



Formulation and Characterization of Matrix and Triple-Layer matrix tablets for Controlled Delivery of Metoprolol tartrate

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ABSTRACT

In the present study matrix and triple layer matrix tablets of metoprolol tartrate were formulated by using xanthan gum as the matrix forming agent and Sodium Carboxy Methyl Cellulose (Na CMC) as barrier layers. The prepared tablets were analysed for their hardness, friability, drug content and *in-vitro* drug release studies. Marked differences in dissolution characteristics of (M3) and (M3L3) were observed and showed a significant difference statistically. Mean dissolution time (MDT) for M3 and M3L3 were found to be 4.02h and 12.75h, while dissolution efficiency (DE₈%) decreased, indicating that the release of metoprolol tartrate is slower from triple layer matrix tablets. The finding of the study indicated that the matrix tablets prolonged the release, but predominantly in a first order kinetics. Layering with Na CMC granules on the matrix core, provided linear drug release with zero order kinetics. The triple layer matrix tablets (M3L3) shows precise controlled release of the drug than that of plain matrix tablets. FT-IR and DSC studies confirmed that there was no chemical interaction between drug and excipients used in the formulation.

Keywords: Metoprolol tartrate, Controlled release, linear drug release, Zero order kinetics.

INTRODUCTION

Oral ingestion has long been the most convenient and commonly employed route of drug delivery due to its ease of administration and flexibility in the design of the dosage form. There are many ways to design modified release dosage forms for oral administration and one of them is multi layered matrix tablet. One to three (multi) layer matrix tablets is a drug delivery device, which comprises a matrix core containing the active solute and one, or more barriers (modulating layers) incorporated during tableting process.^[1] The barrier 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.^[2-3] In the device, the coat layers prevent the water penetration through the protected core for some duration. After this phase during the subsequent dissolution process, the swollen barriers erode and the surface available for drug release slowly increases. In this way the decrease of delivery rate due to the increase in diffusion path length (saturation effect) is counter balanced by the simultaneous

increase of the area available for drug release.^[4-5] Thus by combining a time-dependent control of the hydration rate of the device, the reduction of tablet surface exposed to the dissolution medium, it is feasible to achieve a linear release profile.^[6]

The use of naturally occurring biocompatible gums has been the focus of recent research activity in the design of dosage forms for oral controlled release administration, and hydrophilic polymers matrix systems are widely used because of their flexibility to provide a desirable drug release profile, cost effectiveness, and broad regulatory acceptance.^[7] Xanthan gum (XG) is soluble in water, anionic hetro polysaccharide and to be sensitive to pH and ionic strengths. Xanthan hydrophilic secreted from (a yellow-pigmented bacterium) contains glucose 37%, mannose 43.4%, glucuronic acid 19.5%, acetate 4.5%, and pyruvate 4.4%. It swells in gastric fluid to produce a highly viscous layer around the tablet through which the drug can slowly diffuse^[8] and is used for the fabrication of matrices with uniform drug release characteristics.^[9-10] Xanthan gum is the bacterial polysaccharide produced industrially on a large scale. It is a natural carbohydrate commercially produced by fermenting glucose with the appropriate microorganisms.^[11] Metoprolol tartrate is selective-adrenoreceptor blocking agent used in the treatment of various cardiovascular

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disorders and prophylaxis of migraine. It has been classified as a class I substance according to the bio pharmaceutical classification system (BCS), that it is highly soluble and highly permeable having pKa value of 10.8. The drug is readily and completely absorbed throughout the intestinal tract but is subject to extensive first pass metabolism resulting incomplete bioavailability (about 50%). After a single oral dose, peak plasma concentrations occur after 1-2 hours.^[12] The drug is eliminated within 3 to 4 hours, which depending on therapeutic intention, makes it necessary to administer simple formulation of metoprolol tartrate up to four times daily. Based on these properties and the well defined relationship between the beta blocking effect and plasma drug concentration. Metoprolol tartrate lends itself to a controlled-release (CR) formulation smooth out peaks and valleys in the plasma levels and enable less frequent dosing intervals are typically reduced to once or twice a day.^[13]

This study was carried out to evaluate the effect of thickness of the barrier layers on the matrix core component containing xanthan gum (XG) and Sodium Carboxy Methyl Cellulose (Na CMC) (higher viscosity) as barrier layers and to develop a constant rate delivery formulation along the gastrointestinal tract without breaking up and release of highly water soluble metoprolol tartrate progressively with zero order release kinetics

MATERIALS AND METHODS

Metoprolol Tartrate was obtained as gift sample from Astra Zeneca Pharma Ltd., India, Bangalore. Xanthan gum from Raj enterprises Mumbai, India, Sodium Carboxy Methyl Cellulose (Na CMC) (high viscosity grade) and Micro Crystalline Cellulose MCC (Avicel PH 101) from Reliance Cellulose Product, Hyderabad, India, was used. All other materials were of analytical or reagents grade.

