

Research Article

FORMULATION AND *IN VITRO* EVALUATION OF METOPROLOL SUCCINATE FLOATING TABLETS

Gagan Deep Singh¹, Neetu Kansal¹, Amarjit Singh², Sunil Thakral^{2*}

¹Akal Degree College,
Mastuana Sahib,
Sangrur, Punjab,
(Pb) – 148001, India

²Akal College of
Pharmacy & Technical
Education, Mastuana
Sahib, Sangrur, Punjab,
(Pb) – 148001, India

Submitted: 11-01-2013

Revised: 05-03-2013

Accepted: 020-04-2013

*Corresponding author
Sunil Kumar

E-mail:
sunil.thakral@gmail.com

ABSTRACT

Gastroretentive dosage forms extend significantly the period of time over which the drug may be released. This prolonged gastric retention improves bioavailability, decrease drug waste and improve solubility of drugs that are less soluble in a high pH environment due to their availability in gastric pH for longer duration of time. Floating drug delivery systems have a bulk density less than gastric fluids and hence remain buoyant in the stomach. The main objective of the present study was to develop Gastroretentive (GR) controlled release formulations of Metoprolol to prolong the gastric retention time so that its bioavailability can be improved. The formulations were prepared by using swellable polymers like HPMC K4M, HPMC K15M, HPMC K100M, Guar Gum, Xanthan Gum, Sodium carboxymethyl cellulose and various effervescent compounds, e.g. sodium bicarbonate, and citric acid by the direct compression method. All the formulations were evaluated for different parameters like floating lag time, total floating time, hardness, weight variation, density measurements, drug content and water uptake/swelling index. Dissolution studies were done for all formulations in 0.1N HCl (pH 1.2). Formulations F3, F4 and F10 were found to provide maximum sustained release of metoprolol succinate up to 24 h with optimum floating properties.

Key words : Controlled release; Gastro retentive; HPMC; Guargum; Xantham gum

INTRODUCTION

Oral delivery of drug is the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation, etc. Conventional drug delivery system achieve as well as maintain the drug concentration within the therapeutically effective range needed for treatment only when taken several times a day, which can lead to significant fluctuations in drug levels (Gupta *et al.*, 2010).

Attempts are being made to develop a single dose therapy for the complete duration of treatment, where focus is mainly on the controlled or sustained release drug delivery systems because of the ease of the administration via the oral route as well as the ease and economy of manufacture of oral dosage forms (Hoffman, 1998).

One requisite for successful performance of oral controlled release drug delivery system is that drug should have good absorption throughout the GIT, preferably by passive diffusion. Oral controlled release dosage forms

are not suitable for many drugs, characterized by a narrow absorption window in the upper part of GIT (Stomach & small intestine). This is due to the relatively short transit time of the dosage form in these anatomical segment i.e. 6 hrs. (Patil *et al.*, 2006).

G.I. transit times vary widely between individuals, and depend up on the physical properties of the object ingested and the physiological conditions of the gut. This variability may lead to unpredictable bioavailability and times to achieve peak plasma levels (Longer *et al.*, 1985).

Therefore, in cases where the drug is not absorbed uniformly over the G.I tract, the rate of drug absorption may not be constant. In spite of the drug delivery system, delivering the drugs at a constant rate into the G.I fluids, it may cause incomplete drug release from the dosage form at absorption sites, thus leading to diminished efficacy of the administered dose (Klausner *et al.*, 2003).

It is apparent that for a drug having such an absorption window, an effective orally

controlled drug delivery system should be designed not only to deliver the drug at a controlled rate, but also to retain the drug in the stomach for a long period of time (Mojaverian *et al.*, 1988). After oral administration, such a dosage form would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastro intestinal tract (Singh and Kim, 2000). Incorporation of the drug in a controlled release gastro retentive dosage form (CRGRDF) can yield significant therapeutic advantages due to a variety of pharmacokinetic and pharmacodynamic factors (Timmermans and Moes, 1994).

Controlled release Gastroretentive drug delivery systems (GRDDS) are the systems which are retained in the stomach for a prolonged period of time and thereby improved the bio availability. GRDFs extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form (Sharma *et al.*, 2011).

