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Formulation and Evaluation of Three Layer Controlled Release Matrix Tablets of Tolterodine -L-Tartrate

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ABSTRACT

The aim of the present study is to formulate a three layer oral controlled release Tolterodine -L-tartrate tablets using Hydroxy propyl methyl cellulose K4M (HPMC K4M) and Xanthan gum as rate controlling polymer for the treatment of overactive bladder. This study is based on the application of an inert impermeable coating on different sides of a matrix tablet using Xanthan gum as barrier layer. The powder blends evaluated for Pre-formulation studies showed satisfactory result. The tablets were prepared by direct compression method. The tablets were evaluated for thickness, hardness, uniformity of weight, friability, drug content, content uniformity, in-vitro drug release and finally stability study. Among all the formulations, F10 gave satisfactory results by releasing 99.45% of drug in 24 hours. The drug release from optimized formulation (F10) fitted to various kinetic models and the drug release was found to follow zero-order kinetics and Korsemeyer-Peppas release mechanism. The hydrophilic polymer as matrix core and Xanthan gum as retardant layers in the form of three layer matrix tablets provided a linear release with no burst effect. Stability study was carried out at 40º±2ºC/75±5% RH for 3 months and appeared no change observed in 3 months. This three layer unit dosage form will be good for the treatment of over active bladder/urinary incontinence by improving patient compliance and reducing dosing frequency.

Key words: *Tolterodine -L-tartrate, Three layer, Direct compression, In-Vitro drug release, Xanthan gum, HPMC K4M.*

INTRODUCTION

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 the same drug [1]. There are many ways to design controlled release dosage forms for oral administration: from 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]. Multi-layered matrix tablet is a drug delivery device, which comprises a matrix core containing the active solute and one or more barriers (modulating layers) incorporated during the tabletting process. The modulating layers delay the interaction of active solute with dissolution medium, by limiting the surface available for the solute release and at the same time controlling solvent penetration rate. In this device, the coat layers prevent the water penetration, through the protected core for some duration. This results in reduced hydration rate and controlled area for solute release at the core. Thus burst effect can be smoothened and the release can be maintained at a relatively constant level during the barrier layers' swelling and erosion process. By this way it is feasible to achieve a linear release profile [3].

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 [4]. Hydroxypropyl methylcellulose (HPMC) is a non-ionic aqueous-soluble cellulose ether derivative for use in controlled-release dosage forms. Owing to high swellability and high gelling strength formation this polymer effectively prolongs drug release which has a significant effect on the release kinetics of an incorporated drug [5].

Overactive bladder is a chronic, highly prevalent, and distressing medical condition characterized by urinary urgency and frequency, with or without urge incontinence. Anti-muscarinic agents are the primary pharmacologic 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 (eg, dry mouth, constipation and blurred vision). For these reasons, Tolterodine -L-tartrate was developed as the first anti-muscarinic agent specifically targeted for the treatment of the overactive bladder. The currently available formulation of Tolterodine -L-tartrate requires twice-daily administration but given that overactive bladder is a chronic condition requiring long-term treatment, patient convenience and compliance could be improved with once-daily administration [6]. In market extended release capsules are available but they have some disadvantages like complicated process, aging, and instability. The main objective of the present study is to provide an improved oral controlled release matrix dosage formulation at therapeutic dose, in the tablet form, containing 4-mg Tolterodine -L-tartrate for 24 hour release useful for the treatment of urge incontinence and other symptoms of unstable or overactive urinary bladder.

MATERIALS AND METHODS

Materials:

Tolterodine-L-Tartrate was obtained as gift sample from Aurobindo pharma, Hyderabad. HPMC K4M was obtained as gift sample from MMC healthcare ltd., Chennai. Xanthan gum, Lactose Monohydrate, Magnesium stearate, Aerosil, Lake Ponceau 4R was obtained as gift sample from Bafna pharmaceuticals, Chennai.