Preparation and Characterization of triple-layer matrix tablets of Metoprolol tartrate

Preparation of Metoprolol tartrate matrix core granules

The drug and polymers for the matrix tablets and triple-layer matrix tablets were passed through 180 μ m sieve before their use in the formulation. The matrix formulations were prepared and coded as M1, M2 and M3 respectively presented in Table 1. Matrix core granules were prepared by wet granulation procedure using non-ionic hydrophilic polymer xanthan gum, micro crystalline cellulose as filler, starch paste 10% as binding agent. The cohesive mass obtained was passed through sieve number 18, dried at 50°C for 1hr in a tray dryer. Then the granules were lubricated with magnesium stearate and talc in 1:2 ratio.

Preparation of Na CMC barrier layer granules

The barrier layer containing anionic Na CMC, were prepared by wet granulation technique. The polymer Na CMC and 10% starch paste were mixed well and the resulting wet mass was passed through sieve no 18 and dried at 30°C for an hour. To increase the flow property of the granules and to prevent its adhesion to die and punches the granules were lubricated with talc and magnesium stearate as shown in Table 1.

Preparation of matrix tablets and triple layer matrix tablets

The composition of formulation used in the study containing 100 mg of metoprolol tartrate in each case is shown in Table 1. The granules were compressed using a rotary compression machine (Riddhi, Ahmedabad, India).

Triple layer matrix tablets were prepared by using different combinations of drug loaded matrix core granules and release retardant layer granules, the composition of Na CMC retardant granules is shown in table I. Initially the volume of the die cavity was adjusted equivalent to total weight of triple layer matrix tablets. Then pre weighed amount of polymer granules of Na CMC equivalent to bottom layer 50mg, 75mg, and 100mg were taken and placed in the die cavity and uniformly spread. The upper punch was lifted up and 300mg of matrix core granules were placed over the bottom layer of polymer granules in the die cavity and slightly compressed. The remaining volume of die cavity was filled with pre weighed amount of polymer granules equivalent to top layer 50mg, 75mg and 100mg and finally compressed on a rotary compression machine (Riddhi, Ahmedabad, India). The hardness of matrix tablet and triple layer matrix tablets was adjusted to 5-8kg/cm².

Physical tests for the prepared matrix tablets

Ten tablets from each formulation were taken for measurement of diameter and crown thickness with vernier calipers and an average of ten determinations was carried out. Hardness of the matrix tablets and triple layer matrix tablets was evaluated by using hardness tester (Pfizer) and mass determination was performed for twenty tablets from each batch and average values were calculated. Friability of the matrix tablets and triple layer matrix tablets was determined by first weighing 10 tablets after de dusting and placing in a friability tester (Roche friabilator, Pharma labs, Ahmedabad, India), which was rotated for 4min at 25rpm. After dedusting, the total remaining weight of the tablets was recorded and the percent friability was calculated. The drug content of the prepared tablets of each batch was determined in triplicate.

Table 1: Formulae of matrix and triple- layer matrix tablets of Metoprolol tartrate prepared with xanthan gum as matrix core and layered with Na CMC

Formulation code	Meto prolol tartra te	Ingredients(mg)						Tot al wei ght
		Xanth an Gum	Na CMC	MC C	Star ch	T al c	Mg Stear ate	
M1	100	105	-	62.5	25	5	2.5	300
M2	100	135	-	32.5	25	5	2.5	300
M3	100	165	-	12.5	15	5	2.5	300
M3L1	100	165	50	12.5	15	5	2.5	400
M3L2	100	165	75	12.5	15	5	2.5	450
M3L3	100	165	100	12.5	15	5	2.5	500

Table 2: Physico- chemical characterization of metoprolol tartrate matrix tablets and triple layer matrix tablets (Mean $\pm$ SD)

