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GASTRO - RETENTIVE FLOATING TABLETS OF AN ANTI- HYPERTENSIVE DRUG

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ABSTRACT

The aim of present study was to explore feasibility of polymer in acquiring the drug release profile, floating drug delivery system of Metoprolol Succinate for treatment of hypertension. The drug excipints compatibility study was done by using IR the characteristics Peaks of Metoprolol Succinate with polymers & other excipients was identified. The pre-formulation study of raw material and powder blend were carried out and drug and all excipient showed optimum result. The Tablet of Metoprolol Succinate was prepared by using various synthetic with varying Concentration, evaluated for necessary parameters including Weight variation, friability, Hardness & drug content. It was observed that the results were in considerably good range. The percentage swelling index of all formulation was determined and it was observed that combination batches of polymer showed better swelling than single polymer formulation. The In-vitro drug release study was carried out in dissolution medium PH 6.8 Phosphate Buffer, the percentage drug release obtained in formulation S1,S2,S3 are decreased while in formulation S4 is increased in which concentration of Sodium Alginate to HPMC K100 is 1:2 ratio. The drug release of polymer combined formulation showed synergistically better result than formulation with single polymer. The combination in 1:2 ratio showed better release profile.

KEYWORDS: Feasibility, friability, swelling index, synergistic, Metoprolol Succinate.

INTRODUCTION

Floating system or dynamically controlled systems are low density system that have sufficiently buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. This results in an increased gastric retention time and a better control of the fluctuations in plasma drug concentration. Many buoyant system have been developed based on granules, capsules, tablets, laminated films, and hallow microspheres.

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. After release of drug, the residual system is emptied from the stomach. Floatation of a drug delivery system in the stomach can be achieved by incorporating floating chamber filled with vacuum, air, or inert gas.

MATERIALS AND METHODS

1. Spectral analysis of metoprolol succinate

1.1 Determination of λ max (Metoprolol succinate)

50 mg of Metoprolol Succinate was dissolved in 50ml of PH 6.8 phosphate buffer. Further diluted with the same and the wavelength was determined by using UV-visible double beam Spectrophotometer (UV- 1601 SHIMADZU) in the range of 200-400 nm.

1.2 Standard calibration curve of metoprolol succinate

1.2.1 Preparation of standard calibration curve in 6.8 phosphate buffer:

Accurately weighted 50 mg of Metoprolol Succinate was added in 50 ml of 6.8 phosphate buffer (Stock solution-I). 1ml of above stock solution was diluted up to 100 ml with 6.8 phosphate buffer to make the stock solution-II of concentration 10µg/ml. further serial dilutions (10-60µg/ml) were carried out with 6.8 phosphate buffer. The absorbance of the various concentration were measured against 6.8 phosphate buffer as a blank at 200-400 nm using double beam UV visible spectrophotometer.

2. Formulation and Preparation of floating tablet

The tablets were prepared by Direct Compression technique using 8 mm punch. The tablets of different concentration were prepared. The entire ingredients were mixed and punch in single punch machine (Cadmach). Each tablet containing 50mg of Metoprolol Succinate, polymer, sodium bicarbonate, citric acid and ingredient are listed in table no.1

3. Evaluation of floating tablets

In present study the Floating-tablet of Metoprolol succinate tablet was prepared using different concentrations of synthetic polymers, used alone and in combinations with each other in different concentrations. The tablets were prepared by direct compression, using 8 mm punch. All batches were found good in appearance.

3.1 Tablet dimension

Thickness of floating tablet ranged from 5.3 ±0.251 to 5.88±0.296 and diameter of all the tablets was found to be 6.1±0.00 mm. The thickness of the tablet is determined by the diameter of the die, the amount of fill permitted to enter the die, the compaction characteristic of the fill material and the force applied during compression.

3.2 Hardness

Formulation should be directed at Metoprolol succinate mini tablet hardness without applying excessive pressure. Hardness of the tablet was found to be 5.0 ±0.09 to 5.4 ± 0.08 kg/cm^2.

3.3 Weight variation test

All the formulation passes weight variation test. Tablets were obtained in the range with acceptable weight variation as per Pharmacopoeial specifications, less than 7.5%. Tablets were obtained of uniform weight due to uniform die fill. Weighed of all the tablets were found to be in the range of 500±0.00 to 500.6 ±0.00.

3.4 Friability

All the formulations passes friability test. Tablets were obtained in the range of acceptable friability as per pharmacopoeial specification, less than 1%. Friability below 1% is an indication of good mechanical resistance of the tablets. This ensures that tablets could withstand to the pressure, shock during handling, transportation and manufacturing processes. Friability of all tablets was found to be in the range of % 0.37 to 0.69%. 3

3.5 Drug content uniformity

Drug content uniformity is important in order to get the desired efficacy, release and bioavailability of the drug from the tablet. It was found to be within the range of 91.33 to 98.69 %.

