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## Formulation and Evaluation of Once-Daily Sustained Release Matrix Tablets of Tolterodine Tartrate

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### ABSTRACT

In the present work an attempt has been made to increase therapeutic efficacy, reduce frequency of administration and improve patient compliance by formulating sustained release matrix tablets of tolterodine tartrate a bladder-selective anti muscarinic agent with proven efficacy and tolerability in the treatment of overactive bladder (OAB). Sustained release matrix tablets of tolterodine tartrate were prepared by direct compression method using two different polymers such as HPMC K4M and Xanthan gum as rate controlling polymer in different drug:polymer ratios such as 1:5, 1:10, 1:15, 1:20 with other tablet excipients such as microcrystalline cellulose as diluent, talc, magnesium stearate as glidant and lubricant, PVP K30 as binder, lactose as taste enhancer. The formulations were evaluated for pre-compression and post-compression parameters such as hardness, thickness, weight variation, friability, drug content uniformity, *in vitro* drug release profiles, short term stability studies and drug excipient interactions. Results revealed that among the 10 formulations the STH<sub>3</sub> is considered as promising formulation, displayed almost first order release kinetics, releasing more than 75% drug release in 8.15 hours and remained sustained for more than 12 hours. Short term stability studies of promising formulation STH<sub>3</sub> indicates that there are no significant changes in dissolution parameter values after 3 weeks storage at 45±1°C/75±5% RH.

**Keywords:** Sustained release matrix tablet, Tolterodine tartrate, HPMC K4M, Xanthan gum.

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## INTRODUCTION

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience, and cost effective manufacturing process<sup>1</sup>. Sustained-release oral delivery systems are designed to achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time, thus achieving better patient compliance and allowing a reduction of both the total dose of drug administered and the incidence of adverse side effects<sup>2</sup>. Matrix system is widely used for the purpose of sustained release. In such systems, the drug in the form of powder is mixed with matrix forming component and the mixture is shaped in the required mold. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid nonswellable hydrophobic materials or plastic materials<sup>3</sup>. Hydroxypropyl methylcellulose (HPMC) is a widely used semi-synthetic hydrophilic matrix polymer that has been employed in the design of sustained release formulations due to its rapid hydration, good compression and gelling characteristics as well as its ease of use, availability and very low toxicity<sup>4</sup>. Xanthan gum is a hydrophilic polymer, secreted from *Xanthomonas campestris* (a Gram-negative, yellow pigmented bacterium). Xanthan gum is the only bacterial polysaccharide produced industrially on a large scale. It is a natural carbohydrate commercially produced by fermenting glucose with the appropriate microorganism. Xanthan gum swells in gastric fluid to produce a highly viscous layer around the tablet through which the drug can slowly diffuse. This property makes Xanthan gum a useful ingredient for controlled release and sustained release applications<sup>5</sup>. Tolterodine tartrate is a bladder-selective anti muscarinic agent with proven efficacy and tolerability in the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency and frequency<sup>6,7,8,9</sup>. Among the M1, M2, M3, M4 and M5 subtypes of muscarinic receptors, Tolterodine tartrate has more specificity for the M2 receptor and is in clinical development for the treatment of urge urinary incontinence and other symptoms of unstable bladder but has less affinity for M3 receptor with a direct correlate to dry mouth<sup>10,11</sup>. After oral administration, Tolterodine tartrate is rapidly absorbed and the maximum plasma concentration (C<sub>max</sub>) typically occurs within 1–2 h. The immediate release formulations of Tolterodine tartrate required frequent administration and possess certain limitation in terms of tolerability or dosing regimen issues, both of which may significantly impair patient compliance and therefore overall

efficacy. Thus, the poor tolerability and/or the need for frequent daily dosing with immediate release formulations have led to the need for an alternative drug delivery system. Over active bladder is a chronic condition requires long-term treatment, patient convenience and compliance could be improved with once daily administration. Sustained release formulations for once-daily administration would be a better approach not only to improve the dosing, but also to affect tolerability and efficacy. The main objective of the present study is to provide an improved oral sustain release matrix dosage formulation at therapeutic dose, in the tablet form, containing 4-mg Tolterodine tartrate for 24 hour release useful for the treatment of urge incontinence and other symptoms of unstable or overactive urinary bladder.