Formulation code	Mass (mg) ^a	Hardness ^b kg/cm ²	Thickness (mm) ^b	Friability (%) ^b	Drug content (%) ^c
M1	300.1 $\pm$ 0.01	5.92 $\pm$ 0.10	4.01 $\pm$ 0.01	0.840 $\pm$ 0.015	98.31 $\pm$ 1.8
M2	300.1 $\pm$ 0.01	6.14 $\pm$ 0.03	4.01 $\pm$ 0.02	0.251 $\pm$ 0.025	99.56 $\pm$ 1.21
M3	300.1 $\pm$ 0.01	6.66 $\pm$ 0.01	4.02 $\pm$ 0.02	0.420 $\pm$ 0.028	95.12 $\pm$ 0.71
M3 L1	401.2 $\pm$ 1.02	7.41 $\pm$ 0.03	5.80 $\pm$ 0.01	0.807 $\pm$ 0.013	95.89 $\pm$ 1.58
M3 L2	450.1 $\pm$ 0.13	7.88 $\pm$ 0.03	6.02 $\pm$ 0.02	0.434 $\pm$ 0.001	94.51 $\pm$ 2.05
M3 L3	501.2 $\pm$ 0.12	8.21 $\pm$ 0.02	7.01 $\pm$ 0.01	0.362 $\pm$ 0.026	100.2 $\pm$ 1.07

Mean $\pm$ SD: ^an=20, ^bn=6, ^cn=3

In-vitro drug release studies

In vitro dissolution studies for the prepared matrix tablet and triple layer matrix tablets were conducted for a period of 12h using a six station (1) USP XXII type II apparatus (Lab India Disso 2000 system, India.) at $37 \pm 0.5^\circ\text{C}$ and 50 rpm speed. The dissolution studies were carried out in triplicate for 2h in pH 1.2 medium (900ml) and then the pH of medium was raised to 6.8 by adding 4.6g Sodium hydroxide, 4.005g dibasic sodium phosphate and 3.06g mono basic potassium phosphate at $37 \pm 1^\circ\text{C}$ for 12h. Samples were collected at specific time intervals and assayed by a UV spectrophotometer (Elico, Model SL-150, Mumbai, India.) at a wavelength of 275.7 nm. The experiments were repeated thrice and the results were taken as average of three test readings with standard deviations. The amount of drug present in the samples was calculated with the help of appropriate calibration curves constructed from reference standards. During the drug release studies, the formulations were observed for physical integrity at different time intervals.

Characterization of release data

The description of dissolution profiles has been attempted using different release models. The data were evaluated according to the following equations.

$$\text{Zero order: } M_t = M_0 + K_0 t$$

$$\text{First order: } \ln M_t = \ln M_0 + K_1 t$$

$$\text{Higuchi model: } M_t = K_H \sqrt{t}$$

$$\text{Korsmeyer -Peppas model: } M_t/M_0 = K_k t^n$$

Where M_t is the amount of drug dissolved in time t , M_0 the initial amount of drug, K_1 is the first order release constant, K_0 the zero order release constant, K_H the Higuchi rate constant, K_k the release constant and n is the diffusional release exponent indicative of the operating release mechanism. The correlation coefficient (r^2) was used as an indicator of the best fitting, for each of the models considered.

The dissolution parameters used for comparing the different formulations was MDT and $DE_8\%$. The following equation was used to calculate the mean dissolution time (MDT) from the mean dissolution data.

$$MDT = \frac{\sum_{i=1}^{i=n} t_{mid} \times \Delta M}{\sum_{i=1}^{i=n} \Delta M} \quad \text{eq. [1]}$$

Where i is the dissolution sample number, n is the number of dissolution sample time, t_{mid} is the time at the midpoint between i and $i-1$ and ΔM is the additional amount of drug dissolved between i and $i-1$.^[14] MDT, which is calculated from the amount of drug released to the total cumulative drug. MDT is a measure of the rate of the dissolution process: the higher the MDT, the slower the release rate.

Dissolution efficiency (DE)^[15] after 8 h of release test was used to compare the results of dissolution tests of different formulations:

$$DE_8\% = \frac{\int_0^t y dt}{y_{100} t} \times 100 \quad \text{eq [2]}$$

FT-IR spectroscopy

Infrared spectrum was taken (FT-IR, Spectrum RX1, Perkin Elmer Ltd, Switzerland) by scanning the sample in Potassium bromide discs. The samples of pure drug and formulated tablets M3L3 were scanned individually.