Effervescent drug delivery system utilizes matrices prepared with swellable polymers such as methocel or polysaccharides and effervescent components like sodium bicarbonate and citric or tartaric acid. Different formulations of metoprolol succinate were prepared by using cellulosic hydrocolloids of different viscosity grades HPMC (K4M, K15M and K100M) and gel forming hydrocolloids natural polymers like Guar Gum and Xanthan Gum for sustained release.

Metoprolol succinate is a β -1-selective adrenergic blocking agent. The half-life of metoprolol Succinate is about 3-4 hrs, hence the multiple doses are needed to maintain a constant plasma concentration for a good therapeutic response and improved patient compliance. It has also been reported that drug absorption mainly takes place in the duodenum and jejunum and is directly proportional to the dose available.

MATERIAL AND METHODS

Metoprolol succinate was received as a gift sample from Ranbaxy Drug Laboratories,

Gurgaon (HR), India. The polymers HPMC K4M, HPMC K15M and HPMC K100M were received from Colorcon Asia Pvt. Ltd., Goa, India. Guar gum, sodium bicarbonate, sodium carboxy methyl cellulose, citric acid and magnesium stearate were procured from S.D. Fine Chemicals Pvt. Ltd., Ahmedabad (Guj), India. All other chemicals and reagents used were of analytical grade and were used as received.

Methods

Drug polymer interaction study

This study was carried out by taking the FTIR spectrum of samples of drug and 1:1 mixture of drug and polymer. The FTIR of the samples of drug and mixture were taken in KBr pellets. The pellets were scanned over a wave number range of 4000 to 400 cm^{-1} . The UV spectroscopy was carried out by dissolving the drug in 0.1 N HCl (pH=1.2) and scanned at wavelength 222.0nm.

The tablets excipients were chosen after comprehensive drug-polymer interaction study.

Preparation of floating tablets of metoprolol succinate

Different compositions of floating tablets of Metoprolol Succinate with different polymers were prepared by the direct compression method (Table I). All ingredients were powdered, weighed and mixed properly. Magnesium stearate was added as a lubricant.

Evaluation of floating tablets of metoprolol succinate floating behavior

In vitro floating behavior of tablet was studied by placing the tablet in 500mL container filled with 300mL 0.1N HCl (pH=1.2) and the time taken by tablet to float on the surface was recorded as floating lag time and the total duration of time in which the tablet was floated in the dissolution medium was the total floating time and were determined by visual observation.

Determination of tablet hardness

The crushing strength of tablet was measured by Monsanto tablet hardness tester which applies compression force diametrically to the tablets. The force required to crush the tablet was recorded as hardness of tablet in kg/cm^2 .

Table I. Different compositions of floating tablets of metoprolol succinate

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Drug	200	200	200	200	200	200	200	200	200	200
Sodium CMC	20	20	20	20	20	20	20	20	20	20
Xanthan Gum	-	20	-	20	-	-	-	-	-	-
Guar Gum	20	-	20	-	-	-	-	-	-	-
HPMC K100M	-	-	-	-	20	20	-	-	-	-
HPMC K4M	110	110	-	-	110	-	130	-	-	160
HPMC K15M	-	-	110	110	-	110	-	130	160	-
Sodium Bicarbonate	70	70	70	70	70	70	70	70	70	70
Citric Acid	30	30	30	30	30	30	30	30	-	-
Magnesium Stearate	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%

Table II. Various physical parameters of floating tablets of metoprolol succinate

Formulation Code	Average Hardness (kg/cm ²)	Friability %	Diameter (mm) Mean \pm S.D. (n= 3)	Weight (mg) Mean \pm S.D (n=20)	Height (mm) Mean \pm S.D (n= 3)
F1	4.3	0.75	10.75 \pm 0.01	454 \pm 0.99	5.06 \pm 0.01
F2	4.7	0.42	10.78 \pm 0.03	460 \pm 1.65	5.06 \pm 0.07
F3	4.7	0.45	10.70 \pm 0.02	460 \pm 2.32	5.09 \pm 0.04
F4	4.6	0.43	10.70 \pm 0.01	450 \pm 1.84	5.25 \pm 0.5
F5	4.4	0.36	10.70 \pm 0.01	452 \pm 1.33	5.12 \pm 0.02
F6	4.4	0.45	10.66 \pm 0.02	449 \pm 1.42	5.13 \pm 0.04
F7	4.6	0.75	10.83 \pm 0.02	455 \pm 1.55	5.13 \pm 0.05
F8	4.5	0.44	10.67 \pm 0.02	450 \pm 0.99	5.14 \pm 0.04
F9	4.6	0.46	10.73 \pm 0.02	457 \pm 1.83	5.06 \pm 0.05
F10	4.7	0.39	10.71 \pm 0.03	454 \pm 1.78	5.06 \pm 0.04