## MATERIALS AND METHOD

Tolterodine tartrate was obtained as gift sample from Taj pharmaceuticals Ltd, Mumbai. HPMC K4M and Xanthan gum obtained from Colorcon Asia Pvt Ltd Goa and Bangalore fine chem, Bangalore respectively. Microcrystalline cellulose was purchased from SD fine chem, Mumbai. All other ingredients and chemicals used were analytical reagent grade and were used as received.

### PREPARATION OF CALIBRATION CURVE

#### Standard calibration curve of tolterodine tartrate in methanol

##### Standard stock solution:

Accurately weighed 50 mg of tolterodine tartrate was dissolved in 50 ml of methanol to get a stock solution containing 1000mcg/ml.

##### Stock solution:

From standard stock, a stock solution was prepared to give a concentration of 20 mcg/ml in methanol. Aliquots of 1, 2, 3, 4 and 5 ml of stock solution were pipette out into 10 ml volumetric flasks. The volume was made up to the mark with methanol. These dilutions give 2, 4, 6, 8 and 10 mcg/ml concentration of tolterodine tartrate respectively. The absorbance of prepared solution of tolterodine tartrate in methanol was measured at 281 nm in Shimadzu UV-1800 spectrophotometer against an appropriate blank (methanol). The absorbance data for standard calibration curves are given in table 4. The standard calibration curve yields a straight line (figure 1) which shows that the drug follows Beer's law in the concentration of 2-10 mcg/ml.

#### Preparation of sustained release matrix tablets<sup>12</sup>

Direct compression method has been employed to prepare matrix tablet of tolterodine tartrate using HPMC K4M and xanthan gum as release retarding polymers in different ratios with the other excipients such as microcrystalline cellulose, talc, magnesium stearate, PVP K30 and lactose. All

the ingredients including drug, polymer and excipients were weighed accurately according to formulation table (table 1). The polymer and microcrystalline cellulose is thoroughly mixed on a butter paper with the help of a stainless steel spatula. The mixture of polymer and microcrystalline cellulose were mixed with the drug and then all excipients are added in the order of ascending weights mixture were blended for 10 min in an inflated polyethylene pouch. The prepared blend of each formulation was compressed on 10-station rotatory tablet punching machine (Clit, Ahmadabad) to form flat-faced tablet of 6 mm diameter.

**Table 1: Formulations of Tolterodine Tartrate Sustained Release Matrix Tablets**

Ingredients (mg/tablet)	Formulation Code									
	STH <sub>1</sub>	STH <sub>2</sub>	STH <sub>3</sub>	STH <sub>4</sub>	STH <sub>5</sub>	STX <sub>1</sub>	STX <sub>2</sub>	STX <sub>3</sub>	STX <sub>4</sub>	STX <sub>5</sub>
Tolterodine tartrate	4	4	4	4	4	4	4	4	4	4
HPMC K4M	20	40	60	80	100	-	-	-	-	-
Xanthan gum	-	-	-	-	-	20	40	60	80	100
MCC	109	89	69	49	29	109	89	69	49	29
Talc	2	2	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2	2	2
PVP K30	3	3	3	3	3	3	3	3	3	3
Lactose	10	10	10	10	10	10	10	10	10	10
Total weight	150	150	150	150	150	150	150	150	150	150

**STH-** Formulations containing HPMC K4M; **STX-** Formulation containing Xanthan gum

## Evaluation

### Pre compression parameters<sup>12</sup>

**Angle of repose:** The angle of repose of granules was determined by the funnel method. The accurately weighed powder was taken in funnel. The height (h) of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow from the funnel on the surface. The diameter and height of the heap formed from the powder was measured. The results were shown in Table No. 3. It concluded that all the formulations blend was found to be in the range of 25° to 30° showing that the powder has good flow properties.

