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ORIGINAL ARTICLE **OPEN ACCESS**

Formulation and Evaluation of Controlled Released Floating Matrix Tablets of Metoprolol Tartrate

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ABSTRACT

The purpose of this article is to prepare a controlled released floating matrix tablet of metoprolol tartrate. The basic aim behind this work is to develop a matrix embedded floating tablet of metoprolol tartrate for the sustained activity & prolongation of gastric residence time for improving the bioavailability of the drug. Metoprolol is better absorbed in the stomach than in the lower intestinal tract. The floating tablet was formulated using HPMC K100M &HPMC K4M as the release retardant polymer, andto reduce the floating lag time, sodium bicarbonate as the gas generating agent was used. Tablets containing HPMC K4M (20.00%, w/w), Ethylcellulose (8.0%, w/w) and NaHCO3 (10%, w/w) (formula F9) showed satisfactory results concerning floating lag time, total floating duration, swelling ability, and controlled drug release rates. The concentration and viscosity of the polymer showed a directly proportional relationship with the swelling characteristics of the tablet. As the viscosity and concentration of polymers increased, the release rate of the drug was retarded. As the concentration of ethyl cellulose increases, the percent drug release rate and floating lag time decrease. So it is concluded that ethylcellulose can act as a floating enhancer. The release mechanism of metoprolol tartrate from the matrix tablet was evaluated based on the Korsmeyer & Peppasmodel which indicates the mechanism of drug released from the optimized dosage form as non-fiction transport. The tablets were prepared by the direct compression method. The formulated tablet was evaluated for the weight variation, hardness, friability, swelling index, floating lag time, total floating time & dissolution rate in pH 1.2.

Keywords: *Metoprolol Tartrate, Controlled released drug delivery system, Sustained released drug delivery system, Floating drug delivery, Gastro retentive system.*

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INTRODUCTION

One of the most satisfactory & secure means for administration of the drugs because of their appropriateness & simplicity of administration is the oral drug delivery system. Owing to its potential advantages including a well-establish delivery system, patient-friendly, convenient, cost-effective, & non-invasiveness, it has been the most favored drug delivery system in the pharmaceutical field. The conventional dosage form can partially achieve the goal of delivering the therapeutic response over the time of dose interval. Recent technological development & advances in oral drug delivery have guided the pharmaceutical industry towards the improvement of the dosage form [1-2].

Controlled Release Drug Delivery Systems (CRDDS):

An ideal controlled drug delivery system delivers the drug at a predetermined rate, locally or systemically, for a specific period. For optimum performance, drug concentration in the body should be maintained above the effective level & below the toxic level. However, when the drug is administered to a patient, the initial concentration of the drug in the body is above a toxic level before being gradually diminished to an ineffective level due to excretion. [3,4]

Controlled release drug delivery systems are conveniently divided into four categories;

1. Delayed-release
2. Sustained release
3. Site-specific targeting
4. Receptor targeting

Floating Drug Delivery System:

Floating drug delivery system (FDDS) is developed to retain the drug in stomach and beneficial for drugs having low stability and poor solubility in the intestinal fluids. The aim of FDDS is to make formulation having less density than the gastric fluids, to float the drug on gastric fluid. FDDS is a hydro dynamically controlled low-density system in which drug float over a gastric fluid without affecting the gastric emptying rate for a prolonged time.

