Research article Available online www.ijrpsonline.com ISSN: 2249–3522

International Journal of Research in Pharmacy and Science

Formulation and Evaluation of Floating Tablet of Metoprolol Tartrate

Patel Naveen*, Patil Uma, Lanka Aparna, Patil Swaraj, Patel Krunal

KLE University's College of Pharmacy,
Rajajinagar II[nd] Block, Bangalore 560010, Karnataka, India

ABSTRACT

Metoprolol tartrate, an adrenergic antagonist used as an anti-hypertensive agent has a short half life of 3-4 hours. The aim of the present study was to design and evaluate floating tablets of Metoprolol tartrate with a view to prolong the gastric residence time. The tablets were prepared by using MCC, HPMC K100M and HPMC K4M as polymers. Sodium bicarbonate was used as a gas-generating agent. The floating matrix tablets of Metoprolol tartrate were prepared by direct compression method. The concentration of polymers and a gas-generating agent was optimized to get a controlled release for 8 hours. The prepared tablets were evaluated for physicochemical parameters and were found to be within range. A significant difference in drug release at 1, 4 and 8 hours ($p < 0.0001$) was observed. The floating lag time of all the formulations was within the prescribed limit (< 10 min.) All the formulations showed good matrix integrity and retarded the release of drug for 8 hours. Based on the diffusion exponent (n) value, drug release was found to be diffusion controlled. The swelling studies of all the formulations formulated using HPMC K100M in greater amount showed higher swelling index and hence retarded the drug release better than with formulations containing less amount of HPMC K100.

KEYWORDS: Metoprolol tartrate, Floating tablets, Controlled release, HPMC K4M, HPMC K100M, Gastric residence time

***Corresponding Author:**
Naveen Patel
M.Pharm student,
Dept of Pharmaceutical Technology
KLE University's College of Pharmacy,
Rajajinagar II Block, Bangalore 560010, Karnataka, India.
Phone No: 9880703240
E-mail: naveen.patel5@gmail.com

INTRODUCTION:

Oral ingestion has long been the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, least sterility constraints and flexibility in the design of the dosage form. Hydrophilic polymers are becoming very popular in formulating oral controlled release tablets. Though various formulation approaches are used to control the release of water soluble drugs, floating matrix tablets are proving to be a potential choice.[1,2] The widely used hydrophilic polymers for sustaining the drug delivery are HPMC, NaCMC, Chitosan, HPC, MC, natural gums, etc. A few reports appear in the literature on the use of guar gum, as a carrier, for oral controlled delivery of drugs.[3-5] About 40% of Metoprolol tartrate is hypothesized to be absorbed slowly due to high colonic residence time and good permeability of the drug through colon.[6] Polymeric film coatings have often been used for achieving controlled release of an active substance from a pharmaceutical preparation because a coated dosage form enables prolonged and precise release of drugs with good reproducibility.[7,8] Some formulations of a drug–polymer mixed coat for highly water-soluble drug pellets had a dissolution profile that matched the commercial product.[9] Micro crystalline cellulose is a metabolically inert low density filler and has excellent water absorptive, swelling & dispersion properties.[10] The polymer is usually used in combination with Hydroxypropyl methylcellulose (HPMC) which gives a more hydrophilic nature to the film and alters its structure by virtue of pores and channels through which the drug substance can diffuse more easily. [11] Hypertension results from an increase of both systolic and diastolic blood pressure that causes damage in cardiac, renal, and brain blood vessels. Metoprolol has been and still is one of the most frequently used β-blocker agents. Metoprolol is widely used in the treatment of hypertension, angina pectoris and cardiac dysrhythmias.[12,13] This drug is lipophilic, cardioselective, and exhibits a marked selectivity toward β1 adrenergic receptors —the type of receptors that predominate in cardiac muscles. The efficacy of this drug in the treatment of hypertension, angina pectoris and cardiac heart failure is ascribed to β1 blockade of catecholamines, which are endogenous substances that provoke an increase in blood pressure and induce myocardial contraction.