3.5.1 In-Vitro buoyancy study

The in-vitro buoyancy study were performed by determined total floating time and floating lag time in PH6.8 phosphate buffer solution. The time required for the tablet to rise to the surface and floatwas determined as float lag time.

3.6 Swelling index

The extent of swelling was measured in terms of percentage weight gain by the tablets. The swelling behavior of the formulation was studied .One tablet from each batch was kept in petry dish containing PH 6.8phosphate buffer. At the end of 1,4,8 and 12 hr tablets were withdrawn , soaked on tissue paper and weighed, and then percentage weight gain by the tablet was calculated using formula.

$$\mathbf{SI}=\frac{Mt-Mo}{Mo}\times 100$$

Where, SI = Swelling index
Mt = Weight of tablet at time ' t'
M_0 = Weight of tablet at time '0'

3.7 Total floating time

Floating time of was determined before coating and after coating of tablet. Floating lag time and total floating time was determined as per method described Rosa et al. Tablets were placed in a 100ml beaker containing PH6.8 phosphate buffer. The time required for the tablet to raise the surface and float was determined as floating lag time. The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time.

3.8 In-vitro dissolution study

The in-vitro dissolution studies were carried out using USP dissolution test apparatus II at 50 rpm. The dissolution medium was pH 6.8 phosphate buffer (900 ml) 37±0.5°C, for 1 hours. The dissolution medium was replaced with pH 6.8 phosphate buffer (900ml) and Test sample (1ml) was withdrawn at particular time interval and replaced with fresh dissolution media maintained at the same temperature and the concentration of dissolved drug was determined using U.V. spectrophotometer at λ max 244 nm for Metoprolol succinate.

RESULT AND DISCUSSION

The present study was carried out to prepare Metoprolol Succinate Gastroretentive floating tablet that can used as an antihypertensive drug. The floating drug delivery systems of Metoprolol Succinate were prepared by using polymer such as Sodium alginate, HPMC K100 M, Microcrystalline cellulose, Carbopol934. Different drug to polymer ratios along with a gas generating agent, sodium bicarbonate and citric acid were used in the formulation.

The characterization parameters including solubility, melting point were determind, results obtained showed that Solubility of MS was freely soluble in water. The IR compatability study was carried for single and combination formulation, all the characterstics picks were intact in all the formulations.

The formulation were evaluated for preformulation properties such as angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio, flowability. It was found that all formulations had good flowability which indicated its suitability for direct compression.

The prepared floating tablets were evaluated for hardness, friability, uniformity of weight, uniformity of drug content, swelling index, floating lag time, in-vitro dissolution, short term stability and drug polymer interaction.

The hardness of prepared floating tablets of MS was found to be in range of 5 to 5.4Kg/cm^2. The friability of all the tabletswas less than 1% i.e. in the range of 0.37 to 0.69% . The percentage deviation from the mean weights of all the batches was prepared. Floating tablets were found to be within the prescribed limits as per IP. The low value of standard deviation indicates uniform drug content in all the batches prepared as observed from the data given in table.

The swelling index of the tablets increases with an increase in the polymer content,as can be seen from the data given in table.

In- Vitro floating studies were performed by placing tablets in USP XXIII dissolution apparatus II containing 900ml of PH 6.8 phosphate buffer maintained at tempreture of 37+ 0.5^{0}C. The floating time and floating lag time was noted visually. The results are given in table. For all formulation, lag time is in the range of 40sec. to 69 sec. For the formulation S2 it is lowest as the drug polymer having HPMC K100, MCC, Carbopol 934 while formulation S4, lag time is highest 69 Sec. as drug-polymer having HPMC K100, Sodium alginate, MCC& Carbopol 934. Most of the designed formulation have displayed a floating time of more than 16 hours.

In Vitro drug release study was performed using USPXXIII dissolution test apparatus –II at 50 rpm using 900 ml of PH 6.8 Phosphate Buffer maintained at 37± 0.5^{0}C as the dissolution medium .The result were shown in table, from the above data, it is evident that as the Proportion of polymer in the formulation increases.

Drug release kinetics

In-vitro drug release data of all the floating tablet formulations was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetics equations, Hixson Crowell, and Matrix and Korsmeyer-Peppas models to ascertain the mechanism of drug release. The F4 formulation follows the korsmeyer-peppas model equation, is best fit mode.

Table No. 1: Composition of floating tablet.

