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Formulation and Evaluation of Bilayer Floating Tablets of Trimetazidine hydrochloride and Metoprolol succinate

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ABSTRACT

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The objective of the present investigation was to develop bilayer floating tablets of Trimetazidine hydrochloride and Metoprolol succinate for stable angina pectoris insufficiently controlled by monotherapy with beta-blocker. Bilayer floating tablets was formulated using wet granulation technique and it consists of two layers, i.e. immediate release layer containing Metoprolol succinate and floating sustained release layer containing Trimetazidine hydrochloride. The immediate release layer comprised of Sodium Starch Glycolate as a super disintegrant and the sustained release layer comprised of Ethyl cellulose, HPMC K4M, HPMC K100M and Xanthan gum as release retarding polymers. Sodium bicarbonate was used as a gas generating agent in the floating layer. The immediate release layer (M3) containing 4% Sodium Starch Glycolate was found to be optimum and released 99.61% of Metoprolol in 15 m. The floating sustained release tablet of Trimetazidine hydrochloride (BFT8) containing Ethyl cellulose (5%), Xanthan gum (10%) and HPMC K100M (20%) showed sustained release up to 12 h. The final optimized formulation (BFT8) released 99.87 % of Trimetazidine in 12 h while the floating lag time was 4 m and the tablet remained floatable throughout the studies. The drug release was inversely proportional to the polymer concentration. The formulation BFT8 may be a better alternative to the available combination for the treatment of angina pectoris.

Keywords: Bilayer floating tablet, Trimetazidine hydrochloride, Metoprolol succinate, angina pectoris.

INTRODUCTION

Oral route is considered as the most promising route for drug delivery. The gastric emptying of the oral drug delivery systems is an extremely variable process[1]. The administration of food can delay the gastric emptying. If the dosage form is administered immediately after Phase III of the Migrating Motor Complex the gastric emptying can be rapid[2]. So the control placement of a drug delivery system in a specific region of the gastrointestinal tract is needed. These have led to the development of a unique oral controlled release dosage form with gastro retentive properties.

Various approaches have been used to retain the dosage form in the stomach as a way of increasing the gastric residence time including floating systems, high density systems, bioadhesive systems, magnetic systems, unfoldable, extendible or swellable systems and superporous hydrogel systems[3,4].

Floating dosage forms (hydrodynamically balanced systems, HBS) are oral dosage forms of tablets, capsules containing hydrocolloids that allow floating by swelling. For the following instances, it has been suggested that an active material should be formulated into the form of a HBS to enhance its bioavailability of drugs: a) having dissolution problem in the fluids of the small intestine, b) being effective locally in the stomach, and c) being absorbed only in the stomach and upper part of the small intestine[5].

The current investigation aims at the development of gastro retentive bilayer floating tablets with different release patterns of Trimetazidine and Metoprolol by using a gas generating agent. *In vitro* drug release of water soluble drug is controlled by diffusion out of the gel layer at a rate controlled by the gel viscosity, whereas release for poorly soluble drug is solely by polymer dissolution Xanthan gum, a hydrophilic polymer, upon contact with aqueous fluid is able to form quite viscous gel, and hence retard the drug release from hydrophilic matrix. HPMC polymers are often used in matrix SR tablets because the polymers are nontoxic, easy to handle, economic and do not require any special manufacturing technology for the production of SR tablets. The drug release from HPMC matrix is uniform irrespective of the pH, since the solubility of HPMC is pH independent. Modified release tablet formulations may also be produced using ethyl cellulose as a matrix former. Ethyl cellulose is used as a matrix former for controlled-release tablets of Trimetazidine. Trimetazidine is a coronary vasodilator and also has cellular metabolic reactions to retard the anginal symptoms. Trimetazidine is primarily absorbed from stomach and it has a half life of 6 h[6]. It is administered thrice daily for angina pectoris patients. The drug has better solubility in acidic medium. The increase in gastric retention time may increase the extent of absorption of the drug. It is more suitable to formulate a floating system. Metoprolol is a cardio selective

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beta-1 adrenoceptor blocker used for treatment of angina pectoris. In controlled clinical trials, the immediate release formulation of Metoprolol has shown to be an effective antianginal agent in reducing the number of angina attacks and increasing exercise tolerance. Angina pectoris is a very common symptom of coronary artery disease patients and it was effectively controlled by combination therapy with Trimetazidine and Metoprolol[7]. In the present study, we have attempted to formulate a bilayer floating system of Trimetazidine and Metoprolol.

