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FORMULATION AND EVALUATION OF TOLTERODINE TARTRATE EXTENDED RELEASE CAPSULES USING MULTIPARTICULATE DRUG DELIVERY SYSTEM

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ABSTRACT

Tolterodine tartrate is a muscarinic M2 & M3 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 of Tolterodine tartrate using multiparticulate drug delivery system. To design the dosage form, suitable pellets were selected and drug was coated onto the pellets, followed by extended release coating onto the drug loaded pellets, mixing of the coated pellets with suitable excipients and filling into suitable capsules. Compatibility of Tolterodine tartrate has been established with the proposed ingredients and followed by the formulation optimization. F3 formulation has 2% Ethyl cellulose/Hypromellose coating in 1:1 ratio on to the drug loaded pellets, which was optimized to 8% in F8 formulation to obtain the required release pattern and complete release at 8 hr time point with similar profile as of marketed product with satisfactory similarity values (f2).

Keywords: Tolterodine tartrate, extended release, Multiparticulate, Dissolution, Overactive bladder

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.

Multiparticulate[2] drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05-2.00mm[3]. Thus multiparticulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet and encapsulated or compressed into a tablet. Multiparticulate are discrete particles that make up a multiple unit system. They provide many advantages over single-unit systems because of their small size. Multi particulates are less dependent on gastric empty ting, resulting in less inter and intra-subject variability in gastrointestinal transit time[4]. They are also better distributed and less

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likely to cause local irritation. Recently much emphasis is being laid on the development of multiparticulate dosage forms in preference to single unit systems because of their potential benefits such as increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying. There are many reasons for formulating a drug as a multiparticulate system for example, to facilitate disintegration in the stomach, or to provide a convenient, fast disintegrating tablet that dissolves in water before swallowing which can aid compliance in older patients and children. Multiparticulate systems show better reproducible pharmacokinetic behavior than conventional (monolithic) formulations. After disintegration which occurs within a few minutes often even within seconds, the individual subunit particles pass rapidly through the GI tract. If these subunits have diameters of less than 2mm, they are able to leave the stomach continuously, even if the pylorus is closed. These results in lower intra and inter individual variability in plasma levels and bioavailability. Drug safety may also be increased by using multiparticulate dosage forms, particularly for modified release systems. For example, if the film coat of a single-unit (monolithic) enteric coated tablet is damaged, the complete dose will be released into the stomach where it may cause pain or ulceration or reduced efficacy, depending on the reason for choosing the protection of the enteric coating. Equally, if there is damage to the film coating of a monolithic tablet with a sustained release formulation, this can lead to "dose dumping" and result in dramatic side effects. The oral multi-unit particulate drug delivery systems (MDDS), have gained immense importance, not only because of their ability to control drug release, but also for the modified drug-release profiles they facilitate oral multiparticulate drug delivery systems (e.g. pellets, granules) offer biopharmaceutical advantages in terms of a more even and predictable distribution and transportation through the GI tract, which is fairly independent of the nutritional state[5]. By contrast, in multiparticulate formulation, the release characteristics are incorporated into every single subunit and any damage only affects the release behavior of the subunit involved, which represents a small part of the total dose, reducing the likelihood of safety problems[6].

MATERIALS AND METHODS

Tolterodine tartrate (Zhejiang), Microcrystalline cellulose pellets (Asahi Kasei), Hypromellose: Methocel E5 Premium LV (Dow Chemicals), Ethanol (Merck), Dichloromethane (Ranchem), Ethyl cellulose (Colorcon), Microcrystalline cellulose (FMC Biopolymer), Talc (Luzenac Pharma) and Magnesium stearate: Ligamed MF-2-V (Peter Greven) and Purified water.

Drug-Excipient Compatibility studies:[7]

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 30 days time periods for physical description as well as related substances using HPLC technique to evaluate possible interaction between drug and excipients.

Manufacturing process of Capsules:

Preparation of Drug solution:

1. Tolterodine tartrate was dissolved in Ethanol and stirred for 10 min.
2. Hypromellose was dissolved in purified water and mixed with the above and continued stirring for 10 min.