**Bulk density and tapped density:** Both loose Bulk density (LBD) and tapped density (TBD) was determined. Calculated quantity of 2 g of powder from each formula was introduced into a measuring cylinder and tapped from the height of 2.5 cm at 2 seconds intervals for certain time until no further change in volume was noted. LBD and TBD were calculated using the following formula.

LBD= Weight of the powder/ Volume of the packing

TBD = Weight of the powder/ Tapped Volume of the packing

The bulk density and tapped density were found in range of 0.46 to 0.50 gm/ml and 0.54 to 0.57 gm/ml respectively showing that the powder has good flow properties. The results were shown in Table 3.

**Hausner's Ratio:** It indicates the flow properties of the blend and is measured by the ratio of tapped density to the bulk density.

Hausner's ratio = Tapped density/Bulk density

Hausner's Ratio was carried out and the results were shown in Table No. 3. It was found between 1.12 to 1.21 indicating the powder blend have the required flow property for compression.

**Compressibility index:**

The compressibility Index of the powder was determined by carr's compressibility index

$$\text{Carr's Index (\%)} = (\text{TBD-LBD}) \times 100 / \text{TBD}$$

The compressibility index of all the formulations blend was found to be in the range of 10.42% to 18.04% indicating the powder blend have the required flow property for compression. The results were shown in Table No. 3.

**Post-compression parameters<sup>13</sup>:**

**Thickness:**

The thickness of the formulated tablets were measured by using screw gauze on 3 randomly selected samples and tabulated in Table No. 4. Tablets mean thickness were uniform and found to be in range of 3.05mm and 3.25mm.

**Weight variation:**

The formulated tablets were tested for weight uniformity. Twenty tablets were weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it is within permissible limits or not.

$$\% \text{Weight Variation} = \text{Average weight-Individual weight} / \text{Average weight} \times 100$$

The percentage weight variations for all formulations were tabulated in Table No. 4. All the formulated tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of 5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

**Hardness:**

The tablet crushing strength, which is the force required to break the tablet by compression in the diametric direction was measured in triplicate using Pfizer hardness tester. Hardness of the tablets were found to be in the range of 5 to 5.5 kg/cm<sup>2</sup> and tabulated in Table 4.

**Friability:**

The Roche friability test apparatus was used to determine the friability of the tablets. 20 pre weighed tablets were placed in the apparatus, which was subjected to 100 revolutions. Then the tablets were reweighed. The percentage friability was calculated using the formula.

$$\% \text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

The values of friability test were tabulated in Table 4. The % friability was less than 1% in all the formulations

**Uniformity of drug content<sup>14</sup>:**

Ten tablets were powdered in glass mortar and the powder equivalent to 100 mg of drug was placed into 100 ml volumetric flask containing 70 ml methanol. The content of the flask were filtered through a filter and the residue was washed with another 20 ml of methanol and the volume was made up to the mark. The sample was suitably diluted and absorbance was measured at 281 nm in Shimadzu UV-1800 spectrophotometer against an appropriate blank (methanol). The results were summarized in table 4.