Methods:

Preparation of core layer and barrier layer blends: [5]

To formulate core layer blend, all the raw materials specified in the table: 1 were passed through sieve no. 44. The drug was mixed well with diluents, colouring agent to form homogenous mixture. To the resulting powder mixture Magnesium stearate, Aerosil were added and mixed well to get a uniform powder blend. Similarly barrier layer blends prepared using Xanthan gum without drug and colouring agent. The core and barrier layer blends were evaluated for their flow property (Angle of repose, Carr's index, and Hausner's ratio). The values are shown in **Table. 2**.

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Preparation of three layer matrix tablets: [7]

Bottom layer was prepared by slight compression of Xanthan gum blend in the die cavity, which provided uniform spreading. The upper punch was lifted up, and core layer blend (for middle layer) were placed over the prepared bottom layer in the die cavity and slightly compressed once again. Finally Xanthan gum blend (for top layer) placed over the middle layer and compressed (8mm punch, Rimek, India) with a maximum compression force.

Physicochemical characterization of three layer matrix tablets: [7]

The prepared three layer matrix tablets were evaluated for their hardness, thickness, uniformity of weight, friability drug content and content uniformity. The hardness (n=5), friability and thickness (n=5) of three layer matrix tablets were determined using the Monsanto Hardness Tester (Erweka Mumbai), the Roche friabilator (Electrolab, India) and the Vernier caliper (Mitutoyo, Japan) respectively.

In-vitro release study of the tablets: [8]

The release rate of Tolterodine-L-Tartrate from tablets was determined using USP dissolution apparatus I (Basket type). The test was performed using 900mL of HCL acid buffer pH 1.2 at 37±0.5ºC and 100rpm for first 2Hrs and then with Phosphate buffer pH 6.8 for 24Hours.10ml was withdrawn at regular intervals and replaced with fresh buffer. The samples were estimated for drug content using UV spectrophotometer at a wavelength of 281 nm.

Kinetics of drug release: [9]

The *in vitro* drug release data of optimized formulation was fitted to different kinetic models in order to study the release kinetics and mechanism of drug from three layer matrix tablet.

Zero order release equation $C = K_0t$
First order release equation $Log\ C = logC_0 - Kt/2.303$
Higuchi's square root of time equation $Q = Kt^{1/2}$
Korsmeyer Peppas equation $M_t/M_\alpha = Kt^n$
Hixson Crowell equation $Q_0^{1/3} - Q_t^{1/3} = K_{HC}\ X$

Stability studies: [10]

Optimized three layer matrix tablets were kept in the stability chamber (Technico) subjected to stability at 40 ± 2℃ and 75 ± 5 % RH for a period of 3 months. After 3 months tablets were analyzed for physicochemical characteristics and drug release studies.

RESULTS AND DISCUSSION

The three layer matrix tablets of Tolterodine –L-Tartrate were developed to retard the drug release from the surfaces of matrix core by compressing Xanthan gum on both the surfaces.

Physicochemical characterization of three layer matrix tablets: [11]

The hardness of the tablets was found to be between 3.5 and 4.5 kg/cm^2 and the %friability of tablets ranged between 0.010% and 0.138%. The tablets have the enough hardness to withstand stress during transport and handling. The tablets comply with the test for uniformity of weight. The drug content varied from 97.32% to 101.02% w/w and all the formulations exhibited uniformity of drug content (**Table. 3**).

In-vitro drug release study:

The drug release was prolonged as the amount of core polymeric layer was increased (**Fig. 1**). Drug release from the middle core layer could be modified by delayed diffusion from the two barrier layers. The compression with polymeric layers on both sides of the tablet prolonged the drug release and modified the drug release to achieve a constant release rate. The barrier layer on both surfaces of the three layer matrix tablets reduced the initial burst effect and also delayed the medium penetration and hydration of the middle layer by reducing the surface area. Drug molecules exhibited gradual delayed diffusion through both barrier layers as a result of increasing polymer hydration/dissolution over time. The external hydrated barriers disappeared gradually with time and the diffusion path-length was subsequently reduced promoting drug release at a later stage [2]. The combinations of polymers (Xanthan gum and HPMC K4M) in matrix also significantly retard the release for 24 hours. Therefore the zero-order release could be achieved by the three layer matrix system.