EXPERIMENTAL:

MATERIALS

Metoprolol tartrate, Hydroxy Propyl Methyl Cellulose K4M (HPMC K4M) and Hydroxy Propyl Methyl Celululose K1000M (HPMC K100M) were received as gift samples from Astra Zeneca

Bangalore, India. Microcrystalline Cellulose (MCC), Poly Vinyl Pyrrolidine K30 (PVPK30), Stearic acid, Talc, Sodium bicarbonate were procured from S.D Fine chemicals, Mumbai. All materials used were of analytical grade.

METHOD OF FORMULATION

The floating tablets of Metoprolol tartrate were formulated by direct compression technique using PVP K30 (4%w/w) as a binder. After a set of initial trials with various polymers it was found that HPMC K4M and HPMC K100M were suitable as viscosity forming agents. Talc and Magnesium stearate were used in the ratio 2:1.

Table 1: Formulation Code

INGREDIENT	**N1**	**N2**	**N3**	**N4**
Metaprolol tartarare	100	100	100	100
$NaHCO_3$	100	100	100	100
HPMC K100M	90	80	70	60
HPMC K4M	10	20	30	40
MCC	156	156	156	156
PVP K30	20	20	20	20
Talc	16	16	16	16
Magnesium stearate	8	8	8	8
Total weight	500	500	500	500

**All the quantities are in mg.*

EVALUATION OF FLOATING TABLET FORMULATIONS

Hardness of the tablets was tested using a Monosanto hardness tester. Friability of tablets was determined in Roche friabilator. Ten tablets were selected randomly from each batch and weighed individually to check for weight variation. The results are given in table II.

SWELLING INDEX

The swelling Index of different formulations was calculated by formula using:

$$S.I = \{(Mt-Mo) / Mo\} \times 100$$

Where, S.I = swelling index,

Mt = weight of tablet at time 't'

Mo = weight of tablet at time t = 0.

FLOATING PROPERTIES

The time taken for tablet to emerge on surface of medium is called the floating lag time (FLT) and duration of time the dosage form to constantly remain on surface of medium is called the total floating time (TFT). The buoyancy of the tablets was studied in dissolution apparatus type I, basket method at 37+- 0.5 °C in 900 ml of 0.1N HCL (pH 1.2). The measurements were carried out for each formulation of tablets. The time of duration of floatation was observed visually.

***IN-VITRO* DRUG RELEASE STUDY**

The release characteristics of floating tablets were studied in triplicate using a dissolution apparatus type I, basket method, with a stirring speed of 50 rpm at 37°C $\pm$ 0.5°C in 900 ml of simulated gastric fluid (pH 1.2 $\pm$ 0.1, HCl solution) for 8 hours. The dissolution samples (1 ml) were collected at pre-determined intervals and replaced with an equal volume of dissolution media. The concentration of Metoprolol tartarate released as a function of time was determined at 275 nm by a UV spectrophotometer.

RESULTS AND DISCUSSSION:

The floating matrix tablets of Metoprolol tartrate were prepared by direct compression method. The concentration of polymers and a gas-generating agent was optimized to get a controlled release of for 8 hours. Tablets were evaluated for physical characteristic viz. hardness, friability, weight variation, swelling index, floating capacity and were found to be within range. The measured hardness of tablets of each formulation ranged between 3.0 to 4.0 Kg/cm^2. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable. All the tablets passed weight variation test as the % weight variation was within the Pharmacopoeial limits of ±5% of the weight. A significant difference in drug release at 1, 4 and 8hours ($p < 0.0001$) was observed. The floating lag time of all the formulations was within the prescribed limit (< 10 min.) All the formulations showed good matrix integrity and retarded the release of drug for 8 hours. Based on the diffusion exponent (n) value, drug release was found to be diffusion controlled. The swelling studies of all the formulations formulated using higher amount of HPMC K100M showed higher swelling index and hence retarded the release better than the formulations using lesser amounts of HPMC K100M. N1 having 90:10 mg of HPMC K100M:HPMC K4M had a swelling index of 0.675 and showed a release of 99% at the end of 8th hour. N2 having swelling index 0.621 showed a release of 97% at 6th hour. N3 and N4 having

lesser amount of HPMC K100M than N1 showed lesser swelling indices of 0.619 and 0.612 respectively and could retard the release upto 3-4 hours only.