Drug loading:

1. Core pellets were loaded in to Fluid bed processor and run till up to product temp reached 40 $\pm$ 5°C.
2. The drug solution was sprayed on to the fluidized bed with optimum fluidization.
3. The following are the parameters followed and recorded during the process.

Table 1

S. No	Parameters	Set Values
1	Inlet temp(^{0}C)	48 - 55°C
2	Product temp (^{0}C)	38 - 43°C
3	Exhaust temp (^{0}C)	32 - 37°C
4	Pump (rpm)	10 - 20
5	Spray rate (g/min)	4 - 10
6	Atomization (bar)	1.0
7	Air flow (m^3/hr.)	50 - 70
8	% RH	8 - 11

The yield was calculated and drug loaded pellets were taken to next step of manufacturing.

Preparation of Ethyl cellulose & Hypromellose Coating Solution

1. Hypromellose (Methocel E5 Premium LV) was dissolved in purified water and Ethyl cellulose was dissolved in ethanol and dichloromethane mixture.
2. The above solutions were mixed and continued stirring for 10 min.

Functional coating of the polymer solution on the drug loaded pellets:

1. Drug loaded pellets were loaded in to FBP and dried up to product temp 40 $\pm$ 5°C.
2. The polymer solution was sprayed on to the fluidized bed with optimum fluidization with the following parameters.

Table 2

S. No	Parameters	Set Values
1	Inlet temp(^{0}C)	37 – 40 °C
2	Product temp (^{0}C)	33 – 36 °C
3	Exhaust temp (^{0}C)	32 – 33 °C
4	Pump (rpm)	10-20
5	Spray rate (g/min)	4 - 8
6	Atomization(bar)	1.0
7	Air flow (m^3/hr.)	50 - 70
8	% RH	8 - 11

Blending of the coated pellets with extra-granular ingredients.

The coated pellets were blended with talc and lubricated with Magnesium stearate using bin blender.

Capsule Filling:

The above blend was filled into size 4 capsules with the required fill weight.

Evaluation of blend parameters[8]:

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 Capsules

1.0 In-vitro dissolution by HPLC

Chemicals/Reagents:

Table 3

S. No.	Chemicals/Reagents	Make/Grade
1.	Perchloric acid	Merck (GR-Grade)
2.	Acetonitrile	Merck (HPLC-Grade)
3.	Methanol	Merck (HPLC grade)
4.	Water	Purified water/TKA water

Dissolution parameters:

Table 4

Medium	pH 6.8 phosphate buffer.
Apparatus	Type-I (Basket)
RPM	100
Time points	1, 2, 3, 5, 7 & 8 hours
Temperature	37 °C ± 0.5 °C

Chromatographic conditions:

Table 5

Column	Hiban 150x 4.65µm
Flow rate	1.0 mL / min
Detector wave length	210 nm
Oven temperature	30 °C
Injection volume	10 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 (pH 6.8 phosphate buffer):

Dissolve accurately 68.1 g of Monobasic potassium phosphate in about 8000mL of purified water. Add exactly 1112.0mL of a 0.2M NaOH solution and dilute to 10000mL with purified water. Verify that the pH of the resulting solution is 6.80 ± 0.05.

Preparation of Standard stock solution:

Accurately weigh 10 mg of Tolterodine tartrate working standard into 500 mL volumetric flask, add 10 mL of methanol, dissolve and sonicate for 2 minutes. Make up the volume up to 500 mL with dissolution media.

Preparation of Standard solution:

Further dilute 5 mL of the standard stock solution to 20 mL with dissolution media.

Preparation of Sample solution:

Place 6 Tablets individually in six dissolution vessels containing 900 mL of medium 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 (10 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.