Ingredients (mg)	S1	S2	S3	S4	S5	S6
Metoprolol Succinate	50	50	50	50	50	50
HPMC K 100M	100	150	200	100	150	200
Sodium Alginate	-	-	-	50	50	50
Microcrystalline Cellulose	242.5	192.5	142.5	192.5	142.5	92.5
Carbopol 934p	35	35	35	35	35	35
Sodium Bicarbonate	50	50	50	50	50	50
Citric Acid	10	10	10	10	10	10
Magnesium stearate	5	5	5	5	5	5
Talc	7.5	7.5	7.5	7.5	7.5	7.5
Total wt of tablet	500	500	500	500	500	500

Table No. 2: Standard absorbance of Metoprolol Succinate in 6.8 Phosphate buffer.

Sr. No	Concentration (µg/ml)	Absorbance
1	0	0
2	5	0.172
3	10	0.328
4	15	0.476
5	20	0.662
6	25	0.791
7	30	0.969

Correlation coefficient (R)=0.999
Equation of regressed line; y=0.032x+0.005
Slope of regressed line =0.032

Table No. 3: Evaluation of floating tablet.

Formulations	Hardness ±SD (kg/cm$^{2)}$	Thikness ±SD (mm)	Weight variation ±SD (mg)
S1	5.2±0.05	5.67±0.10	502±0.134
S2	5.3±0.12	5.52±0.168	500±0.098
S3	5.4±0.08	5.3±0.251	500±0.00
S4	5.1±0.11	5.88±0.296	501±0.125
S5	5.0±0.13	5.59±0.59	500±0.00
S6	5.0±0.09	5.33±0141	506±0.00

Table No. 4: Evaluation test of Floating-tablet.

Formulation	Friability (%)	Drug content (%)
S1	0.55	93.57
S2	0.58	92.14
S3	0.69	98.69
S4	0.46	96.27
S5	0.37	91.33
S6	0.42	95.20

Table No. 5: Evaluation test of Floating-tablet.

Formulation	Floating Lag Time +	Total Floating Time(hrs)
S1	50+10	>10
S2	40+8.6	>8
S3	63+7.5	>15
S4	69+1.52	>16
S5	61+1.15	>18
S6	59+10.06	>15

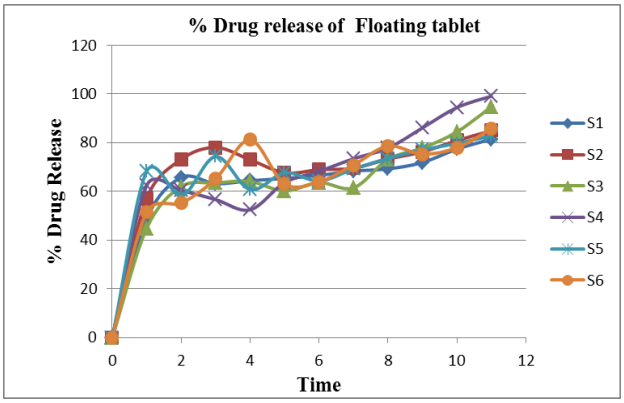
Table no. 6: Swelling index of floating tablet.

Formulations	Swelling Index (%) Time (hr)			
	1	2	3	4
S1	09	22	68	102
S2	10	28	71	105
S3	15	34	83	109
S4	16	26	57	137
S5	08	20	63	121
S6	11	23	66	126

In vitro drug release of floating tablet

Table No. 7: % Drug release for Floating-tablet.

Time (Hr)	S1	S2	S3	S4	S5	S6
2	48.89	57.14	44.86	62.50	68.22	51.40
3	65.71	73.12	61.97	60.30	58.07	55.16
4	64.43	73.01	64.09	52.47	60.77	81.15
5	63.22	78.04	63.46	56.67	74.34	65.16
6	65.35	67.69	60.19	63.61	67.66	63.05
7	66.56	68.90	63.66	68.23	64.33	63.97
8	68.34	69.54	61.46	73.42	69.23	70.87
9	69.27	73.31	73.18	77.76	73.57	78.62
10	71.90	76.24	77.81	86.09	77.06	75.30
11	77.38	80.87	84.43	94.43	79.70	77.94
12	81.45	84.94	94.76	99.08	82.92	85.70



SUMMARY AND CONCLUSION

The aim of present study was to explore feasibility of polymer in acquiring the drug release profile, floating drug delivery system of Metoprolol Succinate for treatment of hypertension.

The result of present investigations obtained from the study of "Formulation & Evalution of Floating Drug Delivery System of an Antihypertensive Drug." Disclose Following Conclusion.

The Characterisation of Metoprolol Succinate was done in 6.8