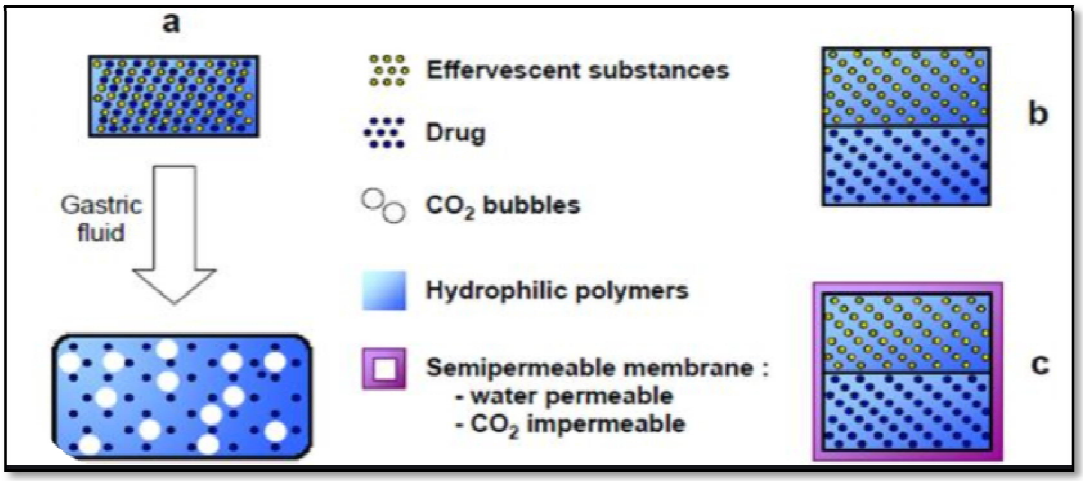

Fig. 2: Mechanism of floating drug delivery system

Advantages of Floating Drug Delivery System:

1) Simple & conventional technique for formulation.
2) Site-specific drug delivery.
3) Controlled delivery of drugs.
4) Delivery of drugs for residual action at a specific site in the stomach.
5) Improved drug absorption with increased GRT & excess duration of contact of dosage regimen at its target site.

Disadvantages of Floating Drug Delivery System:

1) The main disadvantage is requirement of sufficient level of gastric fluids to float without a sink. It can be overcome by coating the dosage form with bioadhesive polymers that easily adhere to the gastric mucosa.
2) The drugs those get significantly absorbed through the gastrointestinal tract, with significant first-pass metabolism, are desirable candidate predominantly.
3) Certain drugs present in the floating system may causes irritation to the gastric mucosal lining.
4) Gastric emptying of floating systems may occur at random & highly dependent on its dimensions. Therefore patients should not have dosage before going to bed.

Application of floating drug delivery system:

- ✓ Enhanced bioavailability
- ✓ Enhanced first-pass biotransformation
- ✓ Sustained drug delivery/reduced frequency of dosing
- ✓ Targeted therapy for local ailments in the upper GIT
- ✓ Reduced fluctuations of drug concentration [5-7]

MATERIAL AND METHODS

Materials:

Table No. 1: List of materials used

Sr. No.	Materials
1	Metoprolol tartrate
2	Hydroxypropyl cellulose (HPC)
3	Hydroxypropyl methylcellulose (HPMC)
4	Ethyl cellulose
5	Sodium Bicarbonate
6	Avicel PH102
7	Talc
8	Aerosil

Characterization of Metoprolol Tartrate

The drug Metoprolol Tartrate was procured as a gift sample from CiplaPvt Ltd., Goa, along with a certificate of analysis (C.O.A). To confirm the identity, purity and suitability of the drug for formulation and to establish a drug profile, Preformulation studies were undertaken.

1. Organoleptic properties:

The drug powder is analyzed for color, odor and taste.

2. Description:

The drug sample (Metoprolol Tartrate) is analyzed for physical appearance and powder nature.

3. Melting point:

Melting point determination of the obtained sample of Metoprolol Tartrate is done by an open capillary method. It is the first indication of the purity of the sample since the presence of a relatively small amount of impurity can be detected by a lowering as well as widening of the melting point range.

4. Solubility analysis:

An excess amount of the drug is mixed with 5 ml of the solvent system. Stir it for 30 minutes. Kept it on a shaker for 48 hrs to achieve equilibrium and centrifuged it for 10 minutes, the supernatant layer is then filtered out. The dilutions made from 5-50 ml and the solubility determined by measuring the UV absorption.

