Effect of *Sodium Alginate* in Combination With HPMC K 100 M in Extending the Release of Metoprolol Succinate from its Gastro-Retentive Floating Tablets.

Ashok Thulluru*[1], Manthena Mohan Varma[2], Chitrali Mallikarjuna Setty[3], Pavan Kumar Chintamaneni[1], Sriharshavardhan Samayamanthula[1]

[1]Dept. of Pharmaceutics Aditya Institute of Pharmaceutical Sciences and Research, Surampalem-533437, E.G.Dist. AP, INDIA.
[2]Dept. of Pharmaceutics Shri Vishnu College of Pharmacy, Vishnupur, Bhimavaram-534202, W.G.Dist. AP, INDIA.
[3]Dept. of Pharmaceutics Vishnu Institute of Pharmaceutical Education & Research Vishnupur, Narsapur – 502313, Medak Dist. AP, INDIA.

ABSTRACT

Aim of work: The aim of present study was to convert Metoprolol Succinate (MS) into Gastro Retentive Floating Tablet (GRFT) and simultaneously to determine the effect of *Sodium Alginate* (SA) in combination with HPMC K 100M in extending the release of MS. **Method:** The drug- excipients compatibility studies of MS and the polymers were carried by FTIR studies. The effervescent GRFT of MS was prepared by non aqueous wet granulation. All Formulations were evaluated for pre-compression, post-compression, *in vitro* buoyancy and accelerated stability studies: for the best formulation for 3 months. **Results:** The drug- excipients compatibility studies reveals that MS and the polymers used are compatible. Evaluation parameters were within the acceptable limits for all formulations. In-vitro dissolution studies, showed the formulation F4 having the combination of 20% HPMC K100M and 10% SA is exhibiting better extended release up to 12 h, with a Floating Lag Time (FLT) of 20 s, Total Floating Time (TFT) and Matrix Integrity (MI) maintained up to 12 h than other formulations. Regression Coefficients of Zero order and Higuchi equations suggested the drug release follows Zero order and is predominantly by diffusion respectively. The Diffusion exponent (n) of Korsmeyer-Peppas model suggested the release mechanism is by non-Fickian transport. DSC studies further confirmed the drug is in the same state even in the optimized formulation F4 with out interacting with the polymers and excipients in the formulation. Accelerated stability studies indicate no significant differences in the optimized formulation F4. **Conclusion:** In conclusion, by optimizing the right ratios of the release-retarding gel-forming polymers HPMC K100M and SA, GRFT of MS with a better extended release up to 12 h was formulated.

Key words: Gastro retentive floating tablets *(GRFT), HPMC K100M, In vitro* buoyancy studies, *Metoprolol Succinate (MS), Sodium alginate.*

Submission Date :06-09-2014
Revision Date :30-10-2014
Accepted Date :05-02-2015

DOI: 10.5530/ijper.49.3.11

Correspondence Address
Mr. Ashok Thulluru
M.Pharm, (Ph.D.)
Associate Professor,
Dept. of Pharmaceutics
Aditya Institute of Pharmaceutical Sciences and Research,
Surampalem-533437,
E.G.Dist. AP, INDIA
E-mail:ashokthulluru@gmail.com

INTRODUCTION

Oral route is one of the most extensively utilized routes for administration of dosage forms. Drugs that have an absorption window in stomach or upper small intestine, have low solubility and stability at alkaline pH were suitable to convert as Gastro Retentive Dosage Forms (GRDFs). GRDFs significantly extend the period of time over which the drugs may be released, they not only decrease dosing interval, but also increase patient's compliance.[1,2] Various approaches for GRDFs include: Floating Drug Delivery System (FDDS), bio adhesive systems, swelling and expanding systems, high density sys-

www.ijper.org

tems.[3,4] FDDS has a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affected by gastric emptying rate.[5-7] When the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This, results in an increase in the GRT and a better control on the fluctuations in the plasma drug concentration.[8-10] Based on the mechanism of buoyancy, two different technologies for FDDS were Effervescent Systems and Non-effervescent Systems.[11-14] Effervescent Systems contain carbonates (sodium bicarbonate) and organic acids (citric acid and tartaric acid) in their formulation to produce carbon dioxide (CO_2) gas, which reduces the density of the system and making it to float.[15] The Non-effervescent FDDS is based on mechanism of swelling of polymer or bio-adhesion to mucosal layer in GI tract.[16] Metoprolol Succinate (MS) is a β1-selective adrenergic blocking agent.[17] Since the half-life is ~3 to 4 h,[18] multiple doses are needed to maintain a constant plasma conc. for a good therapeutic response. MS is highly soluble throughout physiological pH and its solubility was 157mg ml^{-1} in water (pH=5.5) and 183 mg ml^{-1} in 0.1 N HCl (pH=1.0). It has also been reported that MS absorption mainly takes place in the duodenum and jejunum and is directly proportional to the dose available.[19] Gastro retention is particularly useful for drugs that are having better solubility in acidic pH and primarily absorbed in the duodenum or upper jejunum segments.[20] Hence it is a suitable candidate for GRFT.[21] The present study was also interested in determining the effect of *Sodium Alginate* (SA) in combination With HPMC K 100M in extending the release of MS from its GRFT for the better treatment of hypertension.