***In vitro* dissolution studies<sup>15</sup>:**

*In vitro* dissolution studies of tolterodine tartrate SR matrix tablets were carried out in USP XIII tablet dissolution test apparatus, employing a basket stirrer at 50 rpm using 900 ml of pH 1.2 for 2 hr and 7.4 phosphate buffer for 10 hr at  $37 \pm 0.5^\circ\text{C}$  as dissolution medium. At predetermined time intervals, 5 ml of sample was withdrawn by means of a syringe fitted with pre-filter. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium maintained at  $37 \pm 0.5^\circ\text{C}$ . The sample was analysed for drug release by measuring the absorbance at 281 nm using shimadzu UV- 1800 spectrophotometer after suitable dilutions with pH 1.2 and pH 7.4 phosphate buffers respectively. All studies were conducted in triplicate. The results were summarized in table 5. The *in vitro* drug release data was subjected to goodness of fit test by linear regression analysis according to zero order; first order kinetic equations, Higuchi's and Peppas's models in order to determine the mechanism of drug release. The formulations prepared were found to follow first order kinetics since the plots of log cumulative percent drug remaining versus time are linear and the regression coefficient was found to be 0.99. The release of drug from these matrix tablets was found to be governed by diffusion controlled process since the plots of cumulative percent drug released versus square root of time were found to be linear.

**Stability studies<sup>16</sup>:**

Short term stability studies were performed at a temperature of  $45^\circ \pm 1^\circ\text{C}$  and  $75 \pm 5\%$  RH over a period of three weeks (21 days) on the promising sustained release matrix tablet formulation STH<sub>3</sub>.

Sufficient number of tablets (15) were packed in amber colored, screw-capped bottle and kept in hot air oven maintained at  $45^{\circ}\pm 1^{\circ}\text{C}$ . At the end of three weeks, dissolution studies were performed to determine the drug release profiles. Results were mentioned in table 7.

### Drug-polymer interaction studies:

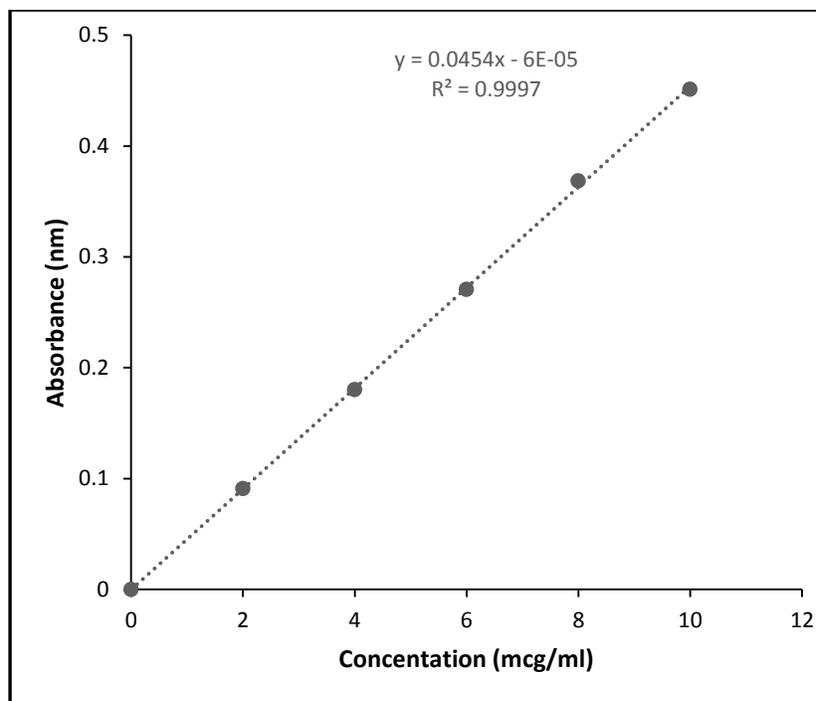
There is always a possibility of drug polymer interaction in any formulation due to their intimate contact. The technique employed in the present study for this purpose is IR spectroscopy. The IR spectra of drug and polymer alone and prepared formulations show no significant interaction between drug and polymer. The study confirmed the presence of all predominant peaks indicating its authenticity.

