

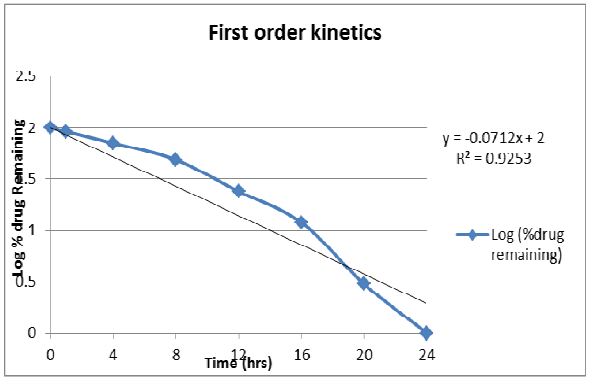

Fig 4: First Order Plot for Optimized formulation (F8)

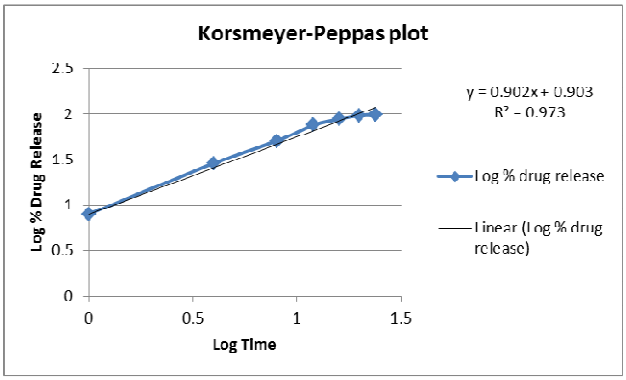

Fig 5: Korsmeyer-Peppas plot of Optimized formulation (F8)

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%.

Pre compression parameters:

Table 6 shows that the angle of repose of different formulations was found between 25.21 to 28.42 which indicate that material had excellent flow property. So it was confirmed that the flow property of blends was very good. The bulk density of blend was found between 0.43g/mL to 0.45 g/mL. Tapped density was found between 0.53g/mL to 0.57 g/mL. These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 16.98-23.21 and Hausner's ratio from 1.20-1.30 which reveals that the blends have fair flow character.

Compression parameters:

Table 7 shows that the hardness of the tablet was acceptable and uniform from batch to batch, which was found to be in between 6 - 9 kp. All the formulations passed the weight variation test as the % weight variation was within the limits of ±5% of the tablet weight. Friability values were found to be less than 1% in all the formulations F1 to 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 composition of the formulation F8. Core tablet composition was optimized in trials F1 to F3 to improve tablet friability as well as other physical characteristics. Formulation F3 to F6 were releasing the drug around 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.

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