MATERIALS

Trimetazidine hydrochloride, Metoprolol succinate, Ethyl cellulose, HPMC K4M, HPMC K100M, and Sodium Starch Glycolate were obtained as gift samples from ATOZ Pharmaceuticals Pvt. Ltd., Chennai, India. Xanthan gum of Pharmaceutical grade was purchased from S.D. Fine chemical Pvt. Ltd.

METHODS

Preparation of Bilayer Floating Tablets:

Bilayer floating tablets (BFT) contain the two layers i.e. immediate release (IR) layer and floating sustained release layer. The immediate release layer contains Metoprolol succinate, Sodium Starch Glycolate (as super disintegrant) and other excipients as given in table 1. The granules were prepared by wet granulation technique. The floating sustained release layer contains the Trimetazidine hydrochloride, Sodium bicarbonate (as gas generating agent) and other excipients as given in table 4. The granules were prepared by wet granulation technique. The optimized immediate release granules of Metoprolol succinate (M3) and the sustained release granules of Trimetazidine hydrochloride were compressed to get bilayer floating tablets.

Drug-Excipients Compatibility Study:

Pure drugs, polymers, excipients, drug – excipients mixture and optimized formulation were subjected to FTIR and DSC studies to investigate the drug – excipients interactions.

Tablet hardness:

The resistance of tablets to breakage under the conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester.

Friability:

Friability of the prepared formulations was determined by using Rochelle friabilator. Pre-weighed sample of tablets was placed in the friability tester, operated for 100 revolutions, dedusted and reweighed.

Drug content:

Simultaneous estimation of Trimetazidine and Metoprolol was carried out using UV spectrophotometric method. Twenty tablets were accurately weighed and the average weight was calculated. The tablets were then ground to a fine powder. The powder was dissolved, diluted suitably and analyzed by UV method at 222 nm and 231 nm[8].

Disintegration studies:

The IR tablets were placed in each of the six tubes of the basket and the assembly is suspended in water maintained at a temperature of 37 ± 0.5°C. The time taken to disintegrate the tablets completely was determined.

Floating behavior:

Floating behavior studies were carried out in a USP dissolution testing apparatus II (Paddle type) at a speed of 50 rpm in 900ml 0.1N HCl at 37° ± 0.5°C for 12 h to mimic *in vivo* conditions. To determine the floating lag time and floating duration of the formulations, the time interval between the introduction of the tablet into the dissolution medium and its buoyancy to the top of dissolution medium was taken as floating lag time. The duration of system floatation and also the relative matrix integrity were observed visually[9].

Swelling Characteristics:

The swelling properties of tablets were determined by placing the tablet in dissolution test apparatus in 900ml of 0.1N HCl at 37 ± 0.5°C. The tablets were removed periodically from the dissolution medium. After draining, the tablets were measured for weight gain. Swelling characteristics were expressed in terms of percentage water uptake (WU %) [10].

$$WU\ \% = \frac{\text{Wt. of swollen tablet} - \text{Initial wt. of the tablet}}{\text{Initial wt. of the tablet}} \times 100$$

In- vitro Dissolution studies:

The release of Metoprolol and Trimetazidine from bilayer floating tablet was determined using USP dissolution testing apparatus Type II (Paddle). The dissolution test was performed using 900 ml of a 0.1 N HCl solution (pH=1.2), at 37±0.2°C with 50 rpm[8]. Aliquot of the solution was collected from the dissolution medium at 5, 10, 15 m and at 1, 2, 4, 6, 8, 10, 12 h and were replaced with fresh dissolution medium. The aliquots were filtered through Whatmann filter paper no.41. The absorbance of the solution was recorded at 222 nm and 231 nm using UV spectrophotometer. The release of Metoprolol and Trimetazidine was determined.

