Asian J. Pharm. Res. Vol 3, Issue 1, 2013, 1-8.

e-ISSN 2231 – 363X
Print ISSN 2231 – 3621

Asian Journal
of
PHARMACEUTICAL RESEARCH
Journal homepage: - www.ajprjournal.com

DESIGN AND IN VITRO DISSOLUTION OF METOPROLOL SUCCINATE FLOATING TABLETS

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ABSTRACT

A sustained release system for Metoprolol succinate designed to increase its residence time in the stomach without contact with the tablets was achieved through the preparation of floating tablets by the direct compression method. Using different grades polymers like HPMC K100M and HPMC K4M were used to retain the drug release and to form the floating tablets. The drug retained in the floating tablets decreased with increase in concentration of polymer content. All floating tablets formulations showed good flow properties. The FTIR shows there is no interaction between drug and polymers. Floating ability in 0.1 N HCl simulated gastric fluid without pepsin was also tested. The formulation F9 containing HPMC K100M and HPMC K4M shows maximum drug release was found.

Key words: Metaprolol Succinate, Floating tablets, HPMC, Carbomer, Sustained release.

INTRODUCTION

Metoprolol succinate is a beta selected adrenoceptor blocking agent, for oral administration in the treatment of hypertension, angina pectoris and heart failure. It has a half-life of 3 to 7 hours. When dose is missing it may causes nocturnal attack, so attention was made to develop the extended release tablets of metoprolol succinate by utilizing hydroxyl propyl methyl cellulose K100M and hydroxyl propyl methyl cellulose K4M. To reduce the frequency of administration and to improve patient compliance, a sustained-release formulation of Metaprolol is desirable. The drug is freely soluble in water and hence judicious selection of release retarding excipients is necessary to achieve a constant in vivo input rate of the drug. The most commonly used method of modulating the drug release is to include it in a matrix system [1].

Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. The purpose of controlled release systems is to maintain drug concentration in the blood or in target tissues at a desired value as long as possible. In other words, they are able to exert a control on the drug release rate and duration. In recent years, considerable attention has been focused on hydrophilic polymers in the design of oral controlled drug delivery system because of their flexibility to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance [1].

The need for gastroretentive dosage forms (GRDFs) has led to extensive efforts in both academia and industry towards the development of such drug delivery systems. Prolonging the gastric residence of a dosage form may be of therapeutic value. Amongst the methods available to achieve this, floating dosage forms show considerable promise [2].

The basic idea behind the development of such a system is to maintain a constant level of drug in the blood plasma in spite of the fact that the drug does not undergo disintegration. The drug usually keeps floating in the gastric fluid and slowly dissolves at a predetermined rate to release the drug from the dosage form and maintain constant drug levels in the blood [2].

Several approaches are used for the formulation of gastroretentive systems such as mucoadhesion, flotation, sedimentation, expansion and modified shape systems. Both single-unit systems (tablets or capsules) and multiple unit systems (Multiparticulates systems) have been

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reported in the literature. Among these, FDDS offer the most effective and rational protection against early and random gastric emptying compared to the other methods proposed for prolonging the gastric residence time (GRT) of solid dosage forms.

Extended-release dosage forms with prolonged residence time in the stomach are also highly desirable for drugs that are locally active in the stomach and those are unstable in the intestinal or colonic environment or which have low solubility at higher pH values. FDDS has a lower density than gastric fluid and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time [2].

Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. Effervescent floating dosage forms prepared with the help of swellable polymers such as methylcellulose and various effervescent compounds such as sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms [2].

The objective of present work was to develop gastro retentive formulation, which releases drug in the stomach and upper gastrointestinal (GI) tract, and form an enhanced opportunity of absorption in the stomach and upper GI tract rather than the lower portions of the GI tract [2].