Kinetics of drug release:

Optimized F10 formulation was fitted to various release kinetic models, Zero-order equation and Korsemeyer-Peppas showed high linearity (R^2=0.961) and (R^2=0.95) respectively. So in this experiment, the *in-vitro* release profiles of tablets could be best expressed by Zero-Order kinetics and Korsemeyer-Peppas kinetics. The 'n' value of drug release is 0.943 therefore the drug release follows super case II transport. The Zero-order and Korsemeyer-Peppas equation showed in **Fig. 2 & 3** respectively.

Stability studies:

When the three layer tablets were stored at 40º±2ºC/75±5% RH for 3 months, there appeared no change in physical parameters, and drug content. When the dissolution study was conducted in the HCL acid buffer pH 1.2 and phosphate buffer pH 6.8, not much difference was observed in the cumulative percentage release of Tolterodine- L-Tartrate from F10. The physicochemical parameter after stability study showed in **Table. 4**.

Table 1: Composition of Formulations

Ingredients(in mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Tolterodine -L- Tartrate	4	4	4	4	4	4	4	4	4	4	4
HPMC K 4M	10	20	30	40					20	10	15
Xanthan GUM					10	20	30	40	20	12.5	15
Lactose Monohydrate	102	92	82	72	102	92	82	72	72	90	82
Magnesium Stearate	2	2	2	2	2	2	2	2	2	2	2
Aerosil	2	2	2	2	2	2	2	2	2	2	2
Lake Ponceau 4R	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Xanthan Gum(Barrier Layer)	2×30	2×30	2×30	2×30	2×30	2×30	2×30	2×30	2×30	2×30	2×30
Average weight	180mg										

Table 2: Micromeritic properties of pre-compression powder blend

Formulation	Angle of Repose (Θ)*	Carr's Index*	Hausner's Ratio*
Barrier Layer	23.29±0.08	13.77±0.32	1.159±0.003
F1	32.41±0.03	14.12±0.41	1.165±0.004
F2	33.01±0.02	14.58±0.24	1.170±0.004
F3	33.52±0.07	14.70±0.23	1.172±0.001
F4	34.07±0.04	13.91±0.31	1.160±0.002
F5	31.57±0.04	15.09±0.40	1.182±0.006
F6	31.57±0.04	15.49±0.21	1.180±0.005
F7	32.01±0.05	15.04±0.24	1.177±0.008
F8	32.47±0.04	14.61±0.26	1.171±0.004
F9	32.56±0.03	13.93±0.25	1.161±0.006
F10	31.13±0.08	14.50±0.25	1.161±0.007
F11	32.01±0.07	14.30±0.26	1.161±0.008

*Mean ± SD (n=3)

Table 3: Physicochemical parameters tablets

Formulations	Uniformity of weight *(gm)	Thickness** (mm)	Hardness** (Kg/cm^2)	Friability %**	Drug content **(%w/w)	Content Uniformity*** (%w/w)
F1	0.181±0.002	3	3.5±0.27	0.0463±0.012	97.32±0.991	98.51±0.569
F2	0.180±0.004	3	3.5±0.3	0.0241±0.009	99.08±1.023	99.25±0.865
F3	0.179±0.003	3	4.0±0.25	0.0102±0.014	98.42±1.022	98.75±0.456
F4	0.182±0.005	3	4.0±0.31	0.0192±0.016	101.02±1.05	99.89±0.159
F5	0.180±0.003	3	3.5±0.33	0.0310±0.011	99.88±1.081	98.36±0.358
F6	0.181±0.004	3	4.0±0.29	0.0307±0.014	97.99±1.036	99.16±0.954
F7	0.179±0.002	3	4.0±0.24	0.1380±0.021	98.76±1.058	98.87±0.658
F8	0.182±0.003	3	4.5±0.23	0.1139±0.023	99.01±0.993	99.89±0.547
F9	0.182±0.004	3	4.5±0.24	0.0907±0.015	99.57±0.975	99.47±0.365
F10	0.179±0.003	3	4.5±0.28	0.0987±0.019	98.0±1.041	97.86±0.452
F11	0.181±0.003	3	4.5±0.30	0.1012±0.014	98.55±1.025	98.25±0.952