Stability Studies:

Stability studies of bilayer floating tablets were carried out according to ICH guidelines. All formulations were packed in blister and kept in humidity chamber at 40° ± 2°C and 75 ± 5

% RH for 3months. At the end of every month, samples were analyzed for drug content, floating characteristics, hardness and *in-vitro* dissolution.

RESULTS AND DISCUSSION

All the excipients used in the formulations were compatible (Fig 1, 2).

Micromeritic Study:

Bulk density, tapped density, compressibility index, hausner's ratio, and Angle of Repose of the granules were determine. The precompression parameter of the formulation was showed satisfactory flow property (Table 2, 5).

Physical parameters:

The physical parameters of the compressed tablets were determined. The friability was within the limit. Hardness of the formulations was found to be 5 to 5.5 kg/cm^2 and the hardness was sufficient to prevent all chipping and breaking during transportation. The drug content of all the formulations was within the limits (Table 3, 6, 7).

Floating characteristics:

All formulations floated for more than 12 h with a floating lag time up to 4 m (Fig 3). During the floating, formulations maintained the matrix integrity. The optimum concentration of Sodium bicarbonate was found to be 8% for obtaining low

Fig 1: IR Spectrum of Metoprolol succinate, Trimetazidine Hydrochloride and BFT8

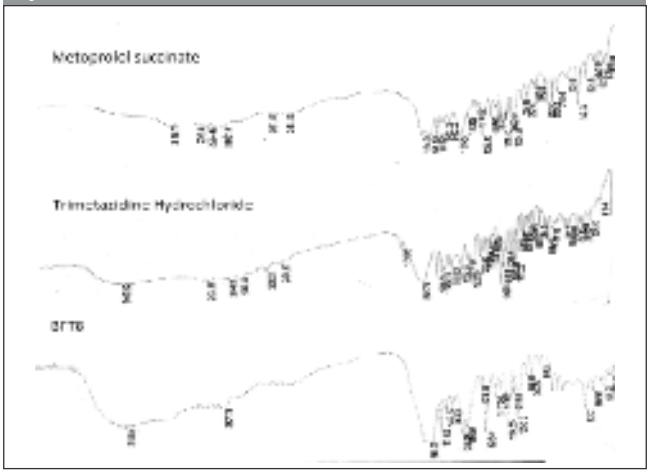


Fig 2: DSC of Metoprolol succinate, Trimetazidine Hydrochloride and BFT8

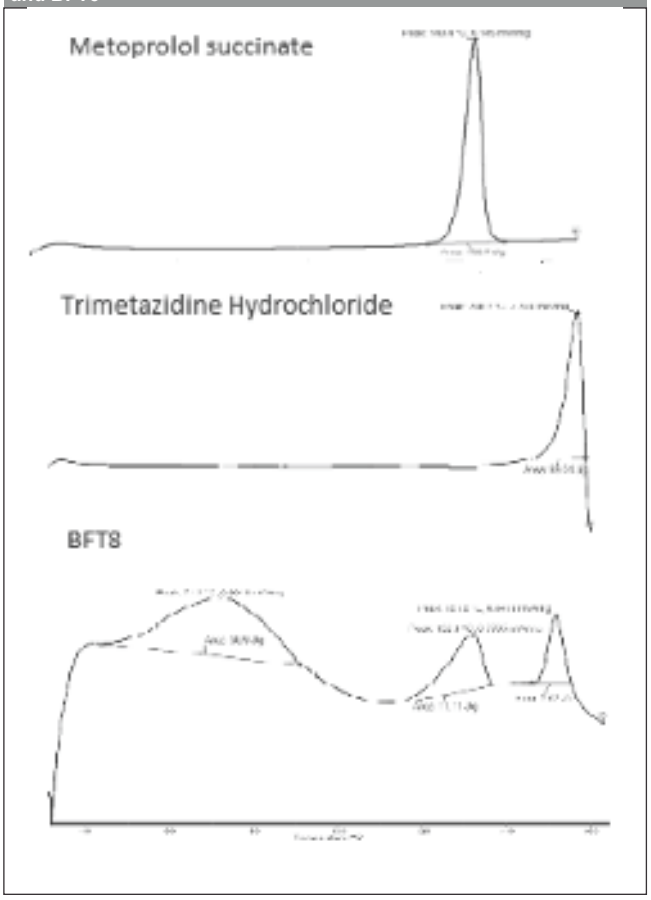


Table 1: Formulation of Immediate release layer.

Ingredients (mg)	M1	M2	M3
