Research Article

Available Online at: www.ijphr.com

International Journal of Pharmaceuticals and Health care Research

ISSN: - 2306 – 6091

FORMULATION AND EVALUATION OF MODIFIED RELEASE MATRIX TABLETS OF TOLTERODINE TARTRATE FOR TREATMENT OF OVERACTIVE BLADDER DISEASE

*[1,2]Rihana Parveen SK, [1]Srinivasa Babu P, [2]Chandrasekar K B

[1]Vignan College of Pharmacy,Vadlamudi, Guntur, Andhra Pradesh - 522 213, India.

[2]Jawaharlal Nehru Technological University Anantapur, Andhra Pradesh - 515 002, India.

Abstract

Many problems are associated with conventional multiple-dosing regimen of long-acting therapy, such as systemic accumulation of the drug leading to side effects or toxicities, flip-flop profile of the plasma drug level, and poor patient compliance. The objectives identified as the outputs for addressing the identified development problem and provide a means to assess performance of modified release formulation. In the present research, an attempt has been made to formulate modified release oral matrix tablets of Tolterodine tartrate to overcome the existing problems using Hydroxypropyl methyl cellulose (HPMC K4M), Sodium carboxy methyl cellulose (SCMC), Guar Gum and Xanthan Gum as rate controlling polymer for the treatment of overactive bladder. The tablets were prepared by wet granulation method and studied the effect of the matrix former such as Guar Gum and Xanthan Gum separately. Tablets were evaluated for uniformity of weight, drug content, friability, hardness, thickness, swelling study, in vitro drug release study and finally stability study. All the formulation had shown compliance with pharmacopoeial standard. As the time increases, the swelling index was increased, later on decreases gradually due to dissolution of outer most gel barrier of tablet into the dissolution medium. Comparison between Hydroxypropyl methyl cellulose (HPMC K4M), Sodium carboxy methyl cellulose (SCMC), it has been observed that swelling index of Hydroxypropyl methyl cellulose (HPMC K4M) was significantly more compared to Sodium carboxy methyl cellulose (SCMC). Similarly, comparison between xanthan gum and guar gum, it has been observed that swelling index of guar gum was significantly more compared to xanthan gum. The drug release study shows that an increase amount of polymer resulted in retarded drug release. The maximum drug release was found to be 95% over a period of 12 hours in guar gum based formulations (F9-F12) at a concentration ranging from 15 to 60mg per tablet. Similarly maximum drug release was found to be 92% over a period of 12 hours in Xanthan gum to gum based formulations (F13-F16) at a concentration ranging from 15 to 60mg per tablet. The drug release from optimized formulation (F12) fitted to various kinetic models and the drug release was found to follow zero-order kinetics and diffusion release mechanism. This modified release matrix tablet dosage form will be good for the treatment of over active bladder/urinary incontinence by improving patient compliance and reducing dosing frequency.

Keywords: Tolterodine Tartrate, Hydroxypropyl methyl cellulose, Sodium carboxy methyl cellulose, Guar Gum and Xanthan Gum, matrix tablets.

Author for Correspondence:
Rihana Parveen SK,
Department of Pharmaceutics,
Vignan College of Pharmacy,
Vadlamudi, Guntur, Andhra Pradesh - 522 001, India.
Email: rihanaparveen@gmail.com

Introduction

The development of modified release tablets have a clinical rational as it may reduce dose related side effects, improve efficacy and improve compliance to drug therapy. Modified release products may be developed to reduce dose frequency, which adds to convenience of use, which in turn may facilitate compliance. Another rationale for developing modified release preparations is smoothing the peaks of the plasma concentration curves (sustained release) in order to prevent peak concentration related adverse events.[1]

Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, least aseptic constraints and flexibility in the design of the dosage form. It is well known that modified release dosage forms may offer one or more advantages over immediate release formulations of same drug. There are many ways to design modified release dosage forms for oral administration such as film coated pellets, tablets or capsules, to more sophisticated and complicated delivery systems. The formulation of drugs in hydrophilic matrix systems remains the easiest and most accessible way to modulate drug release rate and kinetics. The modification of the release surface exposed to the dissolution medium as a way of modulating the release performance of a matrix system.[2]

Nowadays, in order to investigate the suitability of a polymer as a matrix forming agent, it is necessary to gather sufficient information about its physical and mechanical properties, since the properties of the matrix will mainly depend on the characteristics of the polymer.[3] In light of the above, the aim of this present work is focused on knowing the swelling properties and sustained release hydrophilic matrices of Tolterodine tartrate using new modified polymeric natural carbohydrates and compared with semi synthetic polymers.