Determination of tablet friability

The friability was determined by weighing 10 tablets and placing them in a Roche type friability apparatus and rotating it at 25 rpm for 4 minutes (i.e.100 drops). After dusting tablets were weighed for their final weight and % friability was calculated as follows:

$$\% \text{friability: } \left[\frac{(\text{weight}_{\text{initial}} - \text{weight}_{\text{final}})}{\text{weight}_{\text{initial}}} \right] \times 100$$

Measurement of tablet density

To check the floating behavior of tablets the apparent densities of the tablets were calculated from their volume and mass. The volume of the tablets were calculated from their heights 'h' and radii 'r' (both determined by using a micrometer gauge by using the mathematical equation for a cylinder $\{V = \pi r^2 h\}$).

Weight variation

Twenty tablets of each formulation were weighed individually and their mean weight and

standard deviation from mean weight was calculated.

Other physical parameters

Four tablets of each formulation were examined for their diameter, thickness and height of tablets by using micrometer gauge.

In - vitro drug release study

Release study of floating tablets were carried out in 900mL of 0.1N HCl buffer of pH=1.2 dissolution medium using USP apparatus II at 37°C with paddle speed at 75 rpm. The floating tablets of metoprolol succinate were weighed and dropped into the dissolution medium. During dissolution study, every time 5 ml of aliquots of dissolution medium were withdrawn and replaced with 5 ml of fresh medium kept at 37°C. These samples were filtered and the required dilutions were made with the 0.1N HCl solution of pH1.2 and then analyzed at λ_{max} 222.0nm using UV-visible spectrophotometer.

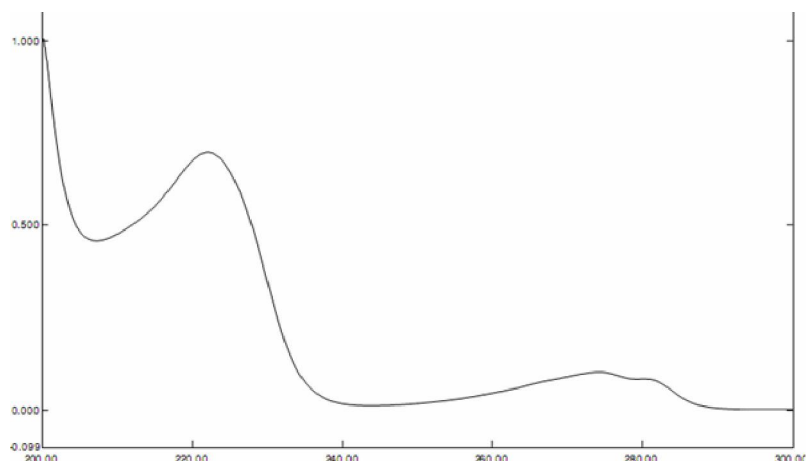


Figure 1. UV spectra of Metoprolol Succinate

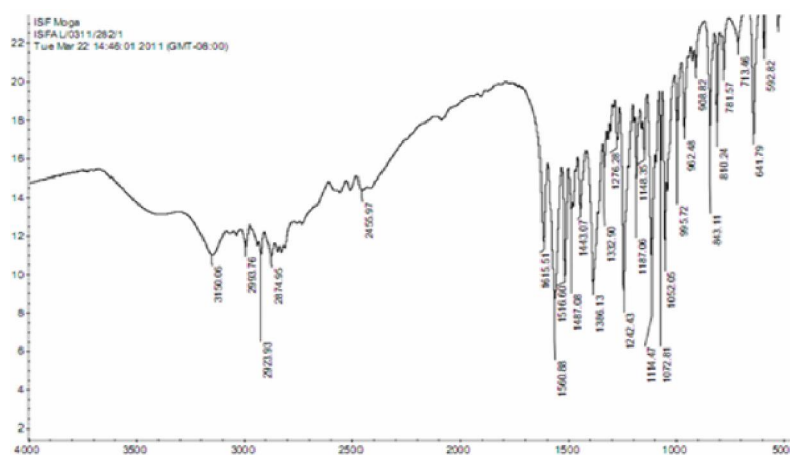


Figure 2. FTIR spectra of Metoprolol Succinate

RESULTS AND DISCUSSION

Drug polymer interface study

Drug Polymer Interface study was carried out to eliminate the possibility of interaction of polymers like HPMC K4M, HPMC K15M, HPMC K100M, Guar Gum, Xanthan Gum, Sodium carboxymethyl cellulose with Metoprolol Succinate. The UV Scan and FTIR spectra are shown in figure 1 and 2 respectively. The peak position for FTIR spectra in case of 1:1 mixture of drug and polymer are same as in the pure drug and pure polymers, the representative spectrum of 1:1 mixture of metoprolol succinate and HPMC K 15M is shown in figure 4. In addition to it none of the polymer tends to shift the λ_{\max} of Metoprolol Succinate.

Evaluation of floating tablets of metoprolol succinate

Physical evaluation and assay of floating tablets

Hardness, friability and weight variation parameters were evaluated and results are given in table II. All these measured parameters of floating tablets of metoprolol succinate were within the USP limits.

When the compression force of the tablet compressing machine increases, hardness of the tablets increases which results in the reduction of floating behaviour of the tablets, that may be due to the reduction of the porosity of tablets and the compacted polymer particles on the surfaces of the tablets cannot hydrate rapidly when the tablet contacts the gastric fluid. On the other hand, if the hardness

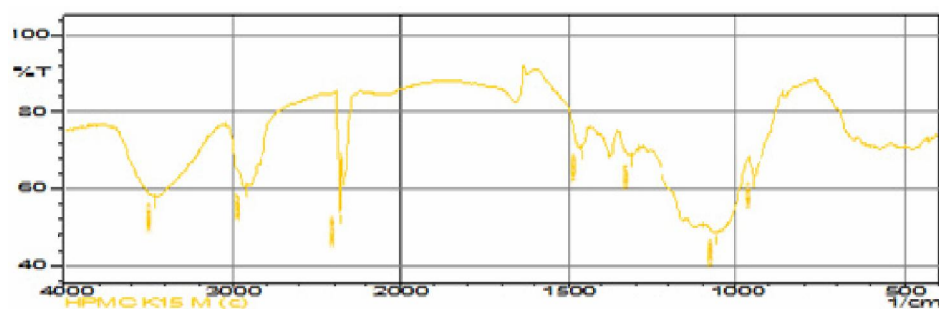
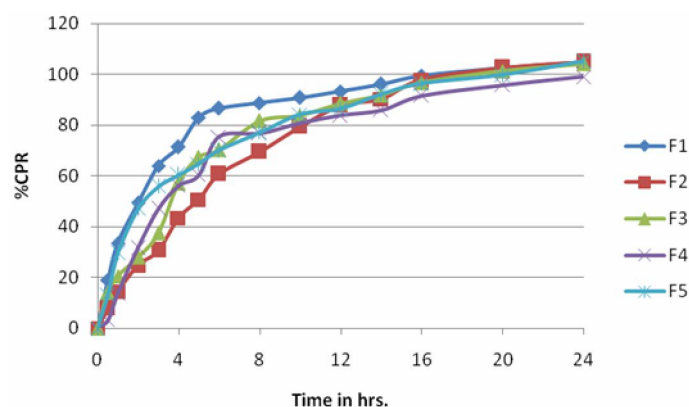


Figure 3 FTIR spectra of HPMC K15M



Figure 4 FTIR spectra of Drug + HPMC K15M

Figure 5 *In vitro* dissolution profile of formulations F1-F5.

too low for the tablets, they will be friable and therefore not acceptable. The hardness of all formulations was found to be in the range of 4-5 Kg/cm², which were well within the USP limits.

Floating behaviour of the tablets

On immersion in 0.1N HCl solution (pH 1.2) at 37°C, all the tablets first sank in the release medium and then they float to the surface. Floating lag time was measured for all

the formulations and it was observed that the tablets were floats within 30-42 secs. and remain buoyant up to 24h (Table III).

Density measurements

The density of floating tablets were found uniform among different batches and ranged from 0.98-1.01 gm/cm³ (Table III). All the formulations were found to have densities less than the release medium.

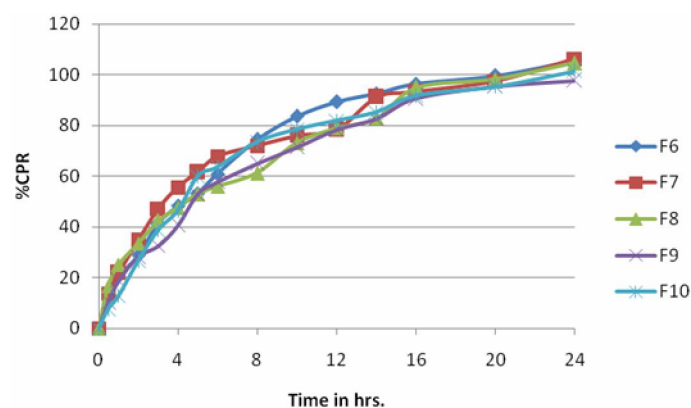
Figure 6 *In vitro* dissolution profile of formulations F6-F10.

Table III. Floating lag times, floating duration and densities of different formulations

Formulation Code	Floating Lag Time (Sec.)	Floating Duration (h)	Density (gm/cm ³)
F1	30	Up to 24	1.012
F2	34	Up to 24	0.995
F3	38	Up to 24	0.998
F4	40	Up to 24	0.982
F5	35	Up to 24	0.979
F6	42	Up to 24	0.981
F7	39	Up to 24	1.012
F8	31	Up to 24	0.996
F9	34	Up to 24	1.001
F10	35	Up to 24	0.994

In vitro drug release studies

All the tested formulations showed sustained release patterns of metoprolol succinate for 24h. The amount of drug (Metoprolol Succinate), polymer (Sodium CMC) and effervescence producing agent (Sodium Bicarbonate) was kept constant.

It was observed that F1 releases the 99% of the total drug content within the 16h. In order to sustain the release of drug from tablets more effectively, formulations with different viscosity grades of HPMC and with the combinations of Sodium CMC, Xanthan Gum and Guar Gum were prepared. The more sustained release of the drug was observed in case of the formulations F2 and F3. Guar gum produced lesser sustained release formulation.

However F4 shows the 99.08% drug release after 24 hrs. Here more sustained effect was produced with X-Gum and HPMC K15M.

F5- F10 formulations were prepared by using the different viscosity grades of HPMC K4M, HPMC K15M and HPMC K100M, in spite of using Xanthan gum or Guar Gum. These formulations showed the better sustained release effect. Formulation F5 (20mg of HPMC K100M + 110mg of HPMC K4M) releases the 96% drug in 16h and 99.8% drug in 20h. The similar results were obtained by using the HPMC K100M.

F6 (20 mg of HPMC K 100M + 110mg of HPMC KM 15) releases the 96.2% drug in 16h and 99.9% drug in 20h. The higher concentrations of HPMC K4M and HPMC K 15M were used to obtain the more sustained release effect. Here, F7 (130 mg of HPMC K4M) releases the 97.4% drug in 20 hrs and almost 100% drug in 24 hrs and F8 (130 mg of HPMC K15M) releases about 99.3% drug in 20h. The results obtained were quite similar.

However, sustained release effect was obtained in case of F9 and F10. F9 (160 mg of HPMC K15M) releases about 97.7% drug in 24 hrs and F10 (160 mg of HPMC K4M) releases about 100% drug in 24 hrs.

The net effect of viscosity enhancing agents as well as swelling effect produced by the various polymers produced the gastro retentive dosage form for 24 hours.

CONCLUSION

The floating drug delivery is promising approaches to achieve sustain release. The addition of swell able gel-forming polymers like HPMC K4M, HPMC K15M, HPMC K100M, Guar Gum, Xanthan Gum, Sodium carboxymethyl cellulose and gas-generating agent sodium bicarbonate was essential to achieve in vitro buoyancy. Addition of citric acid, to achieve buoyancy under the elevated pH of the stomach, caused an enhancement in drug release. Polymers welling is crucial in determining the drug release rate and is also important for flotation. A lesser floating lag time and prolonged buoyancy duration could be achieved by varying the amount of different polymer combinations.

From floating and drug release behavior, it can be concluded that sustained release floating matrix tablets of metoprolol succinate can be formulated using HPMC K15M or HPMC K4M in combination with other polymers and gas generating agents for prolonged residence and controlled release of the drug. Thus, the current study resulted in successful development of once-a-day controlled release gastro retentive formulations of metoprolol succinate.

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