MATERIALS AND METHODS

MATERIALS

MS was received as a gift sample from Dr. Reddy's Labs, Hyderabad. SA was purchased from Anshul Agencies and HPMC K100 M, Micro crystalline cellulose (Avicel PH 101), Sodium Bicarbonate, Citric acid, Magnesium Stearate, and Talc were purchased from S.D. Fine-Chem Ltd., India

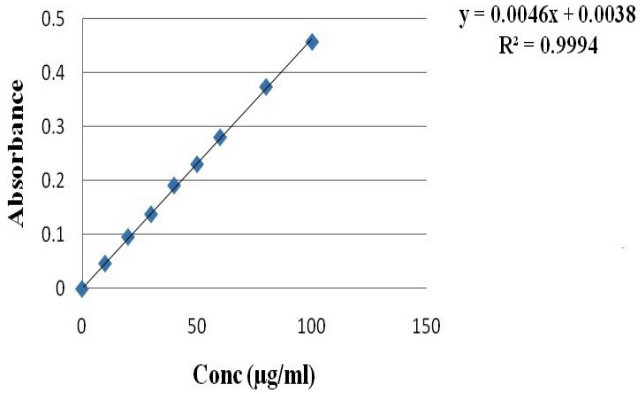

Figure 1: Standard Calibration Curve of Metaprolol Succinate in 0.1N HCl at 274nm.

ANALYTICAL METHOD

Calibration curve of MS was determined in 0.1 N HCl at 274 nm using a UV-Visible spectrophotometer (Labindia UV-VIS 3000+, *Labindia* Analytical *Instruments* Pvt Ltd, India). This calibration curve was used for dissolution studies and drug content determination. (Figure 1 and Table 1).

EXCIPIENT COMPATIBILITY STUDIES

In order to evaluate the integrity and compatibility of the drug with polymers in polymer-drug matrix, FTIR spectra of drug and drug-polymer (1:1) mixture were recorded by the Potassium Bromide pellet method (SHIMADZU, 8400s, FTIR Instrument, Japan.) and the comparative spectra were demonstrated in (Figure 2.)

PREPARATION OF MS GRFT TABLETS

All the formulations were prepared by non-aqueous wet granulation using Isopropyl Alcohol, by keeping the amount of MS constant at 50 mg per tablet. The compositions of other excipients are varied as mentioned in formulation table (Table 2). MS and all the intra granular excipients were co-sifted though Sieve No. # 40 (ASTM), blended uniformly in a poly bag for 10 min and granulated with Isopropyl Alcohol. The wet mass was sieved through Sieve No. # 20 (ASTM) and granules were dried to 40^0c for 30 min. The dried granules were sieved though Sieve No. # 30 (ASTM) and lubricated with Sieve No. # 60 (ASTM) passed Magnesium Stearate and Talc and mixed for additional 2–3 min. Tablets were compressed on a Tabletting machine (Minipress by Clit, 10 stations, Chamunda Pharma Machinary Pvt. Ltd., India) fitted with a 10.4 mm circular shaped standard concave punch with an average hardness of 6.0 kg/cm^2.

Table 1: Standard calibration plot of Metaprolol Succinate in 0.1N HCl at 274 nm

Concentration (µg/ml)	Absorbance at 274nm
0	0.000
10	0.047
20	0.096
30	0.138
40	0.191
50	0.23
60	0.28
80	0.373
100	0.456

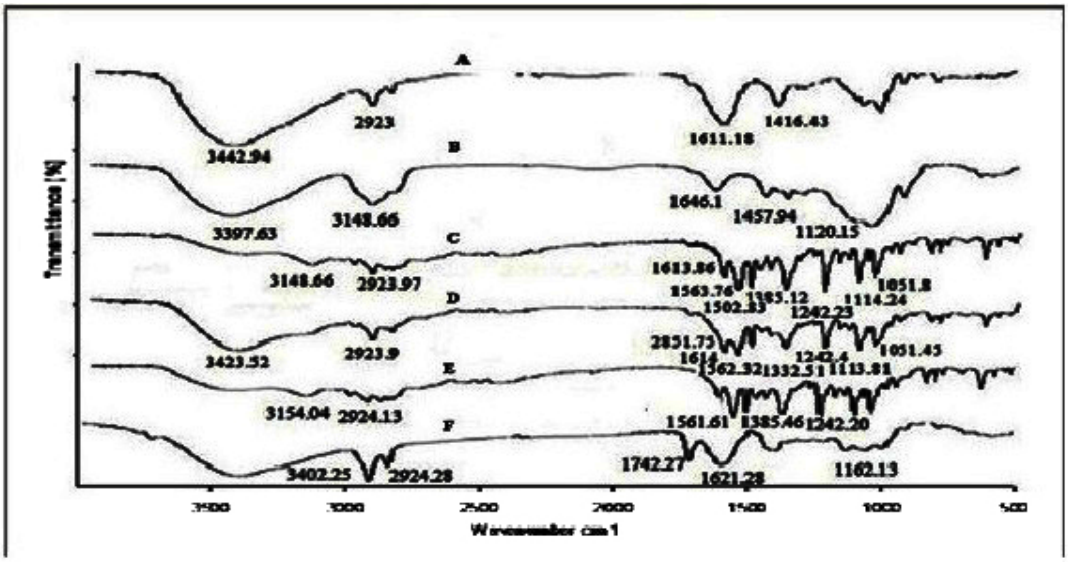

Figure 2: FT-IR Spectrograms of A) *Sodium Alginate* (SA), B)HPMC K100 M, C) Metoprolol succinate (MS), D) MS + SA, E) MS +HPMC K100M, F) MS + SA + HPMC K100M.