## RESULTS AND DISCUSSION

**Table 2: Standard calibration curve of tolterodine tartrate in methanol ( $\lambda_{\text{max}}=281 \text{ nm}$ )**

Concentration (mcg/ml)	Absorbance			Mean $\pm$ SD
	I	II	III	
0	0.000	0.000	0.000	0.000 $\pm$ 0.000
2	0.092	0.091	0.090	0.091 $\pm$ 0.001
4	0.181	0.180	0.180	0.180 $\pm$ 0.000
6	0.270	0.271	0.271	0.270 $\pm$ 0.000
8	0.368	0.369	0.368	0.368 $\pm$ 0.000
10	0.450	0.451	0.452	0.451 $\pm$ 0.001

$$a = -6\text{E-}05, b = 0.0454, r^2 = 0.9997$$



**Figure 1: Standard calibration curve of tolterodine tartrate in methanol ( $\lambda_{\text{max}} 281$ )**

**Table 3: Pre-compression Parameters of Sustained Release Formulations**

Formulation code	Pre-compression parameters				
	Angle of repose ( $\theta$ )	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index %	Hausner's ratio
STH <sub>1</sub>	29.07±0.46	0.50±0.00	0.56±0.00	11.64±0.10	1.12
STH <sub>2</sub>	29.36±0.43	0.48±0.00	0.57±0.00	15.1±1.85	1.18
STH <sub>3</sub>	30.07±0.46	0.47±0.00	0.55±0.00	14.95±1.93	1.17
STH <sub>4</sub>	30.02±0.72	0.48±0.00	0.55±0.01	12.11±0.87	1.14
STH <sub>5</sub>	29.20±0.67	0.48±0.05	0.55±0.00	12.02±1.95	1.14
STX <sub>1</sub>	30.36±0.43	0.46±0.01	0.56±0.02	18.04±4.13	1.21
STX <sub>2</sub>	30.09±0.67	0.46±0.01	0.54±0.01	13.04±1.85	1.17
STX <sub>3</sub>	29.74±0.90	0.50±0.05	0.56±0.01	10.50±1.93	1.12
STX <sub>4</sub>	30.44±0.72	0.49±0.01	0.55±0.01	11.93±2.53	1.12
STX <sub>5</sub>	30.01±0.52	0.48±0.05	0.54±0.00	10.42±1.01	1.14

Mean±SD, n=3

**Table 4: Post-compression Parameters of formulations**

Formulation code	Post-compression parameters				
	Hardness (kg/cm <sup>2</sup> )	Thickness (mm)	Friability (%)	Drug content (%)	Weight variation (mg)
STH <sub>1</sub>	4.97±0.04	3.19±0.16	0.33	98.43±0.01	148.4±0.8
STH <sub>2</sub>	4.87±0.02	3.19±0.09	0.58	96.02±0.44	150.4±0.9
STH <sub>3</sub>	4.99±0.01	3.05±0.13	0.40	97.14±0.22	149.4±1.1
STH <sub>4</sub>	4.95±0.02	3.24±0.17	0.13	95.50±1.85	151.7±0.8
STH <sub>5</sub>	4.85±0.03	3.16±0.08	0.06	95.69±0.63	149.2±0.9
STX <sub>1</sub>	4.91±0.01	3.22±0.11	0.19	96.78±0.48	150.1±0.6
STX <sub>2</sub>	4.90±0.01	3.31±0.06	0.12	95.64±0.40	153.1±0.9
STX <sub>3</sub>	4.83±0.02	3.21±0.18	0.70	95.20±0.36	151.7±0.8
STX <sub>4</sub>	4.85±0.03	3.16±0.12	0.75	96.37±0.25	149.3±1.1
STX <sub>5</sub>	4.97±0.02	3.25±0.11	0.86	101.83±1.13	149.2±0.9

