

## DEVELOPMENT AND EVALUATION OF NOVEL DRUG DELIVERY SYSTEM OF TOLTERODINE TARTRATE

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### ABSTRACT

**Objective:** Tolterodine tartrate (tolterodine) is used for treating overactive bladder (OAB) with symptoms of urinary frequency, urgency and leakage. Tolterodine is an antimuscarinic (anticholinergic) agent. It works by blocking a chemical that causes contractions of the bladder. Present work involved development of a novel drug delivery system of tolterodine intended to be taken once daily.

**Methods:** Extended release (ER) pellets of tolterodine were prepared and optimized for *in vitro* drug release. Subsequently, these pellets were filled into a suitable sized capsule. The resulting capsules were evaluated for *in vitro* drug release. Optimized formulation was subjected to accelerated stability studies for 3 mo and was evaluated for description, average weight, assay and drug release.

**Results:** The optimized ER capsule exhibited similar dissolution profile as that of the reference listed drug (RLD), with approximately 45%, 75% and more than 80% release in 3 h, 5 h and 7 h respectively. Accelerated stability studies indicated good physical and chemical stability of the formulation.

**Conclusion:** ER formulation of tolterodine was optimized and can be used as once a day dosage, reducing the frequency of administration when compared with the immediate release formulation. The developed formulation exhibited similar behavior as that of reference formulation Detrol LA marketed in the US.

**Keywords:** Tolterodine, ER, Surelease, Osmogel, Detrol LA

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### INTRODUCTION

Tolterodine, antimuscarinic (anticholinergic) agent is indicated for treating OAB with symptoms of urinary frequency, urgency and leakage [1, 2]. Tolterodine acts as a competitive antagonist of acetylcholine at postganglionic muscarinic receptors. Both urinary bladder contraction and salivation are mediated via cholinergic muscarinic receptors. After oral administration, tolterodine is metabolized in the liver, resulting in the formation of 5-hydroxymethyl tolterodine (5-HMT), the major pharmacologically active metabolite. 5-HMT, which exhibits an antimuscarinic activity similar to that of tolterodine, contributes significantly to the therapeutic effect. Both tolterodine and 5-HMT exhibit a high specificity for muscarinic receptors, since both show negligible activity and affinity for other neurotransmitter receptors and other potential cellular targets, such as calcium channels [3].

The international continence society (ICS) defines incontinence as the involuntary loss of bladder or bowel control.

Urinary incontinence (UI) is a stigmatized, under-reported, under-diagnosed, under-treated condition that is erroneously thought to be a normal part of aging. One-third of men and women aged 30-70 believe that incontinence is part of aging to accept.

Information on healthy bladder function can help promote the understanding that incontinence is not a normal part of aging but a symptom of another problem.

The social costs of UI are high and even mild symptoms affect social, sexual, interpersonal, and professional function.

For urge incontinence, medications known as anticholinergics/antimuscarinics (tolterodine, oxybutynin chloride, darifenacin, fluoxetine hydrochloride, and solifenacin succinate) can prevent bladder spasms and OAB.

At the time of research, there was no alternative formulation available other than innovator which was patented and costly. The aim of the present study was to develop a formulation using simpler techniques and circumventing the technology used by the innovator

product in order to have technological and commercial advantage along with benefit to society.

In the present research work tolterodine was selected for the development of an ER [4] formulation which was developed as a generic version of Detrol LA, marketed by Pfizer-Pharmacia and Upjohn Co.

The study was directed towards the development of a novel drug delivery system based on pelletization technique and was limited to the development of a formulation which can be commercially exploited for well-being of society in general and meant for the US market in particular.

### MATERIALS AND METHODS

#### Chemicals and reagents

Tolterodine was procured from Cipla, Mumbai, India; surelease E-7-19010, sugar spheres and hypromellose 2910 USP were procured from Colorcon India Ltd, microcrystalline cellulose and mannitol were procured from Signet chemical, Mumbai, India; dibutyl sebacate was received as a gift sample from Vertellus specialties Inc., USA; hypromellose phthalate HP 55 was received as a gift sample from Shin-Etsu, Japan; isopropyl alcohol and methylene chloride was procured from Avantor, India; talc was received as a gift sample from Connell bros., Mumbai, India and empty hard gelatin capsule (EHGC) shells were received as gift samples from Associated capsules Ltd., Mumbai, India.