Table 2: Formulation table of Metoprolol Succinate GRFT

Ingredients	HPMC K100M alone			HPMC K100M + *Sodium Alginate*		
	F1	F2	F3	F4	F5	F6
Intra granular						
Metoprolol Succinate	50	50	50	50	50	50
HPMC K100M	60	90	120	60	90	120
Sodium Alginate	-	-	-	30	30	30
Avicel PH101	146.5	116.5	86.5	116.5	86.5	56.5
Sodium Bicarbonate	30	30	30	30	30	30
Citric Acid	6.0	6.0	6.0	6.0	6.0	6.0
Isopropyl alcohol	*q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Extra granular						
Magnesium Stearate	3.0	3.0	3.0	3.0	3.0	3.0
Talc	4.5	4.5	4.5	4.5	4.5	4.5
Total wt.	300	300	300	300	300	300

*q.s.: quantity sufficient, qty. per each tablet expressed in mg, with Total wt. of tablet: 300 mg.

EVALUATION OF TABLETS

The formulated tablets were evaluated for pre-compression, post-compression, *in vitro* buoyancy and *in vitro* dissolution studies.

Pre Compression studies

Angle of Repose (θ): was determined by funnel method,[22] the granules were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2 cm above hard surface. The granules were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The θ calculated by the equation.

$$\theta = \tan -1\, h / r$$

Where, θ = angle of repose, h = height of heap, r = radius of base of heap circle.

Density[23]

a) Bulk density (BD): A quantity of 2 g of granules from each formulation, previously lightly shaken to break any agglomerates formed, was introduced into a10 ml measuring cylinder and the volume is noted as bulk volume. The BD was calculated by the equation.

$$Bulk\ density = weight\ of\ powder / Bulk\ volume$$

b) Tapped density (TD) [23]**:** After the determination of BD, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 s intervals. The tapping was continued until no further

Table 3: Pre compression studies of Metoprolol Succinate GRFT

Formulation Code	Pre compression studies (n=3)				
	Angle of repose (o)	Bulk density (g/cc)	Tapped density (g/cc)	Carr's Index (%)	Hausner's Ratio
F1	22.17±0.15	0.515±0.015	0.522±0.008	13.15±1.04	1.10±0.07
F2	31.11±0.11	0.471±0.011	0.476±0.012	16.23±0.23	1.21±0.11
F3	25.71±0.13	0.505±0.005	0.527±0.015	14.26±0.65	1.15±0.31
F4	23.31±0.13	0.522±0.023	0.519±0.022	12.36±0.26	1.09±0.23
F5	28.27±0.15	0.496±0.065	0.499±0.053	17.42±0.96	1.12±0.08
F6	24.67±0.12	0.481±0.022	0.511±0.024	18.09±0.52	1.07±0.13

Table 4: Post compression & *in vitro* Buoyancy studies of Metoprolol Succinate GRFT

Formulation Code	Post compression studies						*In vitro* Buoyancy studies		
	Avg. Wt (mg) (n=10)	Thickness (mm) (n=3)	Density (g/cc) (n=3)	Hardness (kg/cm²) (n=3)	% Friability test (n=1)*	%Drug content (%) (n=10)	FLT (S) (n=3)	TFT (h) (n=3)	Matrix Integrity up to 12 h. (n=3)
F1	300.4±0.6	5.82±0.34	0.897±0.032	5.9±0.26	0.59	99.98±0.18	20±0.51	Up to 10	+
F2	300.2±0.4	5.91±0.23	0.872±0.039	6.2±0.25	0.68	100.21±0.20	40±0.21	Up to 12	+
F3	299.6±0.4	5.84±0.1	0.895±0.042	6.3±0.21	0.58	99.67±0.12	80±0.61	Up to 12	+
F4	300.0±0.3	5.88±0.1	0.884±0.036	5.9±0.23	0.59	100.32±0.14	20±0.71	Up to 12	+
F5	300.6±0.3	5.87±0.21	0.888±0.029	6.3±0.13	0.62	100.65±0.18	30±0.81	Up to 12	+
F6	300.9±0.3	5.34±0.14	0.882±0.045	6.1±0.20	0.59	99.89±0.22	35±0.51	Up to 12	+

* i.e. 10 tablets were taken for a single test.

change in volume was noted. The TD was calculated by the equation.

$$Tapped\ density = Weigh\ of\ powder / Tapped\ volume$$

Carr's Index[24]

The flow ability of powder may be evaluated by comparing BD and TD of powder and the rate at which it packs down. The percentage of compressibility index was calculated by the equation.

$$Carr's\ index = (Tapped\ density - Bulk\ density) \times 100 / Tapped\ density$$

Hausner's Ratio[25]

Hausner's Ratio is a number that is correlated to the flow ability of a powder. It was calculated by the equation.

$$Hausner's\ Ratio = Tapped\ density / Bulk\ density$$

The determination of micromeritics of all the formulations were carried out in triplicate, the consolidated results (mean ± SD) were tabulated in Table 3.