5. Micromeritic characterization of Metoprolol Tartrate:

In the Micromeritics properties, angle of repose, loose bulk density, tapped bulk density, Carr's index, Hausner ratio of the pure drug are determined.

Methods for the determination of the angle of repose, loose bulk density, tapped bulk density, Carr's index, Hausner ratio are described in the section of Evaluation of prepared powder mixtures [5, 8, 9].

7. Compatibility studies of drug and formulation components:

The compatibility of drugs and polymers is important criteria before formulating the dosage form. It is important criteria for confirming that the drug is not reacting with the polymers and excipients under experimental conditions and does not affect the shelf life of a product or any other unwanted effects on the formulation. The physical mixture of drug & polymers are used for the determination of Infrared spectrums [5, 10-14].

Preparation of Controlled-release floating matrix tablets of Metoprolol Tartrate (MT) by Direct Compression Method.

The controlled release floating matrix tablets of Metoprolol Tartrate is prepared by direct compression method. The formulation of each controlled release floating matrix tablets of Metoprolol Tartrate is composed of two selected polymers i.e. HPC and HPMC K4 M in alone or in combination with ethyl cellulose. The other excipients are sodium bicarbonate as a gas-generating agent, Avicel PH 102 for its diluent property, Aerosil, and talc. The weight of a tablet is adjusted to 250 mg and each tablet contained 50 mg of Metoprolol Tartrate.

All powders are passed through sieve no.20 separately. Mixing of powders is carried out using a pestle and mortar for 10 min. Aerosil and Talc are then added to the mixed powders. Mixing continued for another 3min. Finally, 250 mg of each mixture were weighed and fed manually into the die of a single punch tablet machine, equipped with 8mm concave punches to produce the desired tablets. The hardness of the tablets may be adjusted at 6-6.5 kg/cm2 using a Monsanto hardness tester. The compressed tablets of each formulation, then evaluated for tablet characteristics such as thickness, hardness, weight variation, friability, and drug content. [15-18]

RESULTS AND DISCUSSION

Micromeritics characterization of the drug:

The Micromeritics characterization of Metoprolol Tartrate was carried out and the following observations were made as given in **table no. 2** below

Table No. 2: Micromeritics characterization ofMetoprolol Tartrate

Sr.No.	Parameters	Result
1	Loose bulk density	0.37±0.02g/cm^3
2	Tapped density	0.55±0.02g/cm^3
3	Carr's Index	32.72±0.03%
4	Hausner's ratio	1.48
5	Angle of Repose	30

Evaluation of prepared Powder mixtures:

All the formulation powder mixtures were evaluated for pre-compression parameters such as Angle of the repose, Loose Bulk Density, Tapped Bulk Density, Carr's Index and Hausner's Ratio and results obtained are shown in table 3.

Table No. 3: Evaluation of physical properties of powder mixtures

Formulation	Loose bulk density (g/cm^3)	Tapped bulk density (g/cm^3)	Carr's index (%)	Hausner ratio (H_R)	Angle of repose (θ)
F1	0.48±0.02	0.53±0.11	9.83±1.1	1.10±0.07	33±1.1
F2	0.46±0.14	0.50±0.07	7.31±1.3	1.07±0.01	29±1.3
F3	0.48±0.17	0.51±0.09	6.40±1.2	1.06±0.02	30±1.3
F4	0.47±0.15	0.53±0.14	11.27±1.2	1.12±0.05	29±1.3
F5	0.46±0.09	0.52±0.17	11.74±1.4	1.13±0.09	32±1.1
F6	0.43±0.08	0.49±0.05	12.85±1.1	1.14±0.09	32±1.4
F7	0.44±0.13	0.50±0.08	12.79±1.3	1.14±0.02	31±1.6
F8	0.41±0.09	0.46±0.12	10.38±1.3	1.11±0.03	32±1.4
F9	0.48±0.07	0.52±0.19	6.51±1.4	1.06±0.04	29±1.1
F10	0.45±0.11	0.49±0.03	8.08±1.3	1.08±0.04	30±1.5

The data is presented as (n = 3) mean value ± S.D.