#### Equipments

rapid mixer granulator (RMG) (Gansons-3I), Gansons Ltd, Mumbai, India; extruder-sperodizer (USPH-60), Umang Pharmatech, India; fluid bed equipment (GPCG 1.1), Pam Glatt, India; blender (3I), RP products, India.

#### Methods

##### Preparation of immediate release core pellets of tolterodine

Trials to formulate the core immediate release pellets of tolterodine (table 1).

**Table 1: Composition of immediate release pellets of tolterodine**

Ingredients	Function	4/F051A	4/F052	4/F079B	4/F113B	4/F117D	4/F127A	4/F187
		mg/capsule						
Drug core by extrusion spheronisation								
Tolterodine tartrate	Active	4	4	NA	NA	NA	4	4
Microcrystalline cellulose (Avicel PH 101)	Diluent	128	128	NA	NA	NA	128	100
Mannitol	Diluent	NA	NA	NA	NA	NA	NA	28
Hypromellose, 2910 (Methocel E5)	Binder	10	10	NA	NA	NA	10	10
Purified water	Solvent	qs	qs	NA	NA	NA	qs	qs
Average weight (mg)		142	142	NA	NA	NA	142	142
Drug core by drug loading in fluid bed equipment								
Tolterodine tartrate	Active	NA	NA	3.6	3.6	3.6	NA	NA
Sugar spheres USNF (20-25#)	Inert core	NA	NA	137.25	137.25	137.25	NA	NA
Hypromellose, 2910 (Methocel E5)	Binder	NA	NA	0.68	0.68	0.68	NA	NA
Purified water	Solvent	NA	NA	qs	qs	qs	NA	NA
Average weight (mg)		NA	NA	141.53	141.53	141.53	NA	NA

mg: milligram, NA: not applicable, qs: quantity sufficient

A total of 7 formulations were prepared. Extrusion and spheronisation was followed for batches 4/F051A, 4/F052, 4/F127A and 4/F187 where Tolterodine, microcrystalline cellulose and mannitol (present only in 4/F187) were sifted through 30 mesh sieve. The resultant material was mixed in a RMG for 10 min. Methocel E5 was dissolved in water and the dry mix was granulated with this binder solution which was followed by extrusion, spheronization and drying.

Pellets of batch numbers 4/F079B, 4/F113B and 4/F117D prepared using fluid bed coating process where Tolterodine and methocel E5 were dissolved in water. This drug solution was sprayed onto sugar spheres in fluid bed equipment and then pellets were dried.

#### Evaluation of pellets

The pellets of all the seven batches were evaluated for loss on drying using Mettler Toledo IR moisture analyzer.

#### ER coating of the core pellets

**Table 2: Formulae for the ER coating of tolterodine immediate release pellets**

Ingredients	Function	4/F051A	4/F052	4/F079B	4/F113B	4/F117D	4/F127A	4/F187
		mg/capsule						
ER coating								
Tolterodine tartrate drug coated pellets	Drug coated pellets	142	142	141.53	141.53	141.53	142	142
Surelease E-7-19010	Rate controlling polymer	21.25	21.25	28.8	19.8	18	21.875	35
Hypromellose, 2910 (Methocel E5)	Channeling agent	3.75	3.75	3.2	2.2	2	3.123	NA
Purified water	Solvent	qs	qs	qs	qs	qs	qs	qs
Average weight (mg)		167	167	173.53	163.53	161.53	167	177

mg: milligram, ER: Extended release, qs: quantity sufficient

Methocel was dissolved in water which was later added into surelease dispersion, this resultant dispersion was sprayed onto

immediate release drug pellets into fluid bed equipment followed by drying.