**Table 5: In-vitro Dissolution Parameters of Formulations**

Time (hrs)	Cumulative percent drug release									
	STH <sub>1</sub>	STH <sub>2</sub>	STH <sub>3</sub>	STH <sub>4</sub>	STH <sub>5</sub>	STX <sub>1</sub>	STX <sub>2</sub>	STX <sub>3</sub>	STX <sub>4</sub>	STX <sub>5</sub>
1	14.37	17.49	23.25	20.38	5.36	9.30	11.44	27.18	17.52	15.73
2	16.99	20.85	30.04	21.82	10.73	13.23	14.27	33.26	20.74	20.03
3	21.82	26.39	35.41	26.11	13.59	16.09	17.52	39.34	26.11	25.39
4	27.90	31.08	43.64	31.83	20.03	20.03	24.68	45.07	30.76	28.61
5	35.41	40.17	49.72	36.12	23.25	23.25	30.04	50.43	36.84	35.05
6	40.42	46.14	57.59	44.35	29.68	27.90	38.63	56.16	43.28	39.34
7	45.78	51.86	65.46	47.21	33.26	31.83	43.64	62.24	45.78	41.85
8	51.15	56.51	72.61	51.51	40.06	36.12	46.86	68.32	48.29	45.07
9	56.16	61.88	78.33	54.37	46.14	45.78	53.29	73.33	55.08	51.51
10	60.09	63.67	84.41	57.59	51.86	50.79	56.87	79.05	57.23	56.51
11	64.03	66.17	90.14	61.16	56.16	56.87	61.16	85.13	61.52	61.88
12	67.24	72.54	95.50	65.81	62.24	61.52	63.67	89.06	64.38	63.31

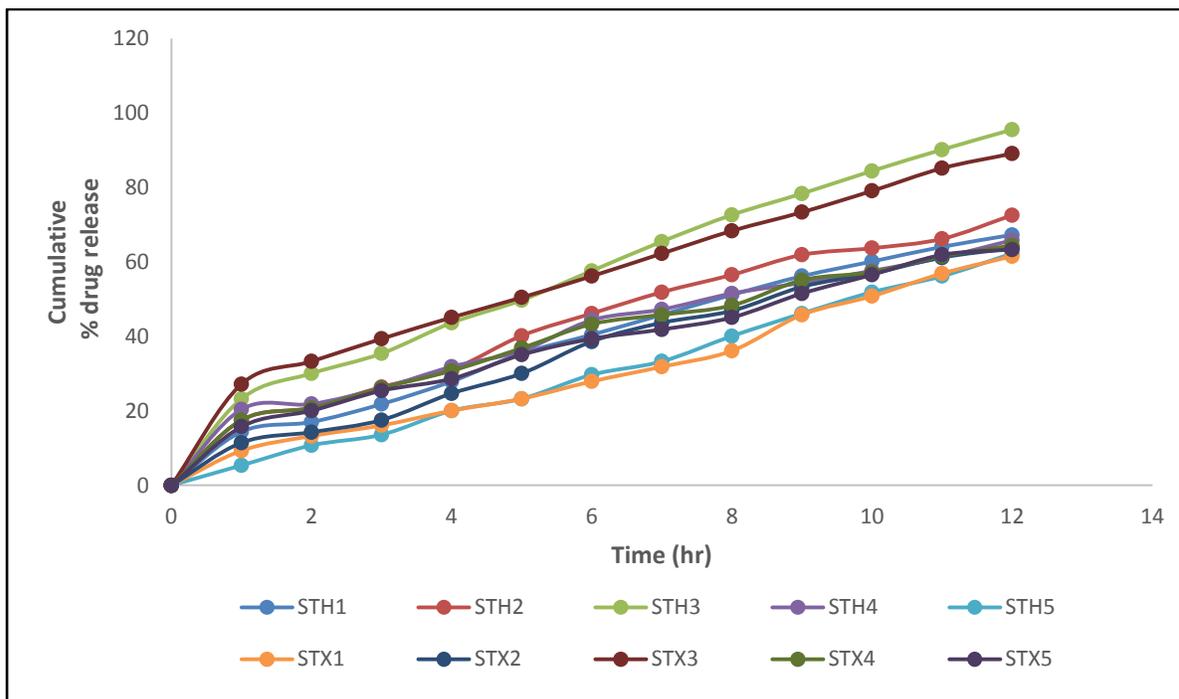
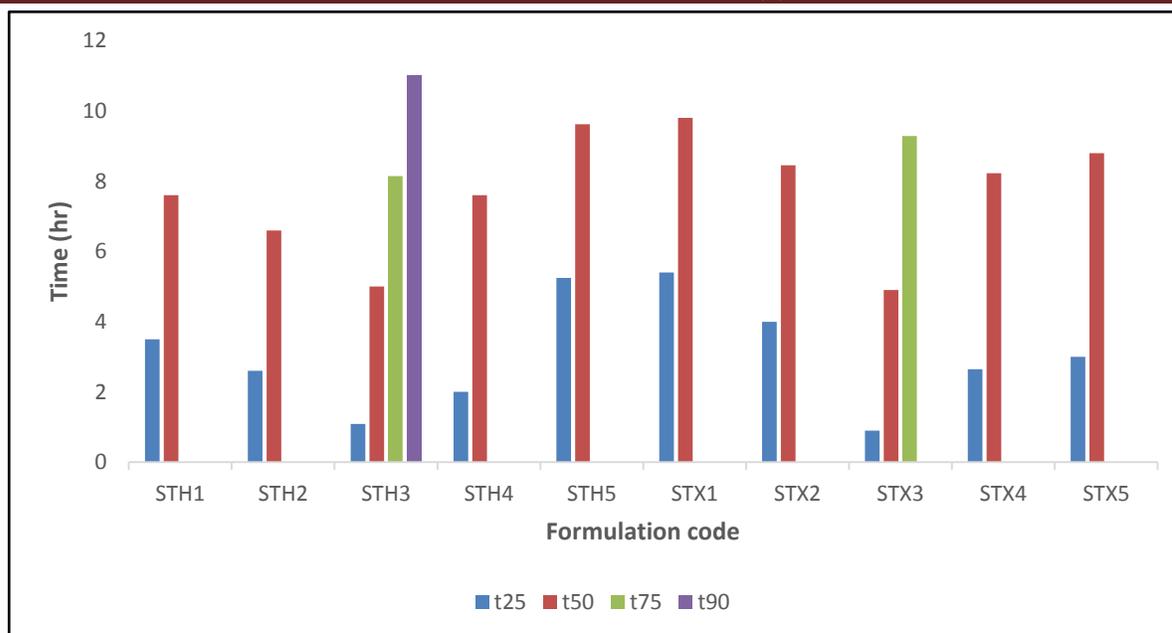