Metoprolol succinate	50	50	50
Lactose	27.4	26.1	23.3
Starch	45	45	45
Poly vinyl pyrrolidone K30	2.5	2.5	2.5
Isopropyl alcohol	q.s	q.s	q.s
Sodium Starch Glycolate	2.6	3.9	5.2
Magnesium stearate	2.5	2.5	2.5
Average weight of the tablet = 130 mg			

Table 2: Precompression study of formulated blends of IR layer.

Formulation	Bulk Density g/cm^3 *	Tapped Density g/cm^3 *	Compressibility Index (%)*	Hausner's Ratio*	Angle of Repose (Degree)*
M1	0.548 ±0.0079	0.756 ±0.015	27.407 ± 0.4496	1.373 ± 0.0081	46.836 ± 0.6086
M2	0.549 ±0.0053	0.750 ±0.010	26.755 ± 0.4038	1.363 ± 0.0085	46.730 ± 0.2551
M3	0.551 ±0.0072	0.760 ±0.014	27.520 ± 0.3956	1.137 ± 0.0069	46.910 ± 0.2156
*Mean ± S.D (n=6)					

Table 3: Physical parameters of the IR tablets of Metoprolol succinate

Formulation	Hardness Kg/cm^2 *	Friability*	Disintegration Time (Minutes)*	% Drug Content*
M1	3.25 ± 0.263	0.260 ± 0.0066	2.15 ± 0.0136	99.71 ± 0.180
M2	3.30 ± 0.258	0.253 ± 0.0107	1.45 ± 0.0080	99.93 ± 0.208
M3	3.10 ± 0.210	0.254 ± 0.0059	1.05 ± 0.0037	99.73 ± 0.128

*Mean ± S.D (n=6)

Table 4: Formulation of Sustained release Tablet*

Ingredients(mg)	BFT1	BFT2	BFT3	BFT4	BFT5	BFT6	BFT7	BFT8
Trimetazidine hydrochloride	35	35	35	35	35	35	35	35
HPMC K100M	27	54	81	27	54	81	27	54
HPMC K4M	-	-	-	27	27	27	-	-
Xanthan gum	-	-	-	-	-	-	27	27
Microcrystalline cellulose	154	127	100	127	100	73	127	100
Ethyl cellulose	13.5	13.5	13.5	13.5	13.5	13.5	13.5	13.5
Sodium bicarbonate	22	22	22	22	22	22	22	22
Polyvinyl pyrrolidone K30	13.5	13.5	13.5	13.5	13.5	13.5	13.5	13.5
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Aerosil	1	1	1	1	1	1	1	1
Magnesium stearate	4	4	4	4	4	4	4	4

