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Formulation and Evaluation of Metaprolol Succinate Floating Matrix Tablets

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Abstract

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. Metoprolol is a beta$_1$-selective (cardioselective) adrenergic receptor blocking agent. This preferential effect is not absolute, however, and at higher plasma concentrations, metoprolol also inhibits beta2-adrenoreceptors, chiefly located in the bronchial and vascular musculature. In this investigation metaprolol succinate floating tablets were prepared by using different grades of HPMC Polymers and xanthum gum by direct compression method. The tablets were evaluated for Precompression and post compression parameters indicating that the formulations made considered being satisfactory. *In vitro* drug release profiles for all formulations were carried out by using 0.1 n Hcl buffer as dissolution medium for about 12 hrs. From the results it was found that the release of drug from f4 formulation (HPMC k 100M as polymer) gave the better release than other formulations.

Keywords: metaprolol succinate, HPMC K100M, floating drug delivery

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1. Introduction

The oral route is considered as the most promising route of drug delivery. Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs. Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach. This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine, as once

the drug passes down the absorption site, the remaining quantity goes unabsorbed. The gastric emptying of dosage forms in humans is affected by several factors because of which wide inter- and intra-subject variations are observed [**4]**. Since many drugs are well absorbed in the upper part of the gastrointestinal tract, such high variability may lead to non-uniform absorption and makes the bioavailability unpredictable. Hence a beneficial delivery system would be one which possesses the ability to control and prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site (i.e. upper part of the small intestine). The identification of new diseases and the resistance shown towards the existing drugs called for the introduction of new therapeutic molecules. In response, a large number of chemical entities have been introduced, of which some have absorption all over the gastrointestinal tract (GIT), some have absorption windows (i.e. absorption sites, especially the upper part of the small intestine) and some drugs have poor solubility in intestinal media. The drugs belonging to the second and third categories, and the drugs which are required for local action in the stomach, require a specialized delivery system.

In recent years scientific and technological advancements have been made in the research and development of controlled release oral drug delivery systems by overcoming physiological adversities like short gastric residence time and unpredictable gastric emptying time. To date, their usefulness is limited to systemic administration. So, to minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development.The goal of many of the original controlled-release systems was to achieve a delivery profile that would yield a high blood level of the drug over a long period of time. With traditional tablets or injections, the drug level in the blood follows the profile shown in Fig 3(a), in which the level rises after each administration of the drug and then decreases until the next administration. The key point with traditional drug administration is that the blood level of the agent should remain between a maximum value, which may represent a toxic level, and minimum values, below which the drug is no longer effective. In controlled drug delivery systems designed for long-term administration, the drug level in the blood follows the profile shown in Fig 3(b), remaining constant, between the desired maximum and minimum, for an extended period of time [**5].**

2. Materials and Method

2.1 Materials

Metaprolol Succinate was obtained as a gift sample from Hitech pharma, Hyderabad. HPMC of different grades, xanthum gum, magnesium state and talc were supplied by Hitech pharma, Hyderabad.

2.2 Construction of calibration curve of Metaprolol succinate drug in 0.1N HCL:

Procedure:

Working standard: **Preperation of calibraion curve for Metaprolol succinate in 0.1N Hcl**

10 mg of Metaprolol succinate was dissolved in 10 ml of**0.**1N Hcl buffer by slight shaking (1000 mcg/ml). 1 ml of this solution was taken and made up to 10 ml with 0.1N Hcl buffer, which gives 100 mcg/ml . 1 ml of the resulting solution was taken and made up to 10 ml with 0.1N Hcl buffer, which gives 10 mcg/ml, Which gives the stock solutionFrom the stock solution, concentrations of 10, 15, 20,25, and 30 µg/ml in **0.**1N Hcl buffer were prepared. The absorbances of these solutions were measured at 222 nm and standard plot was drawn using the data obtained.

2.3 Formulation of gastro retentive floating tablets by direct compression

Processing steps involved in Direct Compression:

The matrix tablets were prepared by following the General Methodology as given below:

All ingredients were weighed accurately and co sifted by passing through #30 sieve, blended in a Poly Bag for 5 min. The above granules were lubricated with # 60 Sieve passed Magnesium stearate & talc. The final blend was then compressed into tablets using 16 station tablet compression machine with an average hardness of 4.0KP, by using 9mm die.

2.4. Evaluation Of Tablets

The formulated tablets were evaluated for the following Pre, post compression quality control studies & In vitro Buoyancy studies and dissolution studies

Evaluation of blends[61]

The powder blend was evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose.

1. Bulk density (D_b): It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and the initial volume was noted. This initial volume is called the bulk volume. From this, the bulk density is calculated according to the formula mentioned below. It expressed in g/cc and is given by:

$D_b =$ Where, M is the mass of powder, V_0 is the bulk volume of the powder

2. Tapped density (D_t): It is the ratio of total mass of powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. Then the tapping was done for 750 times and the tapped volume

was noted (the difference between these two volumes should be less than 2 %). If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. It is expressed in g/cc and is given by:

$D_t =$ Where, M is the mass of powder, V_t is the tapped volume of the powder

3. Carr's index (%): The bulk density is the measurement of weight to the volume of the sample. Tapped density is determined as the measurement of weight of the sample to the volume after tapping the measuring cylinder for 500 times from a height of 2 inches. The percentage compressibility (Carr's index) was calculated as 100 times the ratio of the difference between tapped density and bulk density to the tapped density.