The angle of repose:

The results of the angle of repose of all the formulations were found to be in the range of 29±1.1 to 33±1.1, indicating good flow property and this was further supported by lower compressibility index values. Thus it can be concluded that the powder mixtures for all the batches possessed good flow characteristics.

Bulk Density:

It has been stated that the bulk density values less than 1.2 g/cm^3 indicate good packing & values greater than 1.5 g/cm^3 indicate poor packing. The loose bulk density and tapped bulk density values for all the formulation varied in the range of 0.41±0.09 g/cm^3 to 0.48±0.07 g/cm^3 and 0.46±0.12 g/cm^3 to 0.53±0.11 g/cm^3 respectively. The values obtained lies within the acceptable range. These results may further influence property such as compressibility and tablet dissolution.

Hausner's Ratio:

Hausner's ratio was found to be in the range of 1.06±0.02 to 1.14±0.09, which shows acceptable flow property and good packing ability.

Evaluation of Controlled Release Floating tablet of Metoprolol Tartrate:

Table No. 4: Standard Physical Tests for floating Matrix Tablets:

Formulation	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight Variation (mg)
F1	4.4±0.3	6.0±0.6	0.44±0.1	251.06±2.2
F2	4.3±0.2	6.4±0.5	0.45±0.1	251.15±2.4
F3	4.2±0.3	6.5±0.2	0.43±0.2	250.50±2.1
F4	4.3±0.4	6.3±0.4	0.44±0.5	249.24±1.9
F5	4.4±0.2	6.0±0.5	0.43±0.4	249.36±2.7
F6	4.3±0.1	6.0±0.5	0.42±0.3	248.19±2.9
F7	4.4±0.2	6.3±0.2	0.42±0.5	248.53±2.1
F8	4.3±0.4	6.5±0.6	0.45±0.1	249.08±2.5
F9	4.2±0.3	6.0±0.4	0.41±0.2	248.53±1.9
F10	4.4±0.2	6.2±0.4	0.45±0.5	248.00±2.6

The data is presented as (n = 3) mean value ± S.D.

Uniformity of content

The drug content was found to be uniform among all formulation and ranged from 96.00±1.3 to 99.10±1.2. as shown in table no. 5

Table No. 5: Uniformity of content

Formulation	Uniformity of content (%)	Formulation	Uniformity of content (%)
F1	98.06±1.4	**F6**	98.30±1.5
F2	99.10±1.2	**F7**	99.10±1.5
F3	96.00±1.3	**F8**	97.70±1.3
F4	97.00±1.3	**F9**	98.34±1.1
F5	98.00±1.4	**F10**	98.04±1.2

The data is presented as (n = 3) mean value ± S.D.

Floating Lag Time

Table No. 6: Floating lag time and Buoyancy duration

Formulation	Floating lag time (sec)	Buoyancy duration (hrs)
F1	272±1.3	>4
F2	160±1.7	>6
F3	93±1.6	>7
F4	67±2.5	>8
F5	55±2.2	>9
F6	71±2.1	>7
F7	22±2.5	>8
F8	21±2.6	>9
F9	16±2.8	>12
F10	12±1.9	>12

The data is presented as (n = 3) mean value ± S.D.

% Swelling study

Table No. 7: % swelling data of floating matrix tablet

Batch	Time (hrs)			
	3	6	9	12
	% Swelling			
F1	16±5	25±5	22±3	18±5
F2	23±4	35±3	32±2	26±5
F3	27±3.5	43±4	36±4	31±2
F4	33±3	49±2.5	44±2.2	36±4
F5	41±1	70±5	57±2.3	51±4.1
F6	39±2.6	75±3.9	62±4.3	57±2
F7	49±3.1	74±4.5	65±1.8	59±3.6
F8	50±4.1	78±2.2	71±1.7	62±4.6
F9	53±2.9	81±4.2	74±4.2	67±5.1
F10	64±3	92±2.5	85±3	78±3.6

The data is presented as (n = 3) mean value ± S.D.