Xanthan gum is a hydrophilic natural polymer, swells in gastric fluid to produce a highly viscous layer around the tablet core through which the drug can slowly diffuse. This property makes Xanthan gum as a useful candidate for developing modified release systems. Hydroxypropyl methyl cellulose (HPMC K4M) is a non-ionic aqueous soluble cellulose derivative for use in modified release dosage forms. Owing to high swellability and high gelling strength formation this effectively prolongs drug release, which has a significant effect on the release kinetics of incorporated drug.

Overactive bladder is a chronic, highly prevalent and distressing medical condition characterized by urinary urgency and frequency, with or without urge incontinence.[4] Anti-muscarinic agents is the primary pharmacological treatment for this condition. Previously, Oxybutynin was the drug of choice, although the usefulness of this agent has been limited by the lack of selectivity for the bladder, which gives rise to frequent, bothersome side effects (e.g. dry mouth, constipation and blurred vision). For these reasons, Tolterodine tartrate was developed as the first anti-muscarinic agent specifically targeted for the treatment of the overactive bladder. The currently available formulation of Tolterodine tartrate requires twice-daily administration as overactive bladder is a chronic condition requires long-term treatment, patient convenience and compliance could be improved with once-daily administration.[5]

The main objective of the present study is to provide an improved oral controlled release matrix dosage formulation at a therapeutic dose, in the tablet form containing 4mg of Tolterodine tartrate for 24 hours release useful for the treatment of urge incontinence and other symptoms of an unstable or overactive urinary bladder.

Materials and methods

Materials

Tolterodine tartrate was obtained as a gift sample from Drugs India, Hyderabad. HPMC K4M and SCMC were obtained from Aurobindo Pharma, Hyderabad. Xanthan gum 80 mesh SR-2 and Guar gum 100 mesh Food Grade were purchased from SD fine Chemicals, Mumbai. All other ingredients, chemicals and solvents used were analytical reagent grade and were used as received.

Methods

Formulation of matrix tablets

Tablets were prepared by wet granulation technique.[6] The composition of formulation is given in Table 1. All the powdered were passed through sieved #80. Required quantities of drug and polymer were mixed thoroughly and a

sufficient volume of PVP K30 10% w/v solution was added slowly. After enough cohesiveness was obtained, the mass was screened through the sieve #22/44. The wet granules were dried at 40°C for one hour thereafter kept in the desiccators for 12 hours at room temperature. After dry, the granules retained in 44 mesh were mixed with fines (granules that passed through 44 mesh). Lactose monohydrate was used as a diluent. The granules were blended with 2% Magnesium stearate and 2% Aerosil for 2-3 minutes and, which were used as a lubricant and glident respectively to improve flow property. The granules were subjected for evaluation studies to ensure its flowability, followed by compressed into matrix tablets weighing about 180mg using 2.8 mm shallow biconcave punches in Cadmach rotary tablet punching machine to a hardness of 5-6 kg/cm^2. The prepared matrix tablets were used for further evaluation studies.

Table No. 01: Composition of matrix tablets of Tolterodine tartrate

Ingredients in mg/tablet*	Tolterodine Tartrate	HPMC K4M	SCMC	Guar Gum	Xanthan Gum	Lactose monohydrate
F1	4	15	--	--	--	157.4
F2	4	30	--	--	--	142.4
F3	4	45	--	--	--	127.4
F4	4	60	--	--	--	112.4
F5	4	--	15	--	--	157.4
F6	4	--	30	--	--	142.4
F7	4	--	45	--	--	127.4
F8	4	--	60	--	--	112.4
F9	4	--	--	15	--	157.4
F10	4	--	--	30	--	142.4
F11	4	--	--	45	--	127.4
F12	4	--	--	60	--	112.4
F13	4	--	--	--	15	157.4
F14	4	--	--	--	30	142.4
F15	4	--	--	--	45	127.4
F16	4	--	--	--	60	112.4

*All ingredients were taken in mg, 10% PVP K30 w/v solution was used as granulating agent, 2% w/w of Magnesium stearate and Aerosil were used as a lubricant and glident respectively for all formulations.