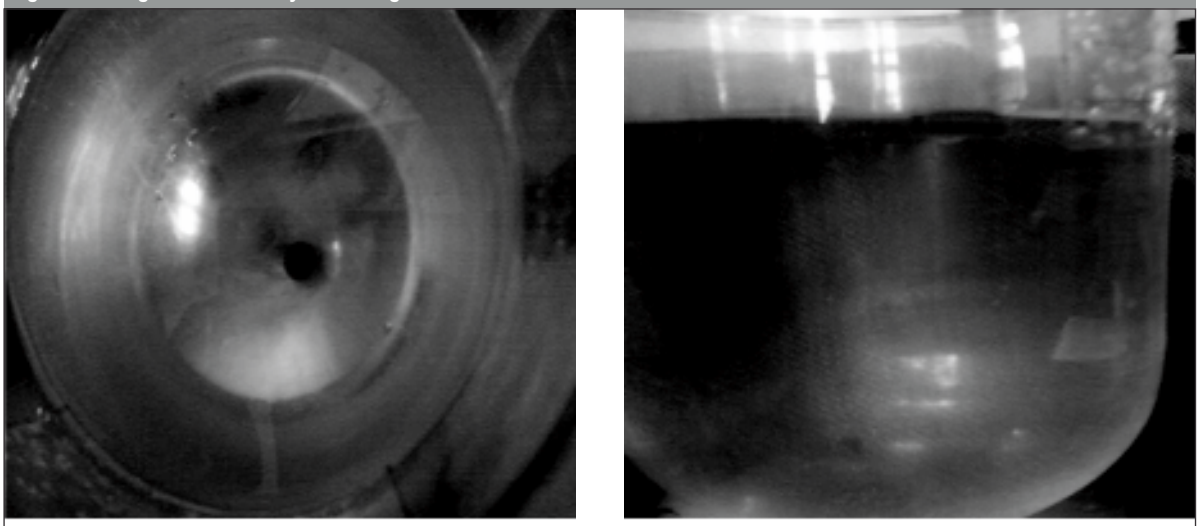
Average weight of the tablet = 270 mg, *The formulation also contains M3 as Immediate Release layer.

Table 5: Precompression study of formulated blends of SR layer

Formulation	Bulk Density g/cm^3 *	Tapped Density g/cm^3 *	Compressibility Index (%)*	Hausner's Ratio*	Angle of Repose (Degree)*
BFT1	0.522 ±0.0065	0.744±0.0023	28.886 ± 0.4353	1.421±0.0204	46.513 ±0.3119
BFT2	0.520 ±0.0064	0.743±0.0019	28.911 ± 0.4745	1.423±0.0078	46.543 ±0.2475
BFT3	0.519 ±0.0058	0.744±0.0030	28.901 ± 0.9488	1.422±0.0133	46.518 ±0.4673
BFT4	0.522 ±0.0069	0.745±0.0034	28.960 ± 0.6442	1.428±0.0088	46.458 ±0.4112
BFT5	0.520 ±0.0055	0.742±0.0041	28.893 ± 0.3404	1.426±0.0047	46.586 ±0.1820
BFT6	0.524 ±0.0049	0.745±0.0032	28.966 ± 0.8060	1.430±0.0128	46.528 ±0.2049
BFT7	0.520 ±0.0044	0.745±0.0056	28.946 ± 0.5703	1.427±0.0131	46.520 ±0.1684
BFT8	0.522 ±0.0040	0.746±0.0042	28.871 ± 0.4898	1.431±0.0069	46.486 ±0.2339

*Mean ± S.D (n=6)

Fig. 3: Floating studies of Bilayer Floating Tablets



a) At 0 m **b) At 4 m**

Table 6: Physical parameters of the Bilayer Floating tablets of Trimetazidine hydrochloride