Post compression studies

- ***Shape of tablet*** and general ***appearance:*** were checked by magnifying lens after compression.[26]
- ***Thickness of tablet:*** thickness of 3 tablets of each formulation was determined using a Vernier caliperse (Mitutoyo Corporation, Japan).[27]
- ***Density:*** If the density of the tablet is less than the density of gastric fluid (1.004 gm/cc) then only the tablets will float. Density of 3 tablets of each formulation were calculated by the equations[28]

$$d = m/v$$

$$v = \pi r^2 h$$

d = density; v=volume of the cylinder; r=radius of tablet; h=thickness of tablet; m=mass of tablet

- ***Tablet Weight Uniformity:*** An electronic balance (Mettler Toledo, 3-MS-S/MS-L, Switzerland) was used to accurately weigh 10 tablets of each formulation which were randomly selected and the results (mean ± SD) are mentioned[29,30].
- ***Hardness test:*** To evaluate tablet hardness, 3 tablets of each formulation were tested for diametrical crushing strength using a hardness tester (Monsanto type hardness tester, MHT-20, Campbell Electronics, India.)[29,30]
- ***Friability test:*** The friability of the 10 tablets (n=1) was tested by a friabilator (ERWEKA, TAR 120, Germany.), at a speed of 25 rpm for 4 minutes. The percentage friability was calculated by the equation.[29,30]

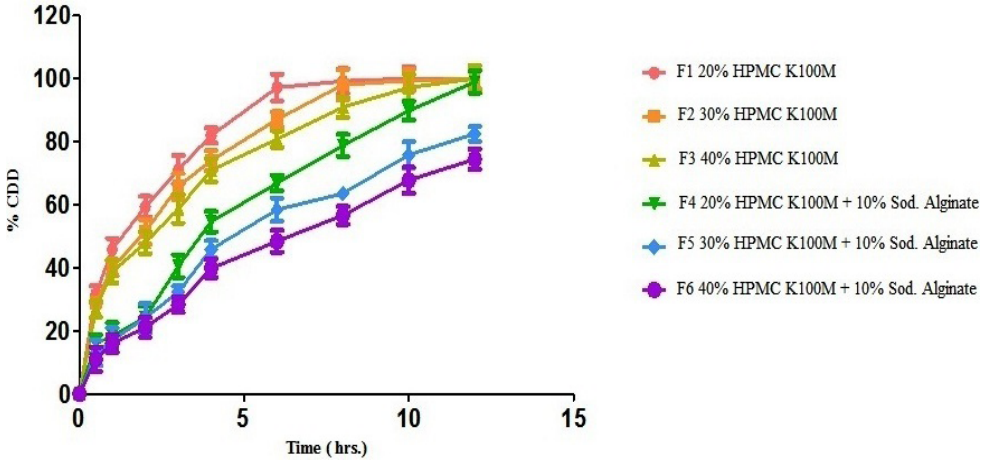

Figure 3: *In vitro* dissolution profiles of Metoprolol Succinate GRFT.

Table 5: *in vitro* dissolution Parameters of Metaprolol Succinate GRFT

Formulation Code	*in vitro* dissolution Parameters			
	Zero-order plot			First Order plot
	K_0(mg/h)	T_{50}(h)	T_{90}(h)	K_1(h^{-1})
F1	7.013	1.3	5	0.589
F2	7.312	1.9	6.7	0.496
F3	7.255	2.2	7.9h	0.322
F4	7.992	3.6	10.0	0.312
F5	6.588	4.4	>12h	0.138
F6	5.904	6.2	>12h	0.108

$$\% Friability = (initial\ wt. - wt.\ after\ friability) \times 100 / initial\ wt.$$

- ***Drug content:*** To evaluate the drug content through a uniformity test, 10 tablets of each formulation were crushed; the quantity of tablet powder equivalent to 100 mg of MS was suspended in 0.1 N HCL to extract the MS from the blend. After 24 hours, media were filtrated, suitably diluted and measured by a UV-Visible spectrophotometer.[29,30]

In vitro Buoyancy studies

- The in vitro buoyancy of 3 tablets of each formulation was determined as per the method described.[31]
- ***Floating Lag Time (FLT):*** is the time taken for a tablet to rise on medium surface. A tablet was placed in a beaker with 100 ml of 0.1 N HCl, and the time required for the tablet to rise on the surface was determined.
- ***Total Floating Time (TFT):*** is the floating duration that a tablet remained on medium surface. A tablet was placed in a beaker with 100 ml of 0.1 N HCl, and the duration of tablet that remained on the surface was determined.
- ***Matrix integrity (MI):*** During the period of TFT the swelled matrix tablets were observed for their integrity. If not disintegrated upto12 h. indicated as '+', and if disintegrated with in 12 h indicated as '-'. The consolidated results of post compression and *in vitro* buoyancy studies are tabulated in Table.4.

In vitro Dissolution Study

A dissolution test was performed for 12 h using the dissolution apparatus (Labindia Disso 2000, *Labindia* Analytical *Instruments* Pvt Ltd, India) according to United States Pharmacopoeia.[32] Each vessel contained 900 ml of 0.1N HCL; the paddle apparatus with 50rpm speed was used, while the temperature was kept stable at 37^0C ± 0.5^0C. At every time interval, 5 ml of media was withdrawn and measured by UV-VIS spectrophotometer at 274 nm. Furthermore, 5 ml of 0.1N HCL was replaced to keep the volume stable. The dissolution test was repeated 6 times for each formulation and all the results were analyzed using Graph Pad Prism 5.0. (Figure 3 and Table 5).

Release Kinetics

The analysis of drug release mechanism from a pharmaceutical dosage form is important but complicated process and is practically evident in the case of matrix systems. The order of drug release from FDDS was described by using zero order kinetics or first order kinetics. The mechanism of drug release from FDDS

Table 6: Diffusion exponent and solute release mechanisms for cylindrical shape in Korsmeyer - Peppas model

Diffusion Exponent(n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45< n<0.89	Non-Fickian diffusion
0.89	Case II transport
n>0.89	Super Case II transport

was studied by using Higuchi equation and the Peppa's-Korsemeyer equation.