Standard solutions

From a stock solution containing 1mg of Tolterodine tartrate/ml in methanol, a standard curve was prepared at the concentration of 1-10µg/ml in 100ml of mobile phase, by vortex mixing for 30 seconds. The concentration range of standard curve was diluted four times in mobile phase and the corresponding solution was subjected to chromatographic analysis at 1-10µg/ml of Tolterodine tartrate.[7]

Chromatographic analyses

The HPLC system was employed using Shimadzu liquid chromatograph, model SPD 10A VP using a variable wavelength UV detector set at 281nm, an LC-10 ADVP pump, a Rheodyne injector and a model CR6-A integrator. Separation was performed on a C18 reversed-phase column at room temperature (28°C). A (35:65) acetonitrile:phosphate buffer pH 7.4 mixture was used as mobile phase, at a flow rate of 1ml/min and injection volume of 20µl.

Preformulation Study

Evaluation of granules is an investigation of physical properties of a drug alone and when combined with excipients. The overall objective of the evaluation of granules was to generate useful information to the formulation in developing stable and bioavailable dosage form.[8] The values for drug and granules of all formulations are given in Table2.

Bulk Density: Apparent bulk density was determined by pouring presieved drug excipients blend into a graduated cylinder and measuring the volume and weight "as it is". It is expressed in g/mL and is given by,

$$Db = M / VO$$

Where, Db is the bulk density, M is the mass of powder and VO is the Bulk volume of the powder.

Tapped density: It was determined by placing a graduated cylinder, containing a known mass of drug- excipients blend, on mechanical tapping apparatus. The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/mL.

$$Dt = M / Vt$$

Where, Dt is the tapped density, M is the mass of powder and Vt is the tapped volume of the powder.

Angle of repose: This is the maximum angle possible between the surface of the pile or powder and horizontal plane. The frictional forces in the lose powder can be measured by Angle of repose. The tangent of Angle of repose is equal to the coefficient friction between the particles. Angle of repose was determined by using funnel method.

$$\theta = \tan\text{-}1\ (h / r)$$

Where, θ is the angle of repose, h is the height in cm and r is the radius in cm.

Carr's Index (I): Compressibility index is an important measure that can be obtained from the bulk and tapped densities. A material having values less than 20 to 30% are defined as the free flowing material, based on the apparent bulk density and tapped density, the percentage compressibility of the bulk drug was determined by using the following formula.

$$I = Dt – Db / Dt \times 100$$

Where, I is the Compressibility index, Dt is the tapped density of the powder and Db is the bulk density of the powder.

Hausner's ratio: It indicates the flow properties of the powder. The ratio of Tapped density to bulk density of the powder or granules is called Hausner's ratio.

$$H = Dt / Db$$

Where, H is the Hausner's ratio, Dt is the tapped density of the powder and Db is the bulk density of the powder.

Table No. 02: Data obtained by preformulation study for pure drug and prepared granules containing Tolterodine tartrate