MATERIALS AND METHODS

Metoprolol succinate, HPMC K100 M, HPMC K4M, carbomer940, lactose, Magnesium stearate were obtained from richer pharmaceuticals Hyderabad. All reagents and solvents used were of analytical grade satisfying pharmacopeial standards.

The Compositions of formulations with different polymers are given in the following tables. Accurately weighed quantities of hydrophilic polymers, Lactose were taken in a mortar and mixed geometrically. To this mixture required quantity of metoprolol succinate was added and mixed slightly with pestle. This mixture was passed through 32# and later collected in a plastic bag and blended for 5 min. Later sufficient quantity of Magnesium Stearate was added and the final blend was again passed through 32#.

Then they obtained blend was mixed thoroughly for 10 min and compressed into tablets with 8.7 mm round concave Punches and corresponding dies at a hardness of 5.5kg/ cm twelve station tablet punching machine. Here each tablet weight is kept constant for 250mg [3,4].

Evaluation Parameters

The prepared floating tablets were evaluated for Uniformity of weight using 20 tablets, Hardness, Friability, I*n Vitro* buoyancy, Swelling behavior (Water uptake studies) and *In Vitro* dissolution studies.

Hardness

The hardness of ten tablets was measured using Hardness tester. Mean and standard deviation were computed and reported. It is expressed in kilopascal (kp) [5].

Friability

The friability of the tablets was determined using thermionic friabilator. It is expressed in percentage (percentage). 10 tablets were initially weighed and transferred into the friabilator. The friabilator was operated at 25 rpm for four minutes. After four minutes the tablets were weighed again. The % friability was then calculated using the formula [5].

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

Weight variation

Twenty tablets were selected at random and the average weight of the tablets was determined. The weight of individual tablets was compared with the average weight [6].

Drug content uniformity

Prepared tablets were accurately weight and finely powdered by pestle in a mortar. A weighed portion of each powder equivalent to 1 mg/ml of prepared tablet was transferred in to a volumetric flask and the drug was extracted with methanol as the solvent. The contents of the flask were sonicated for 10 min and diluted with 0.1 N HCl as the solvent. The samples were analyzed spectrophotometrically at 221 nm [6].

In Vitro Buoyancy Studies

The in vitro buoyancy was determined by floating lag time, per the method described by the tablets were placed in a 100-mL beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time [7].

Swelling study

Swelling of hydrophilic polymer such as Hydroxy Propyl Methyl Cellulose greatly depends upon the contents of the stomach and the osmolarity of the medium. This eventually influences the release, slowing action and the residence time. For each formulation, one tablet was weighed and placed in a beaker containing 200 ml of distilled water. After each hour the tablet was removed from beaker and weighed again upto 8 hours. The percentage weight gain by the tablet was calculated by using the formula [7].

$$\text{Swelling index (S.I)} = \{(Wt-Wo)/WO\} \times 100$$

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Where, S.I. = swelling index
Wt = Weight of tablet at time t
WO = Weight of tablet before immersion.

In Vitro Dissolution Studies

The release rate of Metaprolol succinate from floating tablets (n = 3) was determined using *United States Pharmacopeia (USP)* 23. Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 mL of 0.1N HCl, at 37 ± 0.5°C and 50 rpm. A sample (10 mL) of the solution was withdrawn from the dissolution apparatus hourly for 18 hours, and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45-µ membrane filter and diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 221 nm using a Shimadzu UV-1601 UV/Vis double-beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

Stability Study

The selected batch (F9) was kept at 40° C with 50% RH and the samples were withdrawn at 30, 60 and 90 days for physical and *in vitro* evaluation of drug release.