Zero Order Release Kinetics

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the zero order equation.[33]

$$Q_0 - Qt = K_0 t$$

Rearrangement of above equation yields

$$Qt = Q_0 + K_0 t$$

Where Qt is the amount of drug dissolved in time *t,* Q_0 is the initial amount of drug in the solution (most times, Q_0=0) and K_0 is the zero order release constant expressed in units of conc. / time. The data obtained were plotted as cumulative amount of drug released *vs.* time.

First Order Release Kinetics

The equation that describes first order kinetics is[34]

$$\log C = \log c_0 - Kt / 2.303$$

Where C is the conc. of drug remaining at time't' , C_0 is the initial conc. of drug and Kt is the first order rate constant expressed in units of time^{-1}. The data obtained were plotted as log cumulative percentage of drug remaining *vs.* time, which would yield a straight line with a slope of - Kt / 2.303.

Higuchi equation

The first example of a mathematical model aimed to describe drug release from a matrix system was proposed[35] Initially conceived for planar systems, it was then extended to different geometrics and porous systems.[36]

Simplify form of the Higuchi model can be represented by the equation:

$$Q = K_H t^{1/2}$$

Where, Q is the amount of drug released in time t per unit area and K_H is the Higuchi dissolution constant. The data obtained were plotted as cumulative percentage drug release versus square root of time.

Korsemeyer-Peppas equation

Korsmeyer *et al.* (1983) derived a simple relationship which described drug release from a polymeric system.[37] To find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer - Peppas model equation.

$$\frac{Mt}{M\alpha} = K.t^n$$

Where, Mt / M∞ are a fraction of drug released at time t, k is the release rate constant and n is the release exponent. The n value is used to characterize different release mechanisms for different shaped matrices. In this model, the value of *n* characterizes the release mechanism of drug by cylindrical shape (Table 6). Data obtained were plotted as log cumulative percentage drug release *vs.* log time.

The consolidated release kinetics of MS GRFTs was tabulated in (Table.7).

Differential Scanning Calorimetry (DSC) Studies

DSC scans of MS and the optimized formulation (F4) containing the same amount of drug were performed; using an automatic Thermal Analyser (DSC 60, Shimadzu, Japan). Sealed and perforated Aluminium pans

Table 7: Release kinetics of Metoprolol Succinate GRFT

Formulation Code	r^2 values (Regression coefficient)				Korsemeyer-Peppas n value
	Zero order	First order	Higuchi	Korsemeyer-Peppas	
F1	0.733	0.968	0.927	0.963	0.372
F2	0.809	0.952	0.966	0.985	0.408
F3	0.850	0.971	0.983	0.992	0.421
F4	0.958	0.858	0.978	0.965	0.654
F5	0.955	0.991	0.983	0.985	0.616
F6	0.967	0.993	0.983	0.989	0.618

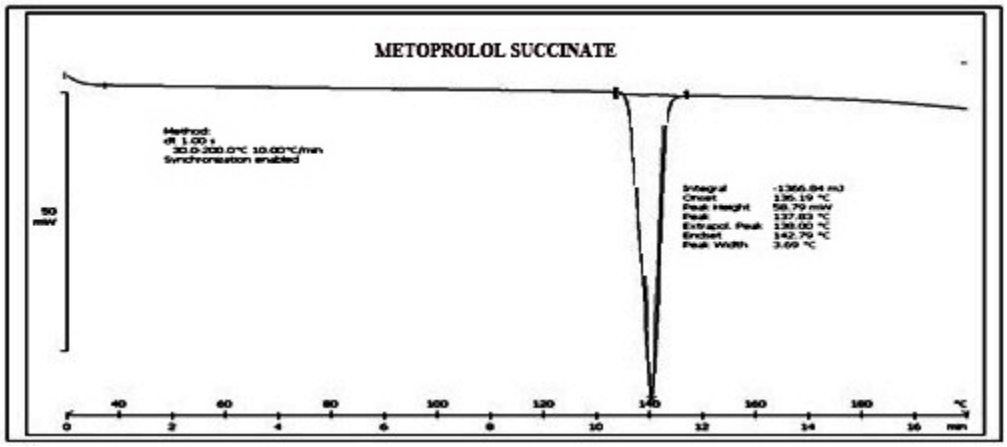

Figure 4: DSC thermo gram of Metoprolol Sucinate (MS).

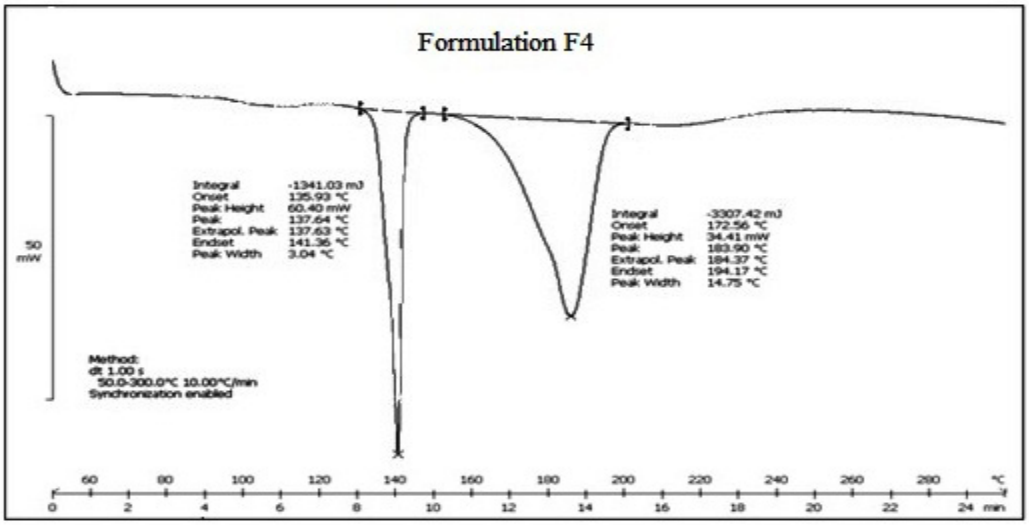

Figure 5: DSC thermo gram of optimized formulation (F4)