F.Code	Derived Properties		Flow Properties		
	Bulk density (mean ± SD)	Tapped density (mean ± SD)	Angle of repose (mean ± SD)	Carr's index (mean ± SD)	Hausner's ratio (mean ± SD)
Pure drug	0.25±0.03	0.39±0.12	14.4±0.13	12.43±0.24	1.13±0.05
F1	0.36±0.02	0.37±0.05	34.17±0.06	22.15±0.04	1.22±0.04
F2	0.38±0.05	0.41±0.04	37.40±0.04	18.52±0.04	1.41±0.02
F3	0.33±0.07	0.37±0.02	33.31±0.04	15.39±0.06	1.29±0.04
F4	0.28±0.06	0.24±0.04	29.52±0.05	12.60±0.05	1.33±0.06
F5	0.52±0.03	0.31±0.06	42.44±0.02	15.30±0.03	1.39±0.06
F6	0.37±0.04	0.32±0.02	43.16±0.07	15.15±0.07	1.26±0.06
F7	0.36±0.05	0.39±0.07	51.26±0.03	13.65±0.04	1.27±0.01
F8	0.39±0.04	0.37±0.03	36.82±0.05	14.74±0.06	1.24±0.06
F9	0.41±0.05	0.35±0.03	37.15±0.03	13.63±0.05	1.27±0.03
F10	0.42±0.06	0.39±0.05	41.29±0.04	17.75±0.04	1.12±0.06
F11	0.33±0.06	0.42±0.02	38.61±0.03	19.12±0.07	1.35±0.04
F12	0.42±0.02	0.52±0.06	39.29±0.02	17.46±0.03	1.29±0.06
F13	0.32±0.04	0.45±0.04	45.29±0.06	17.86±0.07	1.39±0.02
F14	0.39±0.01	0.39±0.02	25.66±0.06	12.45±0.03	1.55±0.05
F15	0.38±0.06	0.38±0.06	37.45±0.02	18.34±0.06	1.38±0.07
F16	0.41±0.04	0.39±0.05	35.49±0.08	16.51±0.31	1.23±0.09

Compatibility studies

The compatibility of the drug in the formulation was confirmed by FTIR spectral analysis. FTIR spectra of pure drug, formulation containing Xanthan gum and Guar gum were determined by using Shimadzu FTIR spectrophotometer by KBr pellet method.[9]

Physicochemical evaluation

The prepared matrix tablets were evaluated for weight variation, thickness, diameter, hardness, drug content, swelling and in vitro studies. Drug content was estimated by HPLC technique using a developed method. Tolterodine from accurately weighed samples was extracted into methanol and the extracts were suitability diluted and assayed for

drug content. The samples were performed using UV detector with flow rate 2ml/min.[10]

Physicochemical evaluation of matrix tablets

Dimension measurement: The thickness and diameter of the tablets was carried out using digital vernier caliper. Three tablets were used from each batch and results were expressed in millimeter. All tablets from individual batch have shown uniform thickness and diameter.

Weight variation test: Twenty tablets were selected randomly, individually weighed in a single pan electronic balance and the average weight was calculated. The uniformity of weight was determined according to I.P. specification. As per IP not more than two of individual weights should deviate from average weight by more than 5% and none deviate more than twice that percentage.

Hardness test: Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shocks of handling in manufacture, packing and shipping. Monsanto hardness tester was used to measure the hardness of tablet. Three tablets from each batch were used for hardness test and results were expressed in Kg/cm^2.

Friability test: It was done in Roche friabilator apparatus where the tablets were subjected to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm for dropping the tablets at a distance of six inches with each revolution. Pre-weighed samples of 20 tablets were placed in the friabilator, which is then operated for 100 revolutions. The tablets are then dusted and reweighed. Compressed tablets that loss less than 0.5 to 1.0% of their weight are generally considered acceptable. The percentage friability was calculated by the following expression,

$$\text{Friability} = \frac{\text{Weight loss}}{\text{Weight of tablets before operations}} \times 100$$

Drug content uniformity: Ten tablets were weighed and taken in a mortar and crushed to make powder form. A quantity of powder weighing equivalent to 100mg of drug was taken in a 100mL volumetric flask and pH 6.8 buffer solution was added. It was then heated at 60°C for 30 minutes. The solution was filtered using membrane filter (0.45µm) and then its absorbance was measured at 281nm using UV-Visible spectrometer. The amount of drug present in one tablet was calculated using standard graph. The results obtained for physicochemical evaluation of matrix tablets are given in Table 03.[11]

Table No. 03: Results of physicochemical parameters of all formulations containing Tolterodine tartrate