Sequence of injections:

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

Compositions of the trials performed

Table 6

S. No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
1	Tolterodine tartrate	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
2	Celpheres CP 507	120	120	120	120	120	120	120	120
3	Methocel E5 LV premium	1.0	1.4	1.6	1.6	1.6	1.6	1.6	1.6
4	Ethanol	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
5	Purified water	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Ethyl cellulose Coating		--	--	**2%**	**3%**	**4%**	**6%**	**10%**	**8%**
6	Drug loaded pellets	--	--	125.6	125.6	125.6	125.6	125.6	125.6
7	Ethyl cellulose	--	--	1.3	1.9	2.5	3.75	6.3	5.0
8	Methocel E5 LV Premium	--	--	1.3	1.9	2.5	3.75	6.3	5.0
9	Ethanol	--	--	Qs	Qs	Qs	Qs	Qs	Qs
10	Dichloromethane	--	--	Qs	Qs	Qs	Qs	Qs	Qs
11	Talc	--	--	0.7	0.7	0.7	0.7	0.7	0.7
12	Magnesium stearate	--	--	0.7	0.7	0.7	0.7	0.7	0.7
	Capsule fill weight		--	**129.5**	**130.8**	**132.0**	**134.5**	**139.6**	**137.0**

RESULTS

Blend Parameters:

Table 7

Formulation	Bulk density	Tapped density	Angle of repose	Carr's index	Hausner's ratio
F1	0.42	0.56	28.92	25.00	1.33
F2	0.47	0.58	26.21	18.97	1.23
F3	0.51	0.62	24.82	17.74	1.22
F4	0.50	0.61	25.36	18.03	1.22
F5	0.49	0.60	24.54	18.33	1.22
F6	0.51	0.63	23.42	19.05	1.24
F7	0.52	0.63	23.56	17.46	1.21
F8	0.51	0.62	22.21	17.74	1.22

NOTE: Parameters of F1 & F2 are of drug loaded pellets and for the remaining trials the parameters are of final blend.

Filled capsules Parameters:

Table 8

Formulation	Weight of 10 filled capsules	Uniformity of net fill weight	Locking length	Disintegration time
F3	1.68 g	Min – 125.3 mg Max – 135.1 mg Average – 129.6 mg %RSD – 2.36	13.61mm to 14.13 mm	2:20 min
F4	1.69 g	Min – 126.2 mg Max – 132.2 mg Average – 130.4 mg %RSD – 1.40	13.68mm to 14.17 mm	2:15 min
F5	1.71 g	Min – 128.0 mg Max – 136.8 mg Average – 132.2 mg %RSD – 2.00	13.70mm to 14.17 mm	2:25 min
F6	1.74 g	Min – 130.1 mg Max – 140.5 mg Average – 134.9 mg %RSD – 2.38	13.65mm to 14.13 mm	2:35 min
F7	1.78 g	Min – 134.2 mg Max – 143.8 mg Average – 139.1 mg %RSD – 2.30	13.67mm to 14.14 mm	2:40 min
F8	1.77 g	Min – 132.3 mg Max – 141.4 mg Average – 136.5 mg %RSD – 2.15	13.69mm to 14.15 mm	2:30 min

In-Vitro Dissolution profiles:

Table 9

Time (hrs)	Detrol LA	% 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	11	15	49	21	42	17	39	15	15	12	7	13	12	12
2	33	8	79	8	75	8	72	8	45	8	21	8	39	8
3	61	7	89	1	86	7	83	6	71	6	45	8	65	7
5	80	5	98	3	96	5	92	4	90	4	64	6	82	5
7	88	4	100	2	99	3	97	3	94	3	77	5	88	3
8	99	2	100	1	100	2	98	2	99	1	89	5	100	2
***f*2 Value**			**25**		**28**		**31**		**52**		**46**		**73**	