Figure 2: Cumulative percent drug release (zero order) of formulations

Table 6: Dissolution Parameters for the Formulations

Sr. No.	Formulation code	$t_{25\%}$ (hrs)	$t_{50\%}$ (hrs)	$t_{75\%}$ (hrs)	$t_{90\%}$ (hrs)	Cumulative percentage drug release within 12 hrs
1	STH <sub>1</sub>	3.57	7.60	-	-	67.24
2	STH <sub>2</sub>	2.60	6.60	-	-	72.54
3	STH <sub>3</sub>	1.09	5.00	8.15	11	95.50
4	STH <sub>4</sub>	2.00	7.60	-	-	65.81
5	STH <sub>5</sub>	5.25	9.62	-	-	62.24
6	STX <sub>1</sub>	5.40	9.80	-	-	61.52
7	STX <sub>2</sub>	4.00	8.45	-	-	63.67
8	STX <sub>3</sub>	0.90	4.90	9.29	-	89.06
9	STX <sub>4</sub>	2.65	8.23	-	-	64.38
10	STX <sub>5</sub>	3.00	8.80	-	-	63.31



**Figure 3: Comparison of dissolution parameters (t<sub>25</sub>%, t<sub>50</sub>%, t<sub>75</sub>%, t<sub>90</sub>%) of formulations**