F.CODE	Thickness (mean±SD) (mm)	Diameter (mean±SD) (mm)	Friability (mean±SD) (%)	Hardness (mean±SD) (kg)	Weight variation (mean±SD) (mg)	Drug content (mean±SD)
F1	4.0±0.1	2.8±0.1	0.08	5.2±0.4	189.65±0.56	99.06±1.09
F2	3.9±0.3	2.8±0.3	0.18	4.9±0.3	186.77±0.54	97.92±1.59
F3	4.1±0.3	2.8±0.3	0.04	5.4±0.3	183.75±0.86	101.81±0.57
F4	3.8±0.2	2.8±0.2	0.21	4.5±0.3	181.45±0.48	102.82±1.03
F5	4.0±0.3	2.8±0.3	0.12	4.6±0.2	184.83±0.35	98.79±1.49
F6	3.8±0.2	2.8±0.2	0.09	5.8±0.1	189.50±0.79	98.74±1.15
F7	3.8±0.1	2.8±0.1	0.15	4.5±0.2	183.86±0.46	99.76±0.73
F8	4.1±0.4	2.8±0.4	0.04	5.6±0.2	183.94±0.69	98.84±1.74
F9	4.0±0.3	2.8±0.3	0.08	5.9±0.2	182.55±0.54	101.04±1.06
F10	3.9±0.3	2.8±0.3	0.04	5.7±0.2	181.51±0.46	102.06±0.98
F11	4.0±0.2	2.8±0.2	0.10	5.4±0.3	183.43±0.42	103.56±1.24
F12	4.0±0.3	2.8±0.3	0.09	5.3±0.2	182.10±0.79	101.81±1.37
F13	4.0±0.2	2.8±0.2	0.18	5.3±0.3	184.27±0.61	103.62±0.60
F14	3.9±0.1	2.8±0.1	0.16	5.5±0.1	186.72±0.55	102.42±0.62
F15	4.1±0.3	2.8±0.3	0.12	4.8±0.4	181.15±0.70	99.61±1.66
F16	3.7±0.2	2.8±0.1	0.11	5.2±0.2	182.23±0.56	98.53±1.03

Each value represents the mean ± standard deviation (n=3)

Swelling behavior of matrix tablets

The extent of swelling was measured in terms of percent weight gain by the tablet. The swelling behaviors of formulations were studied. One tablet from each formulation was kept in petri dish containing distilled water. At the end of one hour the tablet was withdrawn, soaked with tissue paper and weighed. The process is continued for 12 hours. The percentage weight gain by the tablet was taken as swelling index was expressed in terms of percentage, and was calculated from the following equation.

$$SI\ (\%) = \frac{W_t - W_0}{W_0} \times 100$$

Where, SI is swelling index, W_t is weight of tablet at time t, W_0 is weight of tablet before immersion. The swelling indexes of tablets are given in Table4.

Table No. 04: Swelling index of matrix tablets of Tolterodine tartrate

Code	% of swelling with time in hrs Mean ± SD					
	2	4	6	8	10	12
F1	55.44±0.69	59.12±0.64	80.75±0.32	99.45±0.64	127.35±0.47	145.49±1.24
F2	33.24±0.74	55.53±0.22	84.13±0.23	89.39±0.54	131.62±0.54	162.22±1.56
F3	45.05±1.25	62.34±0.36	87.65±0.61	92.68±0.41	132.16±0.15	142.74±1.58
F4	50.59±0.57	52.26±0.61	82.62±0.25	117.49±0.87	152.17±0.58	127.37±0.45
F5	40.93±0.92	63.54±0.54	85.66±0.53	101.16±0.56	118.18±0.27	144.25±0.77
F6	39.22±0.75	59.05±0.43	83.42±0.65	89.64±0.54	145.38±0.54	131.31±0.27
F7	47.54±0.92	56.76±0.14	87.98±0.41	89.99±0.74	124.46±0.75	148.34±0.52
F8	43.05±1.66	55.34±0.98	72.72±0.45	105.46±0.56	152.24±1.24	128.43±0.34
F9	37.14±1.42	55.66±0.44	77.65±1.66	97.77±0.27	139.24±0.15	132.58±0.67
F10	36.53±0.75	53.34±1.34	72.16±1.25	94.06±0.45	124.49±0.34	131.31±0.39
F11	38.26±1.27	56.56±0.36	76.72±0.59	98.81±0.14	150.58±0.24	134.27±0.52
F12	26.35±0.12	48.41±0.63	74.36±0.44	99.57±0.78	118.22±0.64	130.54±0.34
F13	43.67±0.98	75.14±0.58	75.11±0.55	84.88±0.54	134.48±0.47	130.35±1.53
F14	42.45±0.53	72.83±0.24	82.94±0.34	102.35±0.67	112.24±0.25	137.46±0.52
F15	32.12±0.85	58.39±0.56	83.16±0.66	79.39±0.64	126.35±0.24	123.55±0.52
F16	36.42±0.38	59.10±0.82	85.02±0.83	83.04±0.14	112.02±0.41	145.20±0.49