Carr's index =T.D – B.D/T.D*100

4. Hausner's ratio: Hausner's ratio is the ratio of tapped density to bulk density. Lower the value of Hausner's ratio better is the flow property. The powder with Hausner's ratio less than 1.18, 1.19-1.25, 1.3-1.5 and greater than 1.5 indicates excellent, good, passable and very poor flow properties, respectively.

Hausner's Ratio = T.D/B.D

5. Angle of repose ( ): It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane.

Tan θ = $\tan^{-1}$ (h/r)

Where, **θ** is the angle of repose h is the height in cms; r is the radius in cms

Method: The powder mixture was allowed to flow through the funnel with its tip fixed to stand at a definite height (h) from a graph paper placed on a horizontal surface. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. A value for angle of repose 40^0 suggests a poorly flowing material.

2.4.1 Evaluation of tablets (post compression characteristics)

Weight Variation

The USP weight variation test was run by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weights to the average. The tablets met the USP tests that were no more than 2 tablets were outside the percentage limit and no tablets differed by more than 2 times the percentage limit.

Hardness

Hardness of the tablets was determined by breaking it between the second and third fingers with thumb being as a fulcrum. There was a sharp snap the tablet was deemed to have acceptable strength.

Hardness of the tablets are also determined by Stokes Monsanto Hardness Tester and the hardness should be found within the range of 3.5-5.5 kg/cm².

Friability

The friability of tablets are determined by Roche Friablator. 20 tablets were taken and weighed . After weighing the tablets were placed in the Roche friabilator and subjected to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25RPM for minutes dropping the from a distance of six inches with each revolution .after operation the tablets were dedusted and reweighed .

Friability is determined by

F=100(1-Wo/Wt)

Where,

Wo= wt. of tablets before friability test.

Wt= wt. of tablets after friability test.

Content Uniformity

Five tablets were weighed and powdered, 10 mg of equivalent of Metaprolol succinate was weighed and dissolved in suitable quantity of methanol, the solution was filtered suitably diluted and the drug content was analyzed using UV spectrometer at 222nm.

In vitro buoyancy properties:

The buoyancy of the tablet was determined as per method described previously [13]. The tablets (n = 3) were placed in a 100 ml beaker containing 0.1 M HCl. The time taken for tablet to emerge on surface of medium and the duration it remained on the surface of the medium is floating lag time and total floating time respectively.

In- vitro Dissolution studies of metaprolol succinate sustained released tablets.

Apparatus II (Paddle Method)

The same equipment as in apparatus I was used, expected that a paddle replaced the basket, formed from a blade and a shaft as a stirring element. The dosage form was allowed to sink to the bottom of the flask before stirring. A constant temperature of 37±0.5 ºC was maintained. The motor was adjusted to turn at the specified speed of 50rpm, and the samples of the fluid were withdrawn at intervals to determine the amount of drug in solution.

Dissolution of metaprolol succinate sustained release tablets.

The dissolution test was carried out using USP apparatus II. Stirring speed was maintained at 50rpm. 0.1N Hcl was used as dissolution medium (900ml) and was maintained at 37±0.5 for 1 2 hrs and Samples of specified volume

were withdrawn at predetermined time intervals, filtered, dilute suitably and assayed spectrophotometrically. An equal volume of fresh medium was immediately replaced to maintain the dissolution volume. The sample were analyzed spectrophotometrically at 222 nm. Using spectrophotometer to assay the amount of Metaprolol succinate released at each time interval.

2.4.2 Evaluation parameters: (Discussion)

The λ max of Metaprolol succinatein 0.1N HCL buffer was scanned and found to have the maximum absorbance at 222 nm. Standard graph of Metaprolol succinatein 0.1N HCL buffer was plotted. The angle of repose values obtained for the formulations ranged from 22.62 to 29.19 This indicates good flow property of the powder blend. The compressibility index values for the formulations ranged from 12.72 to 21.8. This indicates the powder blend have good flow property. The total weight of each formulation was not maintained uniformly however the weight variation of the tablets within the limits of 5%. The measured hardness of tablets in all batches was ranged from 4.5 – 4.7 kg/cm^2. Friability values were found to be less than1% in all prepared formulations and considered to be satisfactory. *In vitro* drug release profiles for all formulations were carried out by using 0.1 n hcl buffer as dissolution medium for about 12 hrs. From the above results it was found that the release of drug from f4 formulation (HPMC k 100M as polymer) gave the better release than other formulations.