Table 8: Accelerated stability data for Optimized formulation (F4)

Time Interval	Hardness	Drug content	Floating characteristics			% CDD at 12th h.
			FLT (seconds)	TFT (h)	Matrix Integrity up to 12 h	
Initial	6.3±0.21	99.67±0.12	80±0.61	Up to 12 h.	+	99.02±0.23
1 month	5.9±0.11	98.07±0.18	83±0.59	Up to 12 h.	+	98.38±0.14
2 month	5.4±0.20	97.64±0.21	87±0.63	Up to 12 h.	+	97.67±0.17
3 month	5.1±0.18	97.26±0.12	91±0.55	Up to 12 h.	+	97.06±0.22

were used in the experiments. Temperature calibrations were performed using Indium as standard. An empty pan sealed in the same way as the sample was used as a reference. The entire samples were run at a scanning rate of 10°C/min from 50-300°C. The DSC- Thermo grams of MS and optimized formulation (F4) were shown in (Figure 4 and 5) respectively.

Accelerated Stability Studies

Accelerated Stability Studies for 3 months were carried out according to International Conference on Harmonization (ICH) guidelines,[38] to study the quality of the finished optimized formulation F4 under a variety of conditions (time, humidity, and temperature). Tablets were sealed in aluminum packaging having a polyethylene coating on the inside and kept in a humidity chamber (NSW-175, Narang Scientific work, India) maintained at 45°C and 75% RH. At the end of every month the, samples were withdrawn and evaluated for hardness, drug content, floating characteristics (FLT, TFT and MI) and % CDD at 12th h. The consolidated

Accelerated Stability Studies data for optimized formulation, F4 are tabulated in (Table 8).

RESULTS & DISCUSSION

Analytical Method

A spectrophotometric method for estimation of MS, based on the measurement of absorbance at 274 nm in 0.1N HCl, gives a straight line with an equation: y=0.0046 X + 0.0038 and r^2=0.999 (Figure 1 and Table 1).

Drug-Excipients Compatibility Study

The FTIR spectra of drug- polymer (1:1) blends were compared with that of the MS (Figure 2). FTIR spectrum of MS is characterized by the absorption of COOH group at 1612.5 cm^{-1}, OH stretching absorption at 3061.0 cm^{-1} and NH deformation at 1375.5 cm^{-1}. FTIR spectra of drug- polymer (1:1) blends, show same absorption patterns and bands as that of pure drug. Thus, indicates no significant chemical interaction occurred between the drug and polymers used.

Evaluation of tablets

Pre Compression studies

Pre compression studies on lubricated granules of all formulations (Table 2) reveals that the angle of repose was found between 22.17°to 31.11°, bulk density between 0.471 to 0.522 gm/cm^3, tap density between 0.476 to 0.527 gm/cm^3, Carr's index between 12.36 to 18.09% and Hausner's Ratio between 1.07 to 1.21. The micromeritic studies indicate better flow and compression characteristics of all formulations. (Table 3)

Post Compression studies

The avg. wt. of tablet of all the formulations was found to be 300.9 ± 0.3 mg. Tablet thicknesses were found to be 5.91 ± 0.23 mm. The density of the cylindrical shape tablets in all cases was found to be 0.897 ± 0.032 gm/cm^3, indicating satisfactory buoyancy. The hardness of the formulation was 6.3 ± 0.13 Kg/cm^2, indicating satisfactory mechanical strength. Percentage wt. loss in the friability test between 0.59 to 0.68% in all cases, which indicates good mechanical resistance of the tablets. Tablets of all the prepared batches containing MS were found to be within 100.65 ± 0.18% of the labeled content, indicating content uniformity of the prepared formulations.

In vitro buoyancy studies

The results of *in vitro* buoyancy studies showed quick floating of the tablet within 2 min after placing the tablet in dissolution medium. FLT varied between 20 s to 80 s and expect for formulation F1 remaining all formulations maintained TFT up to 12 h. Buoyancy mainly depends upon the ratio of effervescent mixture (Sodium Bicarbonate: Citric Acid). In all the formulations, the ratio was maintained as 5:1 respectively. The consolidated results of post compression and *in-vitro* buoyancy studies of formulations are tabulated in (Table 4).