In vitro drug release study

In vitro dissolution study was carried out using USP Type II apparatus (Lab India) at 50 rpm. Phosphate buffer pH 7.4 was used as dissolution medium, temperature was maintained at 37±0.5°C. An appropriate time intervals samples were withdrawn from the dissolution medium and assayed by developed HPLC method to determine the amount of Tolterodine tartrate release from the matrix tablet. Comparison of drug release pattern of all matrix tablets of Tolterodine tartrate is shown in Fig. 1.

Kinetics of drug release

Dissolution data of all matrix tablets were subjected to the treatment of different kinetic equations. It was found to be that the drug release patterns were best fitted with zero order release equation and involves the combination of polymer relation and consequently swelling.

Zero-order release equation $C = K_0t$

First-order release equation $\log C = \log C_0 - Kt/2.303$

Higuchi's square root of time equation $Q = Kt^{1/2}$

Korsmeyer Peppas equation $Mt/M\alpha = Kt^n$

Stability study

Accelerated stability study was carried out as per ICH guideline 'Q1E Evaluation for stability Data' using Ostwald stability chamber for best formulation. The stability study was carried out at room temperature as well as different accelerated temperature and humidity conditions for a period of twelve months. The stability studies were conducted as per ICH guidelines for the period of twelve months at various accelerated temperature and humidity conditions of 25°C/60%RH, 40°C/70%RH, 50°C/75%RH, 60°C/80%RH. After twelve months, the matrix tablets were analyzed for drug content and drug release profile.