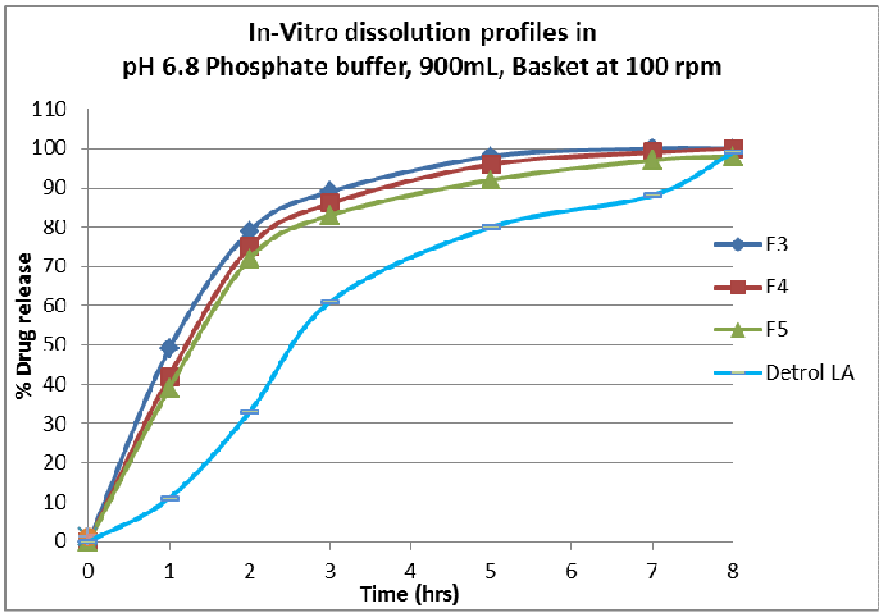

Fig 1: Graphical representation of In-vitro dissolution profiles (F3 to F5)

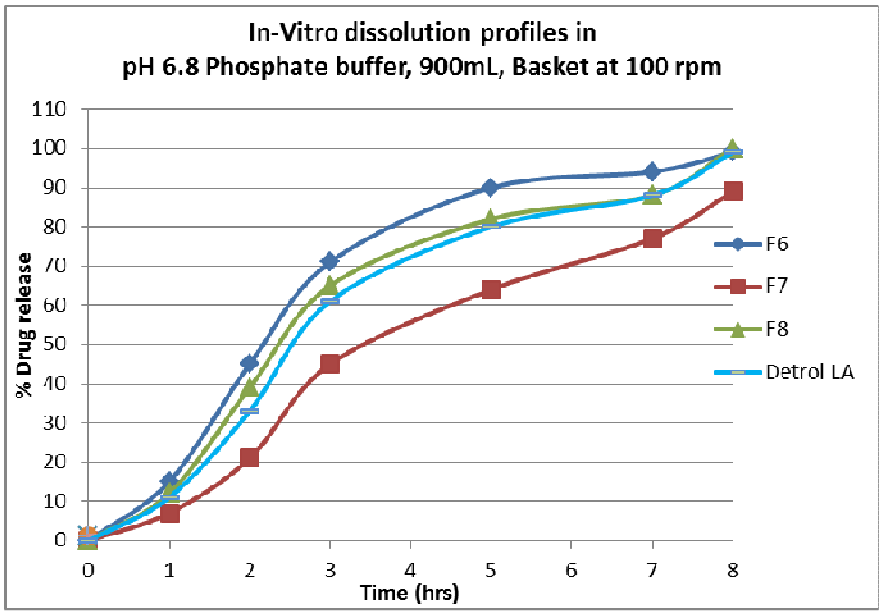

Fig 2: Graphical representation of In-vitro dissolution profiles (F6 to F8)

DISCUSSION:

Drug Excipient Compatibility Studies:

According to guidelines on impurity of drug product the drug product containing 15 mg dose /day acceptance criteria is 1.0%. Drug – excipient compatibility indicates that the all used excipients in the formulation are compatible with the drug by HPLC, impurities was less than 1.0%.

Final blend parameters:

Table 5 shows that the angle of repose of different formulations was found between 22.21 to 25.36 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 0.49 g/mL to 0.52 g/mL. Tapped density was found between 0.60 g/mL to 0.63 g/mL. These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 17.46 – 19.05 and Hausner's ratio from 1.21 - 1.24 which reveals that the blends have fair flow character.

Filled capsule parameters:

Table 6 shows that the individual capsule weights are uniform and well within the acceptable limits. The % drug content for all the formulations were close to 100 and varied between 98.9 to 100.3%. Disintegration time of all the batches was found within the limits.

CONCLUSION:

An optimized formulation was obtained with composition of the formulation F8. Drug loading was optimized in trials F1 to F3 to achieve proper drug loading onto the pellets. Formulation F3 to F6 was releasing the drug around 90% within 5 hours. 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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