**Table 7: Stability Data of Formulation (STH<sub>3</sub>)**

Sr. No.	Time (hr)	Cumulative percent drug released* ± SD at 45±1°C and 75% RH	
		1 <sup>st</sup> Day	21 <sup>st</sup> Day
1.	1	23.25± 0.02	22.96± 0.01
2.	2	30.04± 0.01	29.85± 0.01
3.	3	35.41± 0.00	34.53± 0.00
4.	4	43.64± 0.04	42.81± 0.03
5.	5	49.72± 0.03	48.79± 0.02
6.	6	57.59± 0.01	56.99± 0.00
7.	7	65.46± 0.01	64.52± 0.02
8.	8	72.61± 0.02	71.91± 0.04
9.	9	78.33± 0.00	77.88± 0.01
10.	10	84.41± 0.02	83.48± 0.01
11.	11	90.14± 0.01	90.55± 0.00
12.	12	95.50± 0.04	94.96± 0.03

## DISCUSSION

Sustained release matrix tablets of tolterodine tartrate were prepared by direct compression method using two different polymers such as HPMC K4M and xanthan gum as rate controlling polymer in different drug: polymer ratios such as 1:5, 1:10, 1:15, 1:20 with other tablet excipients such as microcrystalline cellulose as diluent, talc, magnesium stearate as glidant and lubricant, PVP K30 as binder, lactose as taste enhancer.

The formulations were evaluated for pre-compression and post-compression parameters. The flow characteristics of the blend were assessed by determining their angle of repose and carr's index. The values showed good flow ability of the blend for all batches. This shows that the blend had

smooth flow properties ensuring homogenous filling of the die cavity during the compression (punching) of tablets. All the prepared formulations were found to be good without capping and chipping. Hardness of the tablets were found to be in the range of 5 to 5.5 kg/cm<sup>2</sup>. The friability of all prepared tablets was fulfilling the official requirement (not more than 1%). In the weight variation test the percent deviation from the average weight was found to be within the prescribed official limits.

*In vitro* dissolution studies were performed for all the formulations using USP XIII tablet dissolution test apparatus employing basket stirrer at 50 rpm using 900 ml pH 1.2 and pH 7.4 phosphate buffer as dissolution medium. The *in vitro* drug release data was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equations, Higuchi's and Peppas's models in order to determine the mechanism of drug release. The formulations prepared were found to follow first order kinetics since the plots of log cumulative percent drug remaining versus time are linear and the regression coefficient was found to be 0.99. The release of drug from these matrix tablets was found to be governed by diffusion controlled process since the plots of cumulative percent drug released versus square root of time were found to be linear.

When  $t_{25\%}$ ,  $t_{50\%}$ ,  $t_{75\%}$  values and the total amount of drug released within 12 hours are considered, it can be seen that the formulation STH<sub>3</sub> have shown promising results in achieving more than 75% drug release in 8.15 hours and remained sustained for more than 12 hours. Short term stability studies of promising formulation STH<sub>3</sub> indicates that there are no significant changes in dissolution parameter values after 3 weeks storage at 45±1°C/75±5% RH.

#### CONCLUSION:

The aim of the present study was to develop a sustained release matrix tablets containing Tolterodine tartrate. The sustained release matrix tablets were developed by using HPMC K4M, Xanthan gum as polymers such that it delivers 4mg of Tolterodine tartrate over a period of 24 hours. The tablets were prepared by direct compression method. Among 10 formulations, STH<sub>3</sub> gave satisfactory results by releasing 95.50% of drug in 12 hours. The optimized formulation (STH<sub>3</sub>) followed zero-order and Korsmeyer-Peppas release mechanism. Stability study indicates no significant change in physical parameters and the cumulative percentage of drug release. The overall results indicate that the formulation STH<sub>3</sub> was better and that satisfied all the criteria as sustained release matrix tablets. This sustained release unit dosage form will be good in treatment

of over active bladder/urinary incontinence by improving patient compliance and reducing dosing frequency.

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