In vitro dissolution studies

It indicates, the release was extended with the increase in HPMC percentage in tablets due to the increased percentage of swelling and the decreased percentage of erosion.[39] The more the concentration of HPMC, thicker the gel layer offers more resistance to the drug diffusion and gel erosion,[40] which results in the incomplete release. SA matrix had the ability to provide a sustained release for highly water-soluble drug even in the presence of water-soluble excipients like HPMC[41] the pH independent release profile for basic drugs like MS can be attained by combining HPMC with SA. The combined matrix when exposed to an acidic environment, the HPMC hydrates to form a gel layer at the surface of the tablet while the SA remains insoluble, acting as a barrier to diffusion of the drug.[42] Their proportion had significant effect on the release profiles.[43] Formulation F4 (20% HPMC K100M and 10% SA) released 100 % of MS in 12 h, with a FLT of 20 s, TFT and a better MI up to 12 h, when compared to other formulations with HPMC only. Hence, formulation F4 was considered the best formulation with desirable floating parameters and *In vitro* drug release profile. (Figure 3 and Table 5)

Release Kinetics

The drug release kinetics of optimized formulation F4 fitted best to the Zero-order (R^2=0.958). The (R^2=0.978) value in case of Higuchi release was found to be higher than Zero order and First order, suggesting that the drug release process is predominantly by diffusion. The (n=0.654) value for the case of cylindrical shape in Korsmeyer-Peppas model, suggested the release mechanism of the drug is non-Fickian transport (0.45<n<0.89). (Table 6 and 7)

DSC Studies

DSC Thermo grams in Figure 4 and 5 is pure drug and optimized formulation F4 respectively, reveals that the melting point of MS is 140.12°C and that of MS in the formulation F4 is 140.15°C. As there is no much difference in the melting points, it indicates that the drug is in same state even in the optimized formulation F4 without interacting with the polymers and excipients.

Accelerated stability studies

Results of accelerated stability studies of optimized formulation F4 indicate it is stable at 40°C / 75% RH up to 3Months. As there were no significant differences

in hardness, drug content, floating characteristics (FLT, TFT & Matrix integrity) and % CDD at 12thh (Table 8).

CONCLUSION

In the above view of findings the formulation F4 (20% HPMC K100M and 10% SA) is better suited for GRFT of MS than other formulations with HPMC K100M alone. It was concluded that the optimization of HPMCK100M and SA, had significant effect on extending the release profiles of MS. A matrix design of this kind can serve as an alternative strategy to targeted drug delivery by GRFT. This work can be extended to alkaline- BCS class I drugs and their salts, which are having half-life less than 5 h.

CONFLICT OF INTEREST

Authors have no conflict of interest to declare.

ACKNOWLEDGEMENTS

The authors are thankful to Dr. K.Rajeswar Dutt and Dr. K. Ravi Shankar, Principal & Professor, Aditya & Sri Sai Aditya Institute of Pharmaceutical Sciences and Research, Mr. N.Sesha Reddy, Chairman, Mr. N. Satish Reddy, Vice-Chairman, Aditya Educational Institutions for providing us the facilities to carry out this academic research work.