Table 1. Preformulation parameters of Metaprolol succinate

Formulation	Bulk Density (gm/cm^2)	Tapped Density ((gm/cm^2)	Carr's Index	Hausner's Ratio	Angle of Repose
F1	0.390	0.500	22	1.28	28.1
F2	0.378	0.510	25.88	1.35	30.9
F3	0.387	0.496	22	1.28	27.2
F4	0.364	0.506	28.06	1.39	31.3
F5	0.393	0.510	22	1.32	32.6
F6	0.416	0.516	19.37	1.24	34.6
F7	0.374	0.514	27.23	1.37	28.3
F8	0.388	0.526	26.23	1.36	26.7
F9	0.396	0.511	25.50	1.29	29.4

Table 2. Evaluation studies of Metoprolol succinate

Formulation	Average weight of tablets (mg)	Hardness (Kg/cm2)	Friability (%)	% Drug content	Buoyancy lag Time (sec)	Total floating Time (hrs)
F1	250	5.5	0.19	100.01	113	>20
F2	249	5.2	0.14	100.31	129	>20
F3	248	5.5	0.21	101.31	174	>20
F4	248	5	0.15	101.20	150	>20
F5	250	5.2	0.12	99.77	165	>20
F6	252	5	0.21	100.52	140	>20
F7	251	5	0.40	98.21	96	>20
F8	250	5.2	0.13	99.58	109	>20
F9	250	5.5	0.20	100.97	105	>22

Table 3. Swelling index

Formulation	Swelling index (%)			
	Time (h)			
	1	4	8	12
Fl	12.06	22.46	63.21	87.74
F2	14.04	29.94	70.38	98.56
F3	18.29	40.34	81.92	109.95
F4	13.31	34.52	72.77	99.39
F5	20.38	45.74	79.8	115.18
F6	26.62	55.75	91.07	122.50
F7	22.04	44.08	80.67	105.3
F8	27.45	54.89	90.65	119.76
F9	32.86	63.63	99.80	131.6

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Table 4. Dissolution table of formulations in 0.1N HCL

Time in hrs	1hr	2hr	4hr	6hr	8hr	10hr	12hr	14hr	16hr	18hr
F1	32.36	42.57	55.86	68.58	78.21	84.95	95.9			
F2	26	38.14	51.62	65.5	75.21	78.8	87.07	94		
F3	23.3	33.52	47.2	54.7	61.64	76.5	77.25	85.72	96.51	
F4	33.51	45.46	59.91	80.9	96.7					
F5	30.05	42.95	55.09	72.23	87.84	97.86				
F6	25.62	37.75	49.9	64.73	78.98	88.61	98.28			
F7	36.6	50.08	67.42	89	96.31					
F8	24.07	35.63	52.78	66.07	80.9	90.73	95.93			
F9	21.57	34.29	43.53	53.75	60.1	66.65	74.74	82.83	91.88	98.44

Table 5. Stability Data of Formulation 9 at 30±2°c/65 ± 5%RH and 40 ± 2°C / 75 ± 5% RH. * SD- Standard deviation

Time (Days)		Hardness (kg/cm²)	Drug content (%)	Floating lag time (s)
0		5.67 ± 0.14	99.76 ± 0.81	36.10 ± 0.36
30	At 30 ± 2°C 65 ± 5%RH	5.57 ± 0.10	99.06 ± 0.50	37.50 ± 0.2
	At 40 ± 2°C 75 ± 5%RH	5.57 ± 0.10	98.80 ± 0.70	37.7 ± 0.3
60	At 30 ± 2°C 65 ± 5%RH	5.50 ± 0.05	98.14 ± 0.30	38.7 ± 0.3
	At 40 ± 2°C 75 ± 5%RH	5.50 ± 0.05	97.21 ± 0.45	39.2 ± 0.4

Table 6. Zero order kinetic

Time	F9
0	0
1	25.57
2	34.29
4	41.53
6	53.75
8	60.1
10	66.65
12	74.74
14	82.83
16	91.88
18	98.44

Table 7. First order kinetic

Time	First order
0	0
1	1.407
2	1.535
4	1.618
6	1.73
8	1.778
10	1.823
12	1.873
14	1.918
16	1.963
18	1.993