*Mean ± SD (n=20) **Mean ± SD (n=5) ***Mean ± SD (n=10)

Table 4: Physicochemical parameters tablets after stability study

Parameters	Initial	1st month	2nd Month	3rd Month
Thickness (mm)	3	3	3	3
Hardness (kg/cm^2)	4.5 ± 0.28	4.5 ± 0.34	4.5 ± 0.41	4.5 ± 0.29
% Friability	0.0987 ± 0.019	0.0824 ± 0.024	0.0789 ± 0.35	0.0965 ± 0.041
Drug content (%w/w)	97.86 ± 0.452	98.21 ± 0.562	98.41 ±0 .624	97.98 ± 0.412

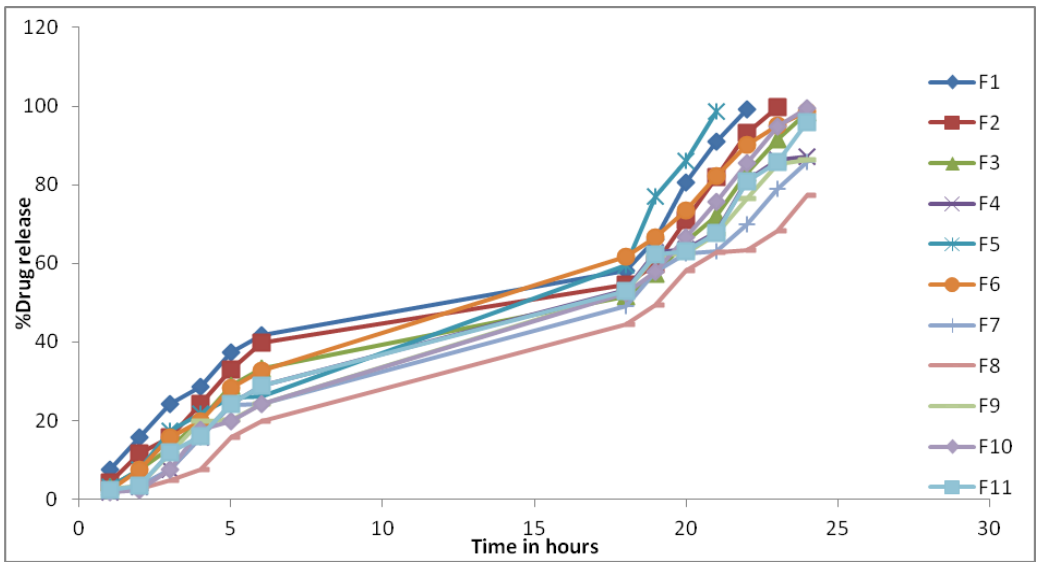

Fig. 1: *In vitro* Drug Release from all formulation

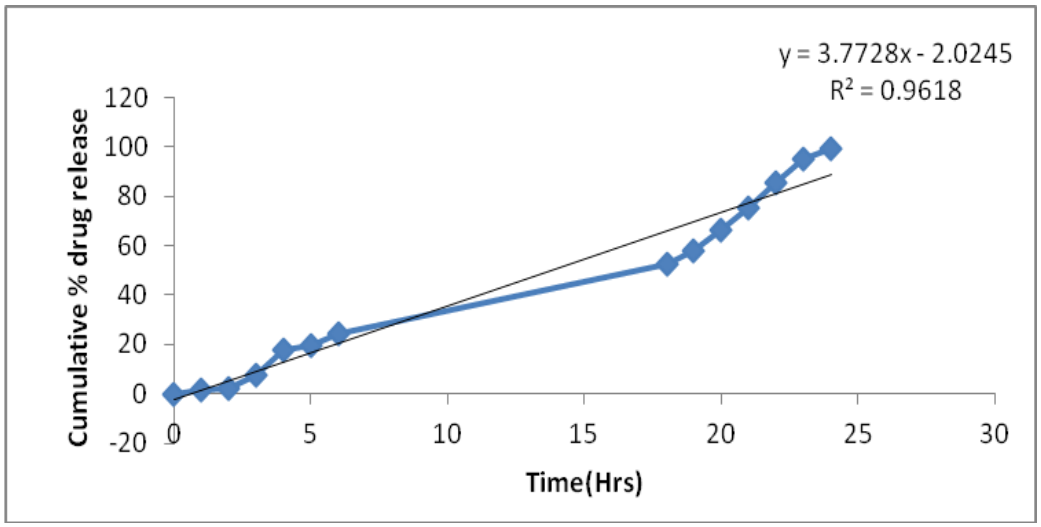

Fig. 2: Zero order release kinetics

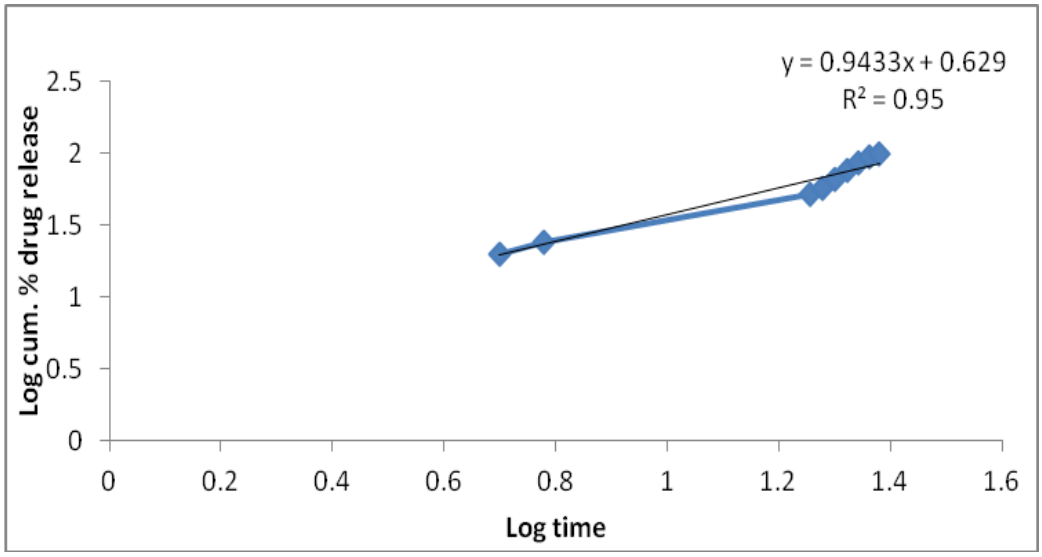

Fig. 3: Korsemeyer-Peppas release kinetics

CONCLUSION

The aim of the present study was to develop a three layer controlled release matrix tablets containing BCS class I drug Tolterodine-L-Tartrate. The three layered controlled release matrix tablet is developed using HPMC K4M, Xanthan gum as hydrophilic polymers such that it delivers 4mg of Tolterodine-L-Tartrate over a period of 24 hours. The tablets were prepared by direct compression method. Among the F1 to F11formulations, F10 gave satisfactory results by releasing 99.45% of Tolterodine-L-Tartrate in 24 hours. The optimized formulation (F10) followed zero-order and Korsemeyer-Peppas release mechanism. The three layered matrix tablets formulation confirmed that the release extended up to 24 hours in controlled manner. The hydrophilic polymers as matrix core and Xanthan gum as retardant layers in the form of three layer matrix tablets provided a linear release. Stability study indicates no significant change in physical parameters, drug content and the cumulative percentage of drug release. The combination of polymers (Xanthan gum and HPMC K4M) in matrix also significantly retarded the release for more than 24 hours. The overall results indicate that the formulation F10 was better and that satisfied all the criteria as three layer controlled release matrix tablets. This three layer 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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