Thermal analysis

DSC scan was performed by accurately weighing the sample of pure drug metoprolol tartrate and the triple-layer matrix tablets M3L3 (DSC- 827e, Mettler, Toledo- Inc., 1900, U.S.A) aluminum pans were used in the experiment and the empty pan were also sealed which are used as references. The temperature was calibrated with indium as standard. The scanning rate of samples was from $50-300^\circ\text{C}$ at $10^\circ\text{C}/\text{min}$, nitrogen gas was allowed at $10\text{ml}/\text{min}$.

Stability studies

Stability studies were conducted for the optimized formulations M3L3. To assess their stability with respect to their physical appearance, drug content and drug release characteristics after storing at $40^\circ\text{C}/75\% \text{ RH}$ for 3 months^[16] was seen.

Statistical analysis

In-vitro release data of metoprolol tartrate from the matrix tablets (M3) and optimized formulations of triple-layer matrix tablets (M3L3) were subjected to the one-way analysis of variance (ANOVA) at different time intervals of drug release up to 12h. By applying Newman-Keuls multiple comparison test using Graph pad prism version 4. (Graph pad prism Software, Inc)

RESULTS AND DISCUSSION

Matrix and triple-layer matrix tablets of metoprolol tartrate were prepared, using xanthan gum to drug in different ratio as matrix forming agent. The triple-layer matrix tablets of metoprolol tartrate were developed to retarded the drug release from the surfaces of matrix core by compressing anionic Na CMC on both the surfaces.

Physicochemical characterization of matrix and triple-layer matrix tablets

The physical parameters such as hardness, thickness, friability, mass and drug content of the matrix and triple-layer matrix tablets are shown in Table 2. All the values were found to be within the limits indicating that tablets were of sufficient standards according to USP. The hardness and thickness of tablets were increased as the amount of barrier layers of Na CMC was increased. The hardness of triple-layer matrix tablets tended to increase, the friability decreased. Drug content uniformity was within the range of $100.2 \pm 1.07\%$ to $94.51 \pm 2.05\%$.

In-vitro dissolution studies

Drug release studies were carried out in pH 1.2 (0.1 NHCl) for 2 h and the pH of the media was raised to pH 6.8 for remaining 10hrs. The amount of metoprolol tartrate released from the matrix tablets (Fig. 3) and triple-layer matrix tablets are shown in (Fig. 3). The percentage drug release from formulations M1, M2 and M3 ranged from $99.87 \pm 0.11\%$, $98.15 \pm 0.14\%$ and $96.78 \pm 0.12\%$ respectively. Matrix tablets after 12h of dissolution study dissolved either completely or near to completion forming a very loose porous mass, sticking to the bottom of the beaker.

XG and MCC (filler) were used along with the highly soluble metoprolol tartrate. The formulation M1, M2 and M3 released the metoprolol tartrate almost completely within the 12 h. It might be due to the effect of pH on XG and formation of the dispersion with MCC in the matrix core. Similarly in case of formulations M3L1, M3L2 and M3L3, the drug release was up to $92.58 \pm 0.13\%$, $89.45 \pm 0.13\%$ and $75.46 \pm 0.11\%$ after 12 h of study. The triple layer matrix tablets were found to be intact at the end of 12 h by forming

loss porous on the surfaces. The results described (Fig. 3 and 4) that the rate and extent of drug release were decreased for the triple-layer matrix tablets, which may be ascribed to increase in the thickness of barrier layers.

Characterization of release data

The dissolution mechanism was characterized by using different release models. The correlation co-efficient (r^2) was used as an indicator of the best fitting for each of the models considered. The correlation co-efficient (r^2) for zero order kinetics, first order kinetics and Higuchi model was shown in Table 3. In the formulation (M1, M2 and M3) there was an initial burst of xanthan gum erosion from the matrices during the acidic pH thereafter, the erosion of xanthan gum slowed considerably. In all the formulations, it has been observed that the release of drug was retarded with increasing in the concentration of the xanthan gum in the matrix core (Table 1). Fig. 3 shows the release profile for the formulations M1, M2 and M3. It shows different concentration of xanthan gum significantly effects the release rate from the matrices. The formulation M1 has release rate of 7.68 mg/h, compared to M2 (7.55mg/h) and 7.31mg/h of release rate by the M3 matrices. Visual observation denoted that the matrices appeared swollen almost from the beginning, a viscous gel mass was created when they come in contact with the dissolution medium. It indicated that although the release rate was decreased with increase in the concentration of xanthan gum and decrease in the concentration of MCC. None of the formulation (M1, M2 and M3) could achieve the desired ideal release rate of 6.13mg/h. Hence the results revealed (Table 3) that formulation M1, M2 and M3 pre-dominantly followed first order kinetics, indicated by their higher correlation co-efficient (r^2).