Formulation	Hardness Kg/cm^2 *	Friability*	Floating Lag Time (Minutes)*	Floating duration (hours)*
BFT1	5.19 ± 0.246	0.309 ± 0.0038	4.51 ± 0.281	11.25 ±0.155
BFT2	5.20 ± 0.258	0.313 ± 0.0018	4.07 ± 0.339	11.41±0.103
BFT3	5.15 ± 0.241	0.302 ± 0.0012	4.18 ± 0.169	11.53±0.043
BFT4	5.25 ± 0.263	0.302 ± 0.0015	4.29 ± 0.357	12.14±0.035
BFT5	5.15 ± 0.337	0.312 ± 0.0031	4.20 ± 0.170	12.39±0.130
BFT6	5.05 ± 0.368	0.307 ± 0.0019	4.30 ± 0.380	12.57±0.114
BFT7	5.25 ± 0.263	0.306 ± 0.0017	4.26 ± 0.205	12.29±0.357
BFT8	5.20 ± 0.349	0.314 ± 0.0024	4.32 ± 0.273	12.58±0.080

*Mean ± S.D (n=6)

Table 7: Drug content of the formulated Bilayer Floating tablets.

Formulation	% Drug content *	
	Metoprolol succinate	Trimetazidine hydrochloride
BFT1	99.82 ± 0.480	99.52 ± 0.330
BFT2	99.61± 0.264	98.05 ± 0.572
BFT3	99.76 ± 0.160	98.32 ± 0.526
BFT4	99.05 ± 0.410	97.76 ± 0.359
BFT5	98.93 ± 0.130	97.77 ± 0.225
BFT6	99.40 ± 0.226	97.16 ± 0.267
BFT7	98.33 ± 0.409	98.89 ± 0.388
BFT8	98.91 ± 0.518	98.05 ± 0.409

*Mean ± S.D (n=6)

floating lag time and prolonged floatation. Floating duration and floating lag time were found to be dependent on the amounts of the polymers incorporated in formulations.

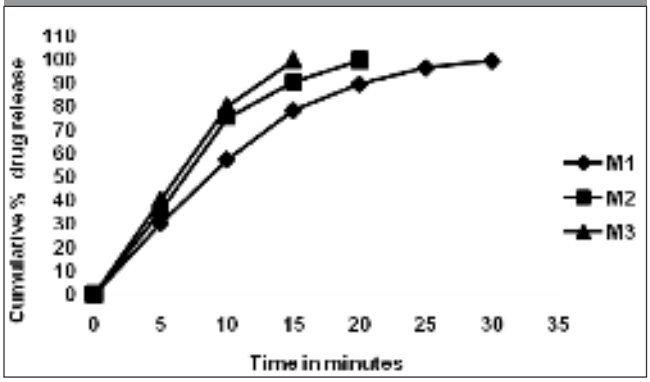
Dissolution study of Immediate Release layer:

The immediate release tablets of Metoprolol succinate were formulated with three different ratios (2%, 3%, and 4%) of Sodium Starch Glycolate as super disintegrant. Sodium Starch Glycolate at 4% concentration was found to be optimum (The release of the Metoprolol was within 15 m and the tablets disintegrated in 1m). The immediate release formulation M3 was found to be optimum (Fig 4).

Dissolution study of Floating Sustained Release layer:

The floating sustained release layer of Trimetazidine hydrochloride (BFT1, BFT2, and BFT3) was formulated with different polymers, Ethyl cellulose (5%) and HPMC K100M (10%, 20%, and 30%). The BFT1, BFT2 and BFT3 were unable to retard the release of the drug from the floating matrix layer and the formulations released the entire drug at the end of 4, 6 and 8 h respectively. The formulations containing both the polymers are not sufficient to retard the release of the drug. Hence another polymer, HPMC K4M (10%) was added to retard the release of the drug. The

Fig 4: *In-vitro* Dissolution of Metoprolol succinate Immediate Release Tablets



formulation BFT4, BFT5, BFT6 retarded the drug release more than the previous formulations. The formulations released the drug at the end of 6, 8, and 10 h respectively. The floating matrix tablets (BFT7 and BFT8) were formulated with Ethyl cellulose (5%), HPMC K100M (10% and 20%) and Xanthan gum (10%). The formulation BFT8 retarded the release of the drug from the polymer matrix for 12 h (fig 5). BFT8 floating matrix tablets of Trimetazidine containing Ethyl cellulose, HPMC K100M and Xanthan gum had

Fig 5: *In-vitro* Dissolution of Bilayer Floating Tablet containing Trimetazidine hydrochloride.