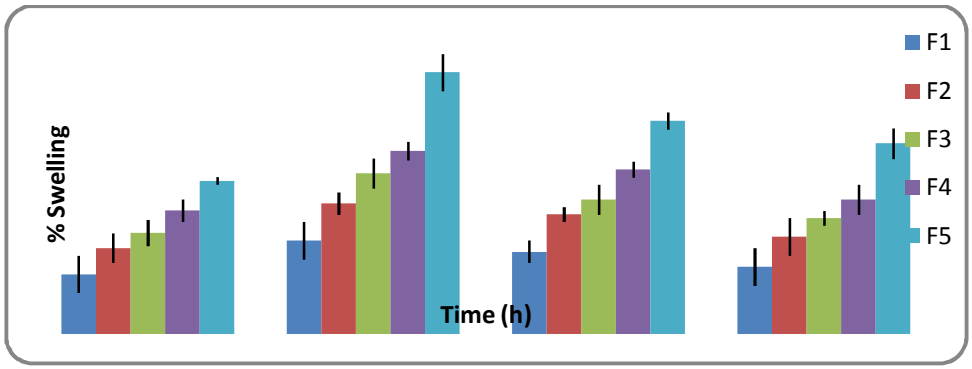

Fig. 3: % Swelling of Hydroxypropyl cellulose polymer offormulation F1-F5

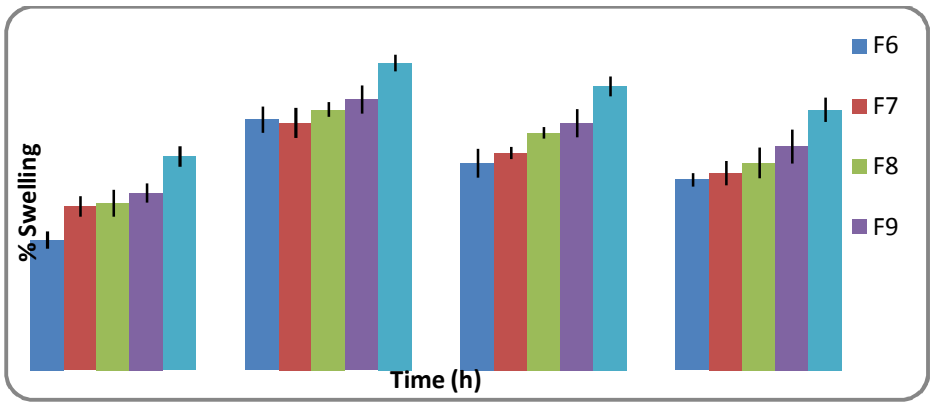

Fig. 4: % Swelling of HPMC K4M polymer of formulation F6-F10

CONCLUSION

Metoprolol Tartrate is a selective-adrenoreceptor β1 blocking agent used in the treatment of various cardiovascular disorders and the prophylaxis of migraines. The drug is readily and completely absorbed throughout the intestinal tract but it is degraded inthe colon and subject to extensive first-pass metabolism resulting incomplete bioavailability (about 30%). The present work showed that promising controlled-release floating matrix tablets of Metoprolol Tartrate were successfully formulated by effervescent technique. Tablets containing HPMC K4M (20.00%, w/w), Ethylcellulose (8.0%, w/w) andNaHCO3 (10%, w/w) (formula F9)showed satisfactory results concerning floating lag time, total floating duration, swelling ability, and controlled drug release rates. The concentration and viscosity of the polymer showed a directly proportional relationship with the swelling characteristics of the tablet. As the viscosity and concentration of polymers increased, the release rate of the drug was retarded. As the concentration of ethyl cellulose increases, the percent drug release rate and floating lag time decrease. So it is concluded that ethylcellulose can act as a floating enhancer.

CONFLICT OF INTEREST

Authors having no conflict of interest.

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