Effect of thickness of barrier- layers Na CMC from the xanthan gum matrix core.

Fig. 4 shows the release profile of the triple-layer matrix tablets (M3L1, M3L2 and M3L3) with Na CMC on both the surface of matrix core. The formulation with (50mg of Na CMC on both the surfaces of the matrix core) lower barrier thickness, has higher release rate constant of 7.21mg/h compared to (75mg of Na CMC on both the surfaces of the matrix core), formulation M3L2 which has release rate constant of 6.79mg/h. This might be attributed to higher thickness of the barrier layer, which leads to longer diffusion path length. Table 3, shows the release rate constants. The triple layer matrix tablets (M3L3) has release rate of 5.94mg/h, it also provided better fit to zero order kinetics than first order due to higher (r^2) values and with lower release rate constant.

On the basis of drug release data, it is evident that as thickness of the anionic Na CMC layers increased the rate of drug release was found to be decreased. The release rate patterns of all the formulations are given in Table 3. The results suggested that the developed triple-layer matrix tablets showed zero- order or case II release. The values of kinetic constant (k) were in accordance with the values of n , the diffusional exponents, with k having lower values when the mechanism was Case II and higher values for the formulations that released the drug by non-Fickian diffusion. The diffusional exponents (n) values for the matrix tablets ranged from 0.41 to 0.81, and that of triple layer matrix tablets ranged from 0.96 to 1.12, with the lower k values ranging from 1.29 to 0.49. It can be inferred that the drug release from matrix tablets is by Fickian mechanism and the

release of drug from the triple layer matrix tablets was (anomalous) non-Fickian mechanism. The poor correlation coefficient (r^2) values for M1, M2 and M3 in kinetic parameter based on zero-order model equation were mainly due to the drug release mechanism (Table 1). It was observed that the triple-layer matrix tablets swelled indicating that absorption of dissolution media and swelling process were taking place simultaneously. This indicates that polymer relaxation had a role in drug release mechanism; as a result the release of metoprolol tartrate was controlled for over a period of more than 12 h, with the linear release fashion. Hence a careful balance has been produced between the matrix core and barrier layer for the diffusion of drug from the matrix core to optimize drug release toward zero order kinetics.

Model independent approaches were attempted to compare the dissolution profiles such as MDT and $DE_8\%$. Table 3 shows that, MDT is increased, while $DE_8\%$ is decreased. The formulations M3 and M3L3 have 4.02h 12.75h and 84.8% and 66.4% respectively. It indicated that the release of metoprolol tartrate is slower from triple-layer matrix tablets.

FT-IR spectroscopy

IR spectroscopy was used as a means of studying drug excipients interaction. The IR spectrum of Metoprolol tartrate exhibits peak at 1162.7 cm^{-1} is due to ether linkage, peak at 821.97 cm^{-1} is due to aliphatic group (C-C stretching) The IR spectrum of M3L3 formulation exhibited peak at 1167.7 cm^{-1} is due to ether formation and exhibited peak at 1167.7 cm^{-1} is due to ether linkage. The formulation M3L3 shows slight difference in peaks is observed at 1590 cm^{-1} . It may be due to the tartrate molecule that has no influence in the structure of metoprolol and there was no drug-excipients interaction is shown in Fig. 1.

DSC Studies

The thermogram obtained by these studies for the pure drug metoprolol tartrate showed sharp endotherm at 125.9°C which correspond to its melting, and thermogram of the formulation (M3L3) showed the endotherm at 124.4°C is shown in Fig. 2. As melting point of metoprolol tartrate and that of the formulation M3L3 are nearer it reveals that there is no much interaction between the drug and excipients used in study.