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Table 8. Higuchi equation

SQRT	Higuchi equation
0	0
1	25.57
1.414	34.29
2	41.53
2.449	53.75
2.828	60.1
3.162	66.65
3.464	74.74
3.741	82.83
4	91.88
4.242	98.44

Table 9. Peppas-korsemeyer equation

Log time	Log % CDR
0	0
0	1.407
0.301	1.535
0.602	1.618
0.778	1.73
0.903	1.778
1	1.823
1.079	1.873
1.146	1.918
1.204	1.963
1.255	1.993

Table 10. Higuchi equation

SQRT	Higuchi equation
0	0
1	25.57
1.414	34.29
2	41.53
2.449	53.75
2.828	60.1
3.162	66.65
3.464	74.74
3.741	82.83
4	91.88
4.242	98.44

Table 11. Peppas-korsemeyer equation

Log time	Log % CDR
0	0
0	1.407
0.301	1.535
0.602	1.618
0.778	1.73
0.903	1.778
1	1.823
1.079	1.873
1.146	1.918
1.204	1.963
1.255	1.993

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Fig 1. Graphs of Dissolution Studies

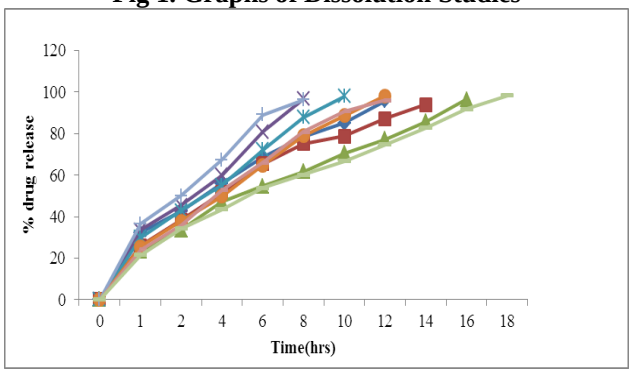

Fig 2. Zero order kinetic graph

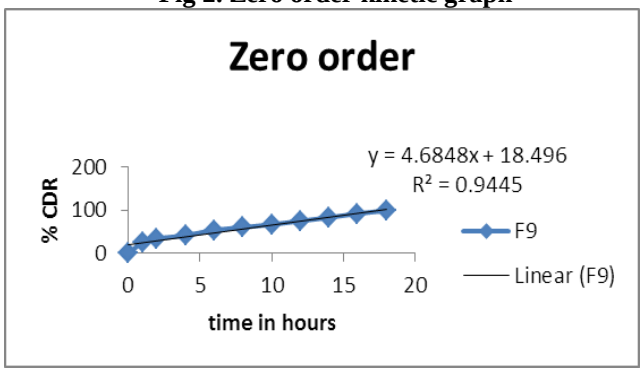

Fig 3. First order kinetic graph

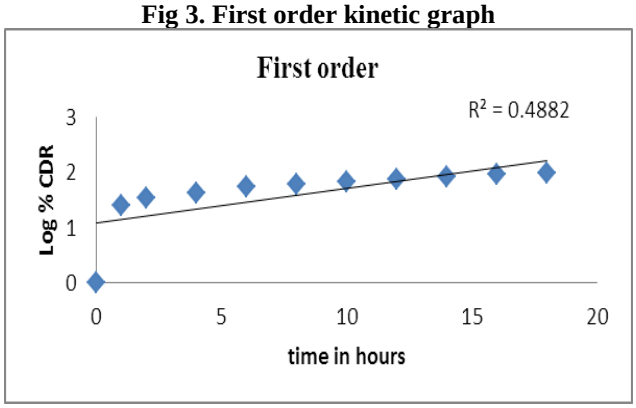

Fig 4. Higuchi equation graph

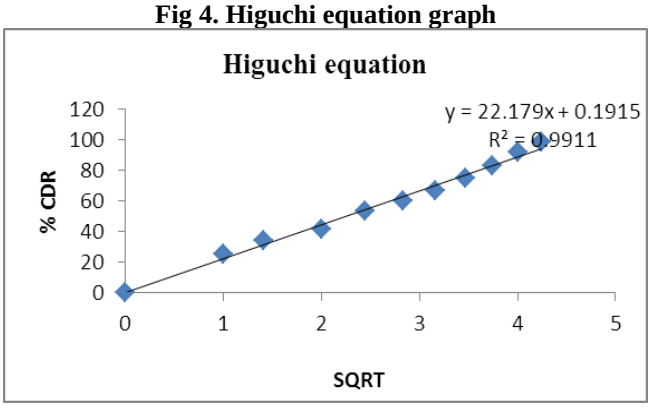

Fig 5. Peppas-korsemeyer equation graph

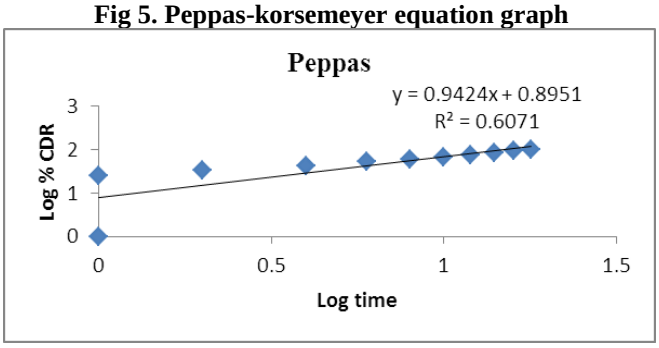

Fig 6. Zero order kinetic graph

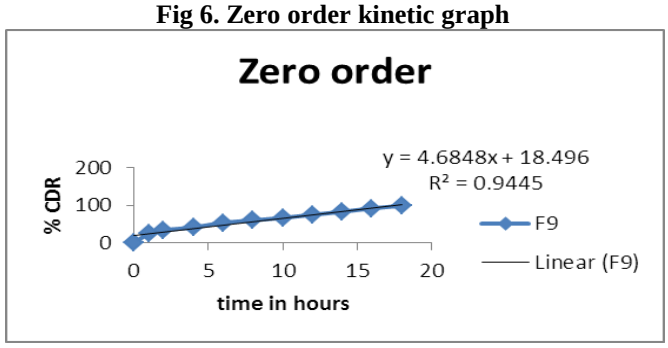

Fig 7. First order kinetic graph

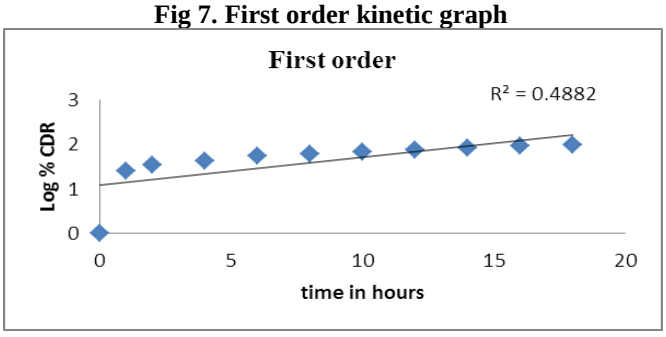

Fig 8. Higuchi equation graph

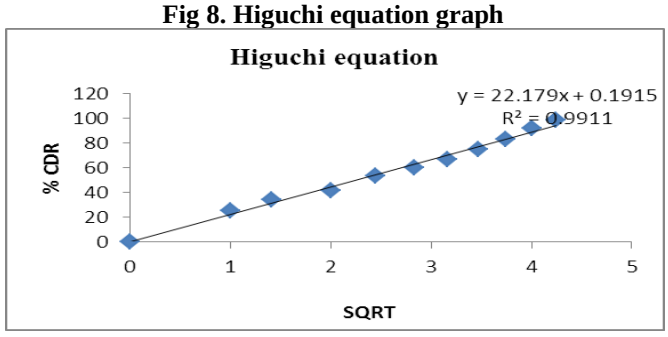

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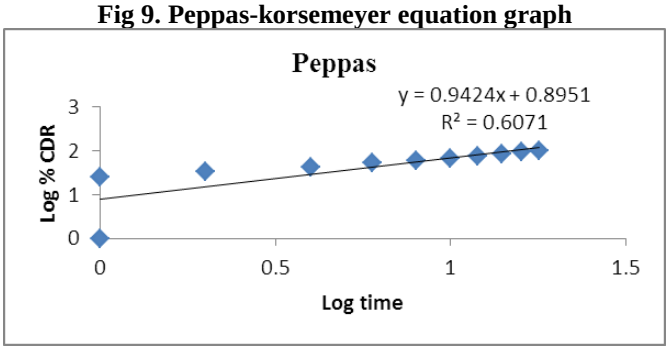
Fig 9. Peppas-korsemeyer equation graph



RESULTS AND DISCUSSION

Flow Properties