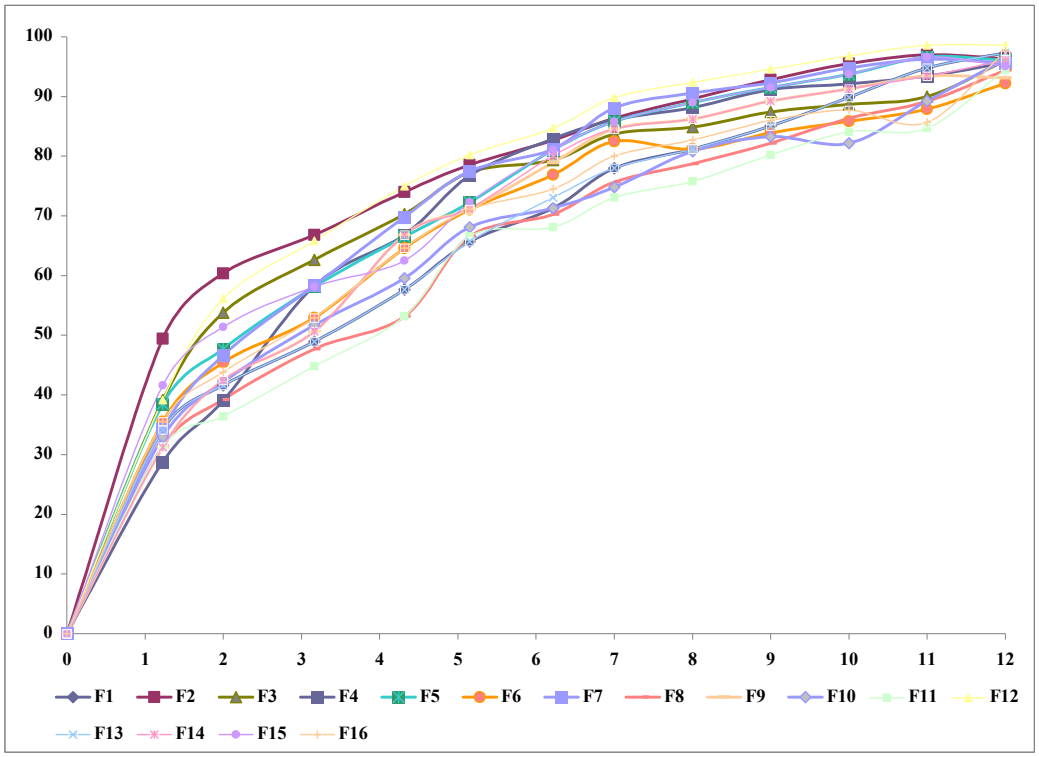

Fig. No. 01: Comparison of drug release pattern of all matrix tablets of Tolterodine tartrate

Results and discussion

IR spectroscopy studies were carried out using Perkin Elmer model 2000 at Laila Impex Research centre, Vijayawada, Andhra Pradesh, India by KBr pellet method. Materials were compressed under 10 tones pressure in a hydraulic press to form a homogeneous sample/KBr pellet. The pellet was scanned over the frequency range from 4400 to 450 cm^{-1} and peaks obtained were identified.[12]

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.

Preformulation study

The angle of repose for pure drugs was very less and hence poor flow of drug was exhibited. Moreover, the Carr's index of the pure drug was found to be high confirming that the drug has poor flow property and compressibility. In view of this, the formulations were prepared by wet granulation technique to improve the flow as well as compressibility. The flow properties and derived properties were evaluated for all formulations, which were proven to be within limits showing good flow properties, standard limits were tabulated in Table 5.

Table No. 05: Standard limits for flow properties of powder

S. No	Type of flow	Angle of repose	Carr's index	Hausner's ratio
1	Excellent	25-30	10	1-1.11
2	Good	31-35s	11-15	1.12-1.18
3	fair	36-40 (aid not needed)	16-20	1.19-1.25
4	passable	41-45 (may hang up)	21-25	1.26-1.34
5	Poor	46-55 (must agitate)	26-31	1.35-1.45
6	very poor	56-65	32-37	1.46-1.54
7	very very poor	>66	>38	>1.60

Physicochemical evaluation

The hardness of the tablets was found to be between 4-6 kg/cm^2 and % friability of tablets ranged between 0.023 and 0.142%. The tablets have the enough hardness to withstand stress during the transport and handling. The tablet

complies with the test for uniformity of weight. The drug content varied from 93.24-102.45% w/w and all the formulations exhibited uniformity of drug content.

Swelling index

As time increased the swelling index was increased, because weight gained by the matrix tablet was increased proportionally with the rate of hydration up to 5 hours. The direct relationship was observed between swelling index and gum concentration, as gum concentration increases, swelling index was increased, but drug release decreases. This is due to slow erosion of gelled layer from the core tablets containing a higher amount of matrix polymer. Comparisons between Xanthan gum and guar gum, it was observed that swelling index of guar gum was significantly more compared to Xanthan gum.

In vitro drug release study

The drug release was prolonged as the amount of polymeric concentration was increased. Comparison between Xanthan gum and guar gum based matrix tablets, release of drug from guar gum based tablets were found to be more slowly compared to Xanthan gum based tablets. This sustained release is because of the formulation of thicker gel barrier structure around the matrix that delayed the drug release from the matrix tablets. Thus, maintain the integrity of tablet and retarding further penetration of the dissolution medium. The maximum drug release was found to be 95% over a period of 12 hours in guar gum based formulations (F9-F12) at a concentration ranging from 15 to 60mg per tablet. Similarly maximum drug release was found to be 92% over a period of 12 hours in Xanthan gum to gum based formulations (F13-F16) at a concentration ranging from 15 to 60mg per tablet. In vitro profiles of tablets could be best expressed by zero-order kinetics and Korsmeyer-Peppas kinetics. The 'n' value of drug release is 0.943. Therefore, the drug release followed non-fickian diffusion.