Stability studies

The triple-layer matrix tablets (M3L3), after storing at $40\pm 2^\circ\text{C}$ / $75\pm 5\%$ RH for 3 months showed no changes in physical appearance and the dissolution profile as shown in Fig. 5.

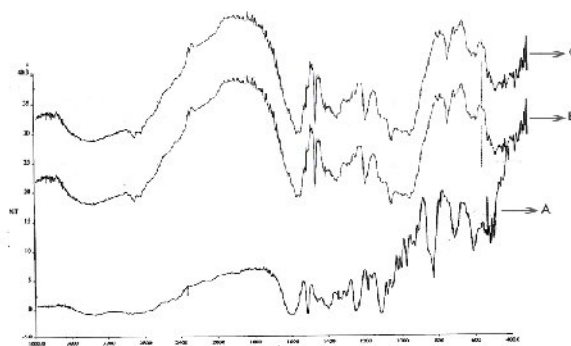


Fig.1: FT-IR spectra of pure Metoprolol tartrate (A), powdered sample of matrix tablets M3 (B) and triple-layer matrix tablets M3L3 (C)

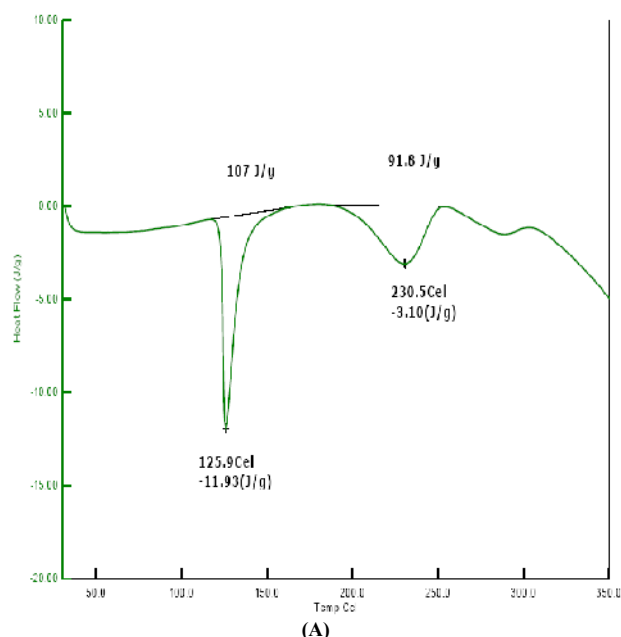


Fig 2: DSC thermogram of metoprolol tartrate (A) and formulation F3L3 (B)

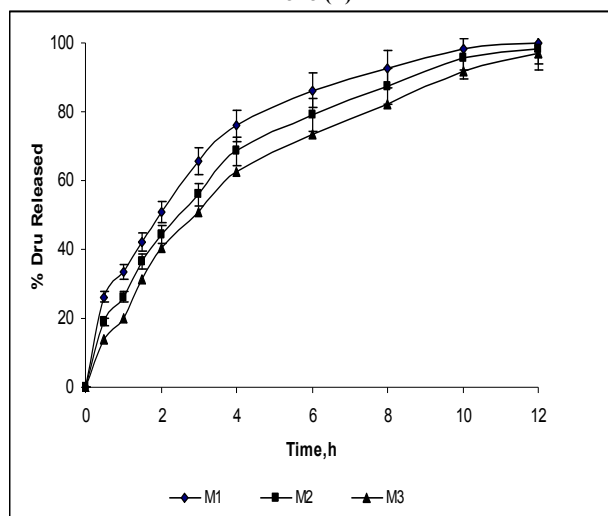


Fig 3: *In vitro* dissolution profiles of matrix tablets containing different formulations

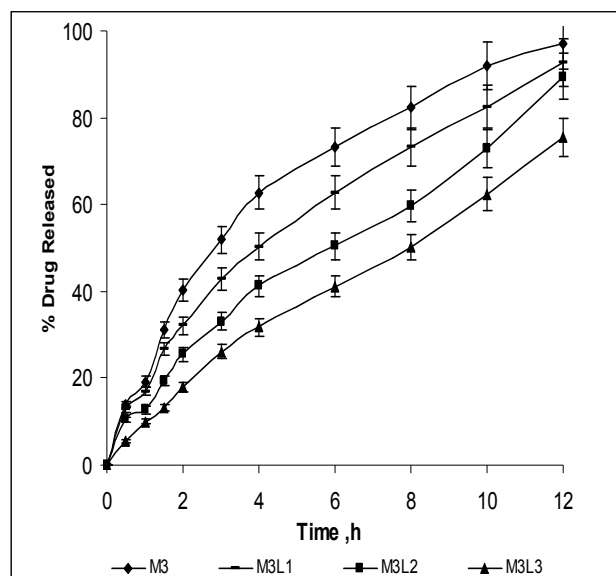


Fig 4: *In vitro* dissolution profiles of matrix and triple layer matrix tablets of metoprolol tartrate prepared by using xanthan gum in the matrix core and Na CMC as barrier layers