Metoprolol along with other excipients were evaluated for bulk density, tap density, angle of repose, compressibility and Hausner ratio, before proceeding to direct-compression. The physical parameters are recorded in Table 1.

[a] Angle of repose: 26 to 30 indicating good, 30-35 indicating passable.

[b] Compressibility index: 19 to 23 indicating passable and 25-28 indicating poor.

[c] Hausner ratio: 1.24 to 1.34 indicating passable and 1.35 to 1.39 indicating poor.

Evaluation Studies

The important parameters in the production of tablets were evaluated and reported in Table 2. The weight variation of the tablets was within the range. The thickness varied from 4.1± 0.1 mm. The hardness varied from 5.5 ± 1.0 kg/cm^2 found satisfactory. The friability test was passed. The percent content uniformity was 100 ± 2 and therefore was satisfactory.

Swelling index

The swelling studies were conducted on matrix tablets of metoprolol on the basis of weight. The weight was taken

Dissolution Studies

Based on the objectives of the present investigation, the tablets were evaluated for release of metoprolol. Dissolution studies were attempted. Since the delivery system was gastro-retentive system (GRDDS), 0.1 N hydrochloric acid solutions was used as dissolution medium. Since the GRDDS was expected to release the metoprolol that is equivalent to the oral controlled drug delivery system, a 24 hour period of study was expected. The polymers, HPMC K100M and HPMC K4M were used in the formulation for GRDDS.