#### Delayed release (DR) and immediate release (IR) coating of the ER pellets

**Table 3: Formulae for the DR coating of tolterodine ER pellets**

Ingredients	function	4/F051A	4/F052	4/F079B	4/F113B	4/F117D	4/F127A	4/F187
		mg/capsule						
DR coating								
Tolterodine ER coated pellets	ER coated pellets	NA	167	NA	NA	NA	167	NA
Hypromellose phthalate HP55	Enteric polymer	NA	6	NA	NA	NA	6	NA
Dibutylsebacate, NF	Plasticizer	NA	0.8	NA	NA	NA	0.8	NA
Hypromellose, 2910 USP (Methocel E5)	Channeling agent	NA	2	NA	NA	NA	2	NA
Talc, USP	Anti-tacking agent	NA	1.2	NA	NA	NA	1.2	NA
Isopropyl alcohol, USP	Solvent	NA	qs	NA	NA	NA	qs	NA
Methylene chloride, NF	Solvent	NA	qs	NA	NA	NA	qs	NA
Average weight (mg)		-	177	-	-	-	177	-
IR coating								
Tolterodine ER coated pellets	ER coated pellets	NA	NA	173.53	163.53	161.53	NA	NA
Tolterodine tartrate	Active	NA	NA	0.4	0.4	0.4	NA	NA
Hypromellose, 2910 (Methocel E5)	Binder	NA	NA	0.07	0.07	0.07	NA	NA
Purified water	Solvent	NA	NA	qs	qs	qs	NA	NA
Average weight (mg)		-	-	174	164	162	-	-
Blending								
Purified talc NF	Glidant	2	2	2	2	2	2	2
Average weight (mg)		169	179	176	166	164	179	179
Capsule filling								
EHGC 1 No.		43	43	43	43	43	43	43
Total weight of capsule (mg)		212	222	219	209	207	222	222

DR: delayed release, NA: not applicable, qs: quantity sufficient, mg: milligram, IR: immediate release

Hypromellose phthalate and Methocel E5 were dissolved in a mixture of isopropyl alcohol and methylene chloride. Dibutyl sebacate was added to this solution followed by dispersion of talc. This dispersion was sprayed on Tolterodine ER pellets of batch number 4/F052 and 4/F127A in fluidized bed equipment and then dried. Dried pellets were blended with talc and filled into capsules shells

#### Reproducibility trial and accelerated stability studies

Batch 4/F191 was prepared similar to the composition of the batch 4/F187 in order to evaluate reproducibility and the stability profile of the formulation. The capsules were packed in 30cc HDPE bottles and subjected to accelerated storage conditions of 40 °C/75 % relative humidity. Samples were evaluated at the time intervals of 1, 2 and 3 mo.

#### Statistical analysis

One way analysis of variance (ANOVA) was employed to assess the difference between the assay values of initial and that of stability samples using Sigma Stat software (Sigma stat 2.03, SPSS). The observed p values of >0.05 were considered statistically significant for the test. Similar statistical test was applied to find difference in the *in vitro* drug release at each time point among stability samples.

#### RESULTS AND DISCUSSION

The aim of the present study was to develop an ER formulation of tolterodine which can be used as once a day therapy and was developed as a generic version of Detrol LA marketed by Pfizer-Pharmacia and Upjohn Co. by employing pelletization technique and layer building method.

Several trials were conducted (as shown in table 1, 2 and 3) using different % of ER coating, employing DR coating on to the ER coating and changing the ratio of ER polymer to channel former.

As seen from the data, drug release from all the trials having batch numbers 4/F051A, 4/F052, 4/F079B, 4/F113B, 4/F117D and 4/F127A with ER polymer ranging between 18 mg to 21.875 mg were slow in release compared to Detrol LA. Further, the batches 4/F052 and 4/F127A with DR coating over ER coating have not shown much improvement with respect to drug release. The batches 4/F079B, 4/F113B, 4/F117D with IR coating on ER coating have not shown much improvement with respect to drug release. Surprisingly batch number 4/F187 with highest ER polymer of 35 mg showed more drug release compared to other batches and was similar to the drug release profile of Detrol LA.

The ER coating of batch 4/F187 was formulated without a channel former. Surprisingly it showed improvement in release. This was attributed to the presence of mannitol in core pellets of the batch 4/F187, which has helped in dissolution of drug in the core and this solution in the core has created an osmotic effect. Since there was no channel former in the outer ER layer, the ethyl cellulose present in the outer layer was forced to swell and the osmotic pressure from core pellets expelled the drug in a controlled fashion through the swollen ethyl cellulose layer. There are references which mentions that osmotic pressure created by using osmotic agent/osmogent [5, 6] causes pellets to burst and dump the drug [7], however the tolterodine formulation developed as pellets in this study does not cause the burst and does not dump the drug, this is evident by similar dissolution of the formulation 4/F187 (with an osmotic agent) compared against reference product Detrol LA where osmotic agent is not part of formulation.