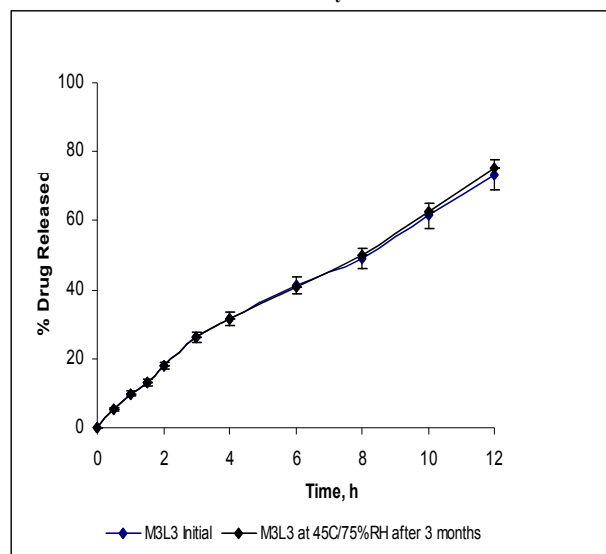


Fig 5: *In vitro* dissolution profiles of triple-layer matrix tablets (M3L3) before and after storage at $40\pm 2^{\circ}\text{C}$ / $75\pm 5\%$ RH for 3 months

Statistical analysis

Analysis of variance (single factor ANOVA) showed a significant difference ($P < 0.05$) for the amount of drug released from matrix tablet (M3), and triple-layer matrix tablet (M3L3).

The hydrophilic polymer Xanthan gum (XG) matrices at higher concentration produced a greater sustaining effect on the release of metoprolol tartrate but predominately in a first order kinetics. The results indicated that a combination of XG as matrix core and Na CMC as barrier layers in the form of triple-layer matrix tablets controlled the release of metoprolol tartrate following case II transport ($n=1.12$) with zero order release kinetics. Hence the triple layer matrix tablets can be prepared successfully by appropriate hydrophilic polymer (XG) in the matrix core and cellulose derivative Na CMC as layers in the design of oral controlled release tablets. These dosage forms can be developed on large scale using layered tablet press.

Table 3: *In-vitro* dissolution kinetics, MDT and DE₈% of metoprolol tartrate released from matrix tablets and triple-layer matrix tablets (n=3).

Formulation code	Zero order		First order		Higuchi		Korsemeyer-peppas			MDT hrs	D.E ₈ %
	R ²	K ₀ (mg/h ⁻¹)	R ²	K ₁ (h ⁻¹)	R ²	K (mg.h ⁻¹)	R ²	n	K ₀		
M1	0.818	7.31	0.918	0.088	0.956	28.46	0.977	0.41	1.56	2.93	92.57
M2	0.875	7.55	0.980	0.310	0.977	30.23	0.983	0.54	1.45	3.52	88.89
M3	0.903	7.68	0.974	0.004	0.984	31.20	0.977	0.81	1.36	4.02	84.85
M3L1	0.949	7.21	0.970	0.046	0.997	29.39	0.990	0.91	1.29	4.93	79.42
M3L2	0.994	6.79	0.919	0.036	0.982	27.74	0.987	1.01	1.17	6.52	66.78
M3L3	0.997	5.94	0.972	0.029	0.983	24.69	0.997	1.12	0.49	12.75	66.40

ACKNOWLEDGEMENTS

The authors are thankful to Astra Zeneca Pharma Ltd, Bangalore, India, Raj Enterprises, Mumbai, India, and Reliance cellulose products, Hyderabad, India for generously giving the samples of metoprolol tartrate, Xanthan gum, Micro Crystalline Cellulose and Sodium Carboxy Methyl Cellulose respectively.

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