Since the dosage form was floating type, the matrix tablet was fixed to the sinker and used for dissolution. During the dissolution process, the dosage forms were observed for its integrity. Even after 18 hours of drug release, the tablet remained intact, though in the gel form.

Drug release Kinetics

Zero order release rate kinetics

To study the zero order release kinetics the release rate data are fitted to the following equation

$F = K_0 t$

Here, F is the fraction of drug release

K_0 is the rate constant

T is the release time

First order model

This model has also been used to describe absorption and /or elimination of some drug, the release of the drug which followed first order kinetic can be expressed by the equation

$LogC = logC_0 - Kt/2.303$

Where, C_0 is the initial concentration of drug

K is the first order rate constant

t is the time

Higuchi release model

To study the Higuchi release kinetics, the release rate data was fitted to the following equation

$F = K_H.t^{1/2}$

Where, F is the amount of drug release

K_H is the release rate constant

t is the release time

Korsmeyer and peppas model

The release rate data were fitted to the following equation,

$Mt/M8 = K_M.t^n$

Where, Mt/M8 is the fraction of drug release

K_M is the release constant

t is the release time

CONCLUSION

It was concluded that the metoprolol succinate floating tablets can be formulated with good release profile for a prolonged period of time up to 18 hours. It could decrease the frequency of dose administration, prevent nocturnal attack and improves patient compliance. Further *in vivo* studied are required to correlate *in vitro* release data.

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