Table 4: Evaluation of capsule formulations of tolterodine

Evaluation parameter	C100378 Detrol LA	4/F051A	4/F052	4/F079B	4/F113B	4/F117D	4/F127A	4/F187
Average weight (mg)	229±2.2	212±2.7	222±1.7	218.53±2.1	208.53±2.5	206.53±1.9	222±0.9	222±1.8
Lock length (mm)	15.9±0.3	15.9±0.3	15.9±0.3	15.9±0.3	15.9±0.3	15.9±0.3	15.9±0.3	15.9±0.3
Assay (%)	100.2±0.9	99.5 ±2.2	99.8 ±2.2	100.3 ±2.7	99.5 ±1.8	100.8 ±0.9	100.3 ±2.7	99.5 ±2.2
Drug release at 1 h (%)	8±2.1	8±2.2	7±0.9	10±0.9	12±0.9	13±4.5	7±2.2	8±1.8
Drug release at 3 h (%)	45±0.8	40±1.8	40±1.8	20±0.1.2	24±0.9	29±2.2	40±1.8	43±0.9
Drug release at 5 h (%)	73±2.3	58±0.9	64±0.9	33±2.2	38±2.8	44±3.1	66±0.9	74±2.7
Drug release at 7 h (%)	81±1.2	66±4.5	75±3.6	44±2.1	50±1.9	56±1.8	77±1.2	83±1.8
Drug release at 9 h (%)	85±1.9	70±1.8	82±4.5	52±0.9	60±2.2	65±1.2	83±0.9	85±3.1
Drug release at 12 h (%)	86±0.9	78±3.9	89±0.9	62±2.2	69±0.9	74±0.9	91±1.8	86±1.4

mm: millimeter, h: h, mg: milligram, Values of assay and drug release are represented as mean±standard deviation, n=3, n=6 respectively

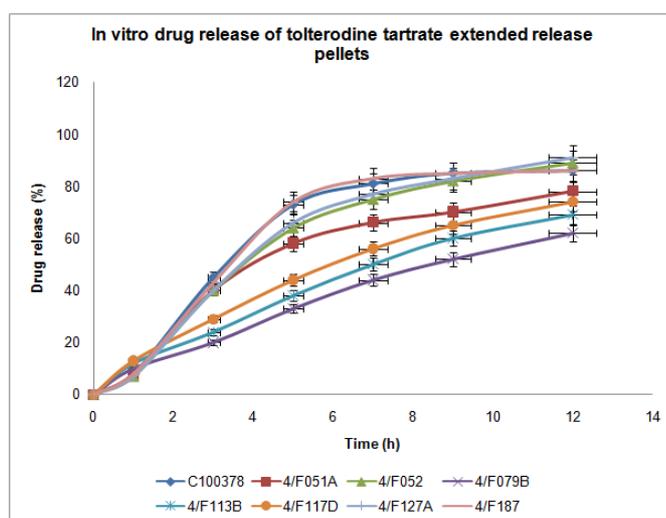


Fig. 1: *In vitro* drug release of tolterodine tartrate from Extended Release pellets prepared with different palletization techniques and different composition, (Values of *in vitro* drug release are represented as mean, n=6).

**Accelerated stability studies**

Batch 4/F191 a reproducibility batch of 4/F187 behaved similar as that of batch 4/F187. Since batch 4/F187 was having similar dissolution profile as that of RLD (C100378) and batch 4/F191 was reproducibility batch of 4/F187, it was chosen for stability studies. Stability samples of batch 4/F191 when evaluated at various time

intervals, showed no significant difference in appearance or other physical traits as compared to initial samples (table 6). Statistical analysis of assay values of stability samples indicated no significant difference. *In vitro* release profiles of samples when compared with that of initial using ANOVA exhibited no significant difference thus indicating overall good stability of the formulation at accelerated conditions.

**Table 6: Evaluation of stability samples of batch 4/F191**

Test	Specification	Initial	1 mo	2 mo	3 mo
Description	White to off-white colored capsules.	complies	complies	complies	complies
Average weight	222 mg±5%	complies	complies	complies	complies
Assay	90-110%	99.8±0.7	100.3±1.7	99.3±1.1	99.1±2.0
Drug release	3 h: 45±10%	43±0.9	43.9±2.7	46.4±3.5	42.6±3.2
	5 h: NLT 70%	74±2.7	73.9±2.7	76.4±3.5	72.6±3.2
	7 h: NLT 80%	83±1.8	93.2±1.4	95.2±2.5	91.5±1.9

Values of assay and drug release are represented as mean±standard deviation, n=3, n=6 respectively

**CONCLUSION**

ER pellets prepared using mannitol as an osmotic agent/osmogen have shown the *in vitro* release of the drug similar to Detrol LA and subsequently exhibited complete release (more than 85%) at 12 h. This osmotic ER controlled formulation of tolterodine when administered once a day can thus be expected to achieve similar therapeutic effect as that of Detrol LA.

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**CONFLICT OF INTERESTS**

Declare none

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