3. Results and Discussion

Table 1: Preparation of different batches of floating matrix tablets of Metaprolol succinate

Formulation code/ingredients	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)	F6(mg)
Metaprolol succinate	50	50	50	50	50	50
HPMCK 15M	-	35	-	-	-	-
HPMC K 100M	-	-	-	35	-	-
PEO WSR 303	35	-	-	-	-	-
HPMC K 200M	-	-	35	-	-	-
HPMC K4M	-	-	-	-	35	-
XANTHUM GUM	-	-	-	-	-	35
Microcrystalline cellulose	80	80	80	80	80	80
Sodium bicarbonate	30	30	30	30	30	30
Magnesium stearate	2	2	2	2	2	2
Talc	3	3	3	3	3	3
Total	200	200	200	200	200	200

Weight Variation Tolerance for Uncoated Tablets

Table 2: Weight variation tolerances for uncoated tablets

S.No	average weight of tablets (mg)	Maximum Percentage Difference Allowed
1	130 or less	10
2	130 to 324	7.5
3	More than 324	5

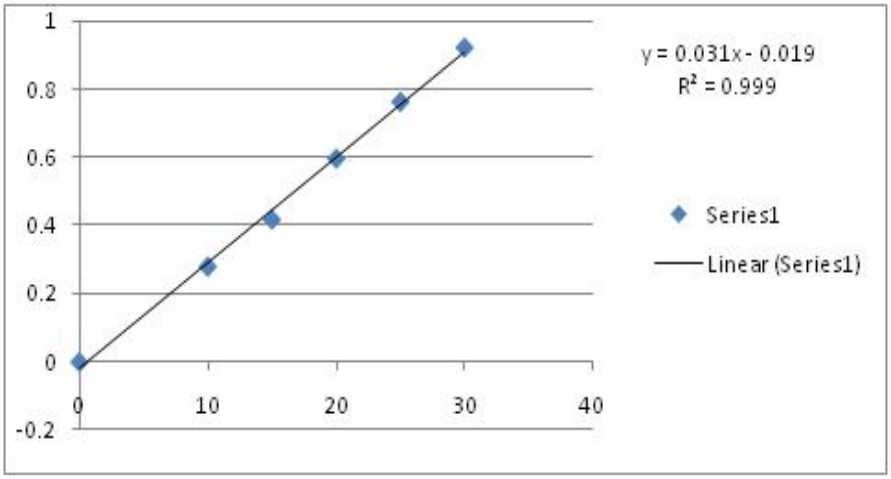

Figure 1: Calibration curve of Metaprolol succinatein 0.1N Hcl

Calibration curve of metaprolol succinate (API):

Table 3: Calibration curve of metaprolol succinate (API)

S.No	Concentration (µg/ml)	Absorbance (λ_{max} =222nm)
1.	10	0.280
2.	15	0.418
3.	20	0.597
4.	25	0.763
5.	30	0.922

Preformulation Charecteristics of Blend

Table4: Preformulation Charecteristics of Blend

Formulation code/Parameter	Bulk density	Tapped density	Angle of repose	Compressibility index	Hausners ratio
F1	0.462	0.591	26.06	21.8	1.25
F2	0.469	0.561	25.42	21.39	1.19
F3	0.46	0.55	22.62	16.36	1.19
F4	0.59	0.68	29.19	13.04	1.15
F5	0.49	0.57	27.40	14.04	1.16
F6	0.48	0.55	26.06	12.72	1.14

Post Formulation Stusies: (Compression Parameters)

Table 5: Postformulation Charecteristics of Tablets

Formulation code/Parameter	Hardness	Weight variation	Friability	Content uniformity	Floating lag time	Total floating time
F1	4.5	Pass	0.23	99.65	5 sec	4 hrs
F2	4.7	Pass	0.54	99.34	10 sec	12 hrs
F3	4.6	Pass	0.61	98.34	8 sec	12 hrs
F4	4.7	Pass	0.27	99.21	20sec	12 hrs
F5	4.6	Pass	0.12	100.34	18 sec	12 hrs
F6	4.6	Pass	0.51	99.96	3 min	2 hrs

Dissolution Profile of Formulations

Table 6: Dissolution Studies of Tablets

Formulation code/ Parameter	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)
0.5hr	29.6	19.23	12.78	14.11	24.8	6.09
1 hr	44.68	27.5	18.99	21.47	28.76	58.91
2 hr	67.5	36.9	24.84	32.68	39.67	61.5
3 hr	93.46	52.76	36.48	43.71	54.15	78.14
4 hr	97.68	68.14	54.15	61.5	71.75	92.86
6 hr	100.10	85.62	67.53	78.99	91.05	97.08
8 hr	-	94.07	82.01	89.84	100.10	-
10 hr	-	98.29	89.24	95.87	-	-
12 hr	-		94.67	99.49	-	-

4. Conclusion

In conclusion, HPMC K100M can be successfully employed in the preparation of controlled release floating tablets of Metaprolol succinate. The formulations were prepared and succeeded with gas generating agent. Combination of polymers can be successfully employed for better results. The research study provided useful information for the formulation scientists working on formulation, characterization during development of controlled drug delivery systems of Metaprolol succinate using these polymers.

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