Stability studies

The stability studies were conducted as per ICH guidelines for the period of twelve months at various accelerated temperature and humidity conditions of 25°C/60%RH, 40°C/70%RH, 50°C/75%RH, 60°C/80%RH. The stability study revealed that the matrix tablets of F12 may be stable for the period of two years.

Conclusion

The modified release matrix tablets contain Tolterodine tartrate were prepared using Hydroxypropyl methyl cellulose (HPMC K4M), Sodium carboxy methyl cellulose (SCMC), Guar Gum and Xanthan Gum as rate controlling polymer for the treatment of overactive bladder. The tablets were prepared by wet granulation method and studied the effect of the matrix former such as Guar Gum and Xanthan Gum separately. Hydrophilic polymers delivers drug over a period of 12 hours. Formulation F12 shows satisfactory results by releasing 98.6% of drug in 12 hours and followed zero-order and Korsmeyer-Peppas release mechanism. The overall results indicate that the formulation F12 was better and that satisfied all the criteria as modified release tablets. This modified release dosage form will be good in treatment of over active bladder/urinary incontinence by improving patient compliance and reducing dosing frequency.

References

1. Cheryl H Agris, Method for preparing modified release pharmaceutical compositions, Patent No. US20070122482A1, May 21, 2007.
2. Raghuram Reddy K, Mutalik S, Reddy S. Once-Daily Sustained-Release Matrix Tablets of Nicorandil: Formulation and In Vitro Evaluation. AAPS PhagrmSciTech. 2003; 4(4): Article 61.
3. Bruce, L.D., Shah, N.H., Malick, A.W., Infeld, M.H., McGinity, J.W. Properties of hotmelt extruded tablet formulations for the colonic delivery of 5-aminosalicylic acid. Eur. J. Pharm. Biopharm., 59, 2005, 85–97.
4. Modiri, A.R., Alberts, P., Gillberg, P.G., Effect of muscarinic antagonists on micturition pressure measured by cystometry in normal, conscious rats. Urology 59, 2002, 963–968.
5. Kerrebroeck PV, Kreder K, Jonas U, Zinner N, Wein A. Tolterodine once-daily: superior efficacy and tolerability in the treatment of the overactive bladder. *Urology*, 2001; 57(3): pp. 414-421.
6. Phaechamud T. Comparison Drug Release from Simple and Layered Matrix Systems Containing Hydroxypropyl Methylcellulose.

Thai Pharm. Health Sci. J., 2008; *3(2):* pp. 219-228.

7. Ramathilagam N, Meeradevi M, Solairaj P, Rajesh SC, Development and validation of HPLC method for the estimation of Tolterodine tartrate in tablets, International Journal of Pharmacy and Biological Sciences, 2(4), 2012, 332-337.
8. Patra CN, Arethi BK, Pandit HK, Singh SP, Meduri VD. Design and evaluation of sustained release bilayer tablets of Propranolol hydrochloride. 2007; 57: 479-489.
9. Chavda HV, Patel MS, Patel CN. Preparation and *in vitro* evaluation of guar gum based triple-layer matrix tablet of diclofenac sodium. *Research in Pharmaceutical Sciences*, 2012; 7(1): pp. 57-64.
10. Patel CN, Patel SA, Patel MM. Spectrophotometric Methods for the Estimation of Nicorandil in Tablet Dosage form. 2005; 103-105.
11. Jaimini M, Rana A.C. Formulation and Evaluation of Famotidine Floating Tablets. Current Drug Delivery. 4, 2007, 51-55.
12. P. Narayana Raju, K. Prakash, M. Lakshmi Narasu. Compatibility Study of Lamivudine with Various Cellulose Polymers, E-Journal of Chemistry, 6(S1), 2009, S17-S20.
13. Haydee J, Giovanna R, Leopoldo V. Influence of admixed carboxymethylcellulose on release of 4aminopyridine from hydroxypropyl methylcellulose matrix tablets. Int. J. Pharm. 2001; 216:115-125.