REFERENCES

1. Yeole PG. Floating Drug Delivery System: Need and Development, Ind. J. Pharm Sci. 2005; 67 (3): 265-72.
2. Shweta Arora,Javed Ali, Alka Ahuja, Roop K. Khar, and Sanjula Baboota. Floating drug delivery systems: A review. AAPS Pharm Sci Tech. 2005; 6(3): E372-E390.
3. Libo Yang. A New Intragastric Delivery System for the Treatment of H. *Pylori* associated with gastric ulcers. J. Cont. Rel. 1999; 34(3): 215-22.
4. Singh BN, Kim H. Floating drug delivery system an approach to control delivery via gastric retention. J. Cont. Rel. 2000; 63(3): 235-59.
5. Choi BY, Park HJ. Preparation of alginate beads for floating drug delivery system: effect of CO_2 gas forming agent. J Cont Rel. 2000; 25(1): 488-91.
6. Timmermans J, Moes AJ. The cut off size for gastric emptying of dosage forms. J Pharm Sci. 1993; 82(3): 854.
7. Ichikawa M, Watanabe S, Miyake YA. New multiple-unit oral floating dosage system: Preparation and *in-vitro* evaluation of floating and sustained-release characteristics. J Pharm Sci. 1991; 80(11): 1062-6.
8. Menon A, Wolfgang AR, Saks A. Development and evaluation of monolithic floating dosage form for Furosemide. J. Pharm. Sci.1994; 83(2): 239-45.
9. Ozdemir N, Ordu S, Ozkan Y. Studies of floating dosage forms of Furosemide: *in-vitro* and *in vivo* evaluations of bilayer tablet formulations. Drug Dev. Ind Pharm. 2000; 26(8): 857-66.
10. Streubel A, Siepmann J, Bodmeier R. Floating matrix tablets based on low density foam powder: effects of formulation and processing parameters on drug release. Eur J Pharm Sci. 2003; 18(1): 37-45.
11. Nur OA, Zhang JS. Captopril floating and/or bioadhesive tablets: design and release kinetics. Drug Dev. Ind Pharm. 2000; 26(9): 965-9.
12. Shah S, Quaqish R, Patel V, Amiji M. Evaluation of the factors influencing stomach specific delivery of antibacterial agents for H. *pylori* infections. J Pharm Pharmacol. 1999; 51 (6): 667-72.
13. Hilton AK, Deasy BP. *In vitro* and *in vivo* evaluation of an oral sustained-release floating dosage form of *Amoxycillin trihydrate*. Int.J Pharm. 1992; 86(1): 79-88.
14. Basak SC. Development and *in vitro* evaluation of oral matrix floating tablets formulation of Ciprofloxacin. Ind. J Pharm Sci. 2004; 66(3): 313-6.
15. Himasankar K. Design and Biopharmaceutical evaluation of gastric floating drug delivery system of Metformin HCl. Ind. J Pharm Edu Res. 2006; 40(2): 369-82.
16. Dave BS, Amin AF, Patel MM. Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and *in-vitro* evaluation. AAPS Pharm Sci Tech. 2004; 5(2): 1-6.
17. Hardman JG, Limbird LE, Gilman AG. Goodman and Gilman's: The Pharmacological Basis of Therapeutic. 10th ed., McGraw-Hill Publishers, New York; 2001. pp. 255–6.
18. Kendall MJ, Maxwell SR, Sandberg AG. Westergren, Controlled release metoprolol. Clinical pharmacokinetic and therapeutic implications, Clin. Pharmacokin. 1991; 21(5): 319–30.
19. Jobin G, Cortot A, Godbillon J, Duval M, Schoeller JP, Hirtz J, Bernier J. Investigation of drug absorption from the gastrointestinal tract of man. I. Metoprolol in stomach, duodenum, and jejunum. Br. J. Clin. Pharmacol. 1985; 19 (Suppl. 2):97S-105S.
20. Narendra C, Srinath MS, Babu G. Optimization of bilayer floating tablet containing metoprolol tartrate as a model drug for gastric retention. AAPS Pharm Sci Tech.2006; 7: 23–9. DOI: 10.1208/pt070234.
21. Ravishankar H, Patil P, Samel A, Petereit H-U, Lizio R, Iyer-Chavan J. Modulated release metoprolol succinate formulation based on ionic interactions: *in-vivo* proof of concept. J. Control. Rel. 2006; 111(1): 65–72.
22. Cooper J, Gunn C. Powder flow and compaction, In: Carter SJ, eds. Tutorial Pharmacy. New Delhi, India: CBS Publishers and Distributors; 1986. 211-33.
23. Shah D, Shah Y, Rampradhan M. Development and evaluation of controlled release diltiazem hydrochloride micro particles using cross-linked poly (vinyl alcohol). Drug Dev. Ind. Pharm. 1997; 23 (6): 567–74.
24. Aulton ME, Wells TI. Pharmaceutics: The Science of Dosage Form Design, London, England: Churchill Livingstone; 1988.
25. United States Pharmacopeia 24/NF19, The Official Compendia of Standards. Asian Rockville, M.D. (Ed.), United States Pharmacopoeia Convention Inc; 2000.pp. 1913–4.
26. Deshpande RD, Gowda DV, Mohamad N, Marambar DN. Bi-LayerTablets-An Emerging Trend: A Review. International Journal of Pharmaceutical Science and Research 2011; 2 (10): 2534-44.
27. Singh BN, Kim KH. Floating drug delivery systems an approach to oral controlled drug delivery via gastric retention. J Control Rel. 2000; 63(3): 235-59.
28. Chaudhari S, Bawaskar M, Shirsat A. Formulation and Evaluation of bilayer Floating tablets of Carvedilol Phosphate. Journal of Drug Delivery and Therapeutics 2012; 2(5): 9-19.
29. Leon Lachman, Herbert lieberman A, kanic Joseph L. The theory and practice of industrial pharmacy, Varghese publishing house, third edition; pp. 293-345.
30. Remington. The Science and Practice of Pharmacy, 19th edition; 1669-70.
31. Rosa M, Zia H, Rhodes T. Dosing and testing *in vitro* of a bioadhesive and floating drug delivery system for oral application. Int J. Pharm. 1994; 105(1): 65-70.
32. United States Pharmacopoeia 30, National Formulary 25, USP Convention, Rockville; 2007. p. 2648.
33. Release kinetics, data interpretation. in: Encyclopedia of Controlled Drug Delivery. Narashimhan B, Mallapragada SK, Peppas NA. Eds. John Wiley and Sons, Inc New York; 1999. p. 921.
34. Bourne DW. Pharmacokinetics. in: Modern pharmaceutics. 4th ed. Banker GS, Rhodes CT, Eds., Marcel Dekker Inc, New York; 2002.
35. T. HIGUCHI. Mechanism of Sustained- Action Medication Theoretical Analysis of Rate of Release of Solid Drugs Dispersed in Solid Matrices J. Pharm. Sci. 1963 ;52(12):1145-49
36. Grassi, Mario; Grassi, Gabriele.Mathematical Modelling and Controlled Drug Delivery: Matrix Systems.Current Drug Delivery, 2005; 2(1):97-116
37. Richard W. Korsmeyer, Robert Gurny, Eric Doelker, Pierre Buri, Nikolaos A. Peppas. Mechanisms of solute release from porous hydrophilic polymers. Int. J. Pharm. 1983; 15 (1):25-35.

38. Jain SK, Awasthi AM, Jain NK. Calcium silicate based microspheres of rapiglinide for gastro retentive floating drug delivery: Preparation and *in vitro* characterization. J. Control. Rel. 2005; 107(4): 300-9.
39. Maderuelo C, Zarzuelo A, Lanao JM. Critical factors in the release of drugs from sustained release hydrophilic matrices. J. Control. Release. 2011; 154(1): 2-19.
40. Wan Lucy SC, Heng Paul WS, Wong LF. Relationship between swelling and drug release in a hydrophilic matrix. Drug Dev. Ind. Pharm. 1993; 19(10): 1201-0.
41. Celine Valeria Liew, Lai Wah Chan, Ai Ling Ching, Paul Wan Sia Heng. Evaluation of sodium alginate as drug release modifier in matrix tablets Int. J. Pharm. 2006; 309 (1-2): 25-37.
42. Li Li, Huijuan Sun, Jing Gao, Tao Jiang, Yuan Gao, Jianjun Zhang. Optimization of sustained release matrix tablet of metoprolol succinate using central composite design Pak. J. Pharm. Sci. September 2013; 26(5): 929-37.
43. Howard JR. Peter Timinis, pH dependent polymer, pH independent hydrocarbon gelling agent and binder" US Patent; 1998. 4792452.