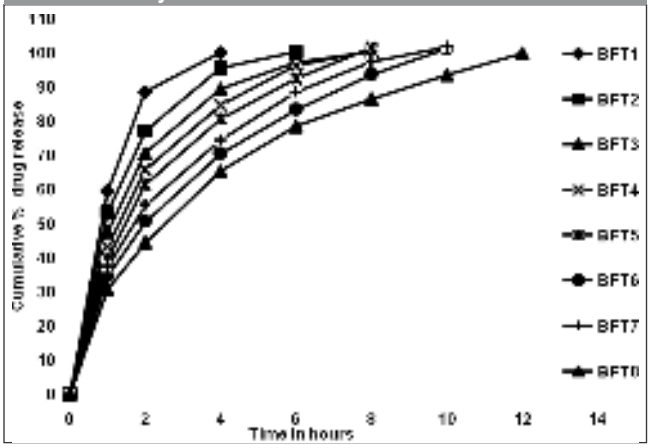


Table 8: Stability studies of the optimized formulation

Time Interval	Drug Content*		Cumulative % Release*	
(month)	Metoprolol succinate	Trimetazidine hydrochloride	Metoprolol succinate	Trimetazidine hydrochloride
1 month	98.55 ± 0.537	98.07 ± 0.463	98.38 ± 0.379	98.50 ± 0.366
2 month	98.14 ± 0.181	97.64 ± 0.484	97.67 ± 0.385	97.38 ± 0.339
3 month	97.70 ± 0.513	97.26 ± 0.234	97.06 ± 0.297	96.52 ± 0.359

*Mean ± S.D (n=6)

satisfactory sustained release due to more swelling property and high viscosity of Xanthan gum[8].

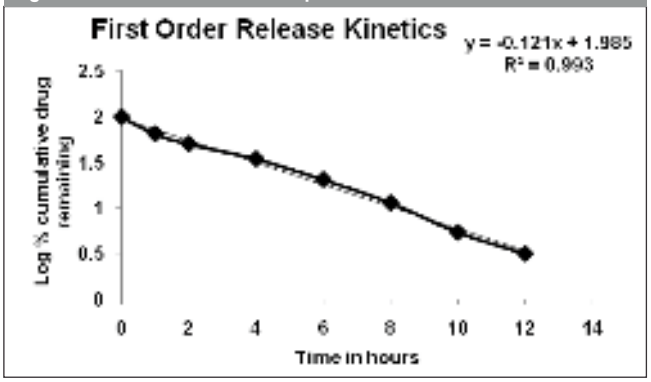
Release Kinetics:

The release kinetics of the optimized formulation followed first order release (R = 0.993) (fig 6). The n value of Peppas equation was found to be more than one. It revealed that drug release from the polymer matrix layer followed non-Fickian release. The drug release mechanism was found to depend on the swelling, erosion and predominantly dissolution.

Stability studies:

The optimized bilayer floating tablets were subjected to stability studies and showed no significant changes in the physical parameters, drug content, floating characteristics and *in vitro* dissolution (table 8).

Fig. 6: Release kinetics of the optimized formulation



CONCLUSION

The present study was aimed to develop bilayer floating tablets of Trimetazidine hydrochloride for sustained release and Metoprolol succinate for immediate release for treating angina pectoris. The tablets prepared showed sustained release of Trimetazidine when the combination of hydrophobic polymer and hydrophilic polymers were used in the floating matrix layer. The immediate release layer showed dissolution of 99.61% of Metoprolol succinate at 15 m when the superdisintegrant was used in 4% concentration. The tablets were formulated to reduce the anginal symptoms in patients by acting on the different determinants of cardiac cells.

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