Table 2: Hardness, friability, weight variation of tablets of different Formulation N1 to N4

Formulation	Hardness (kg/cm^2)	Friability (%)	Weight variation(mg)
N1	3.5	0.73	506±5%
N2	3.0	0.78	504 ±5%
N3	3.0	0.85	502±5%
N4	4.0	0.91	504±5%

**Values are mean± S.*

Table 3: swelling index and lag time profile of different formulations

Sl no.	Swelling Index	Lag Time(seconds)
N1	0.675	26.95
N2	0.621	16.11
N3	0.619	41.00
N4	0.612	36.93

The swelling studies of the formulation N1 formulated using higher amount of HPMC K100M (90 mg) with less amount of HPMC K4M (10 mg) showed higher swelling index(0.675) and hence retarded the release of the drug for a greater time(99% at the end of 8th hour) than compared to formulations N2, N3, N4 using increasing amounts of HPMC K4M(20,30,40 mg) with decreasing amount of HPMC K100M (80,70,60 mg) which showed lesser swelling indices.

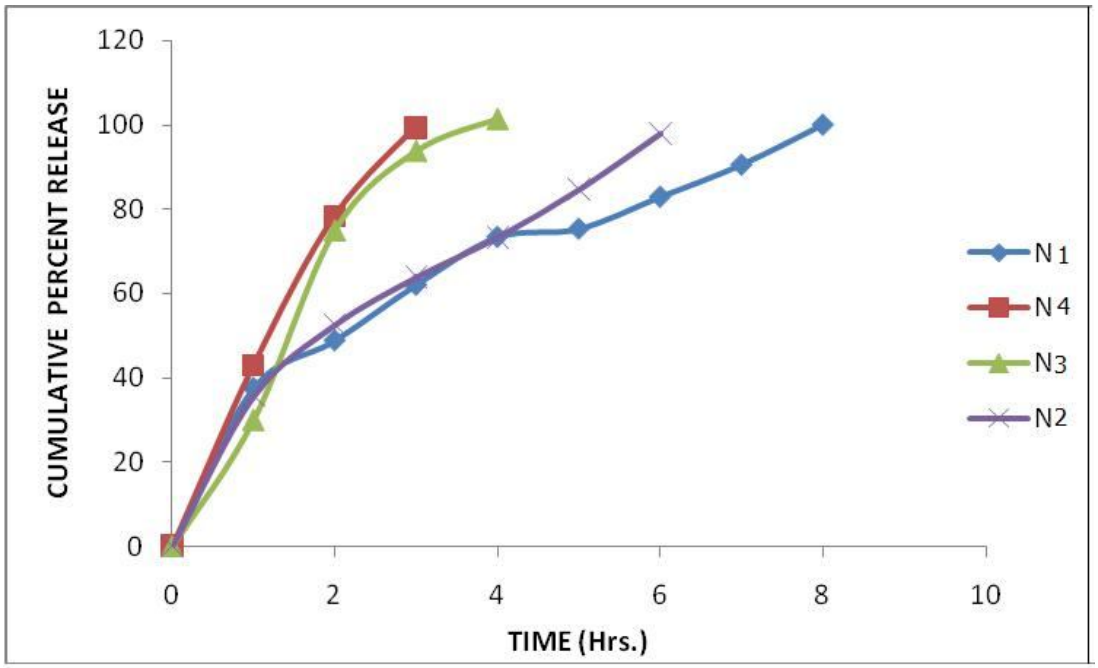

Figure 1: Percentage release profile of different formulations

In other words, HPMC K4M tended to attribute for quick release of the drug and HPMC K100M retarded the release of the drug. Thus, floating tablets of Metoprolol tartrate that could retard the release of drug upto a period of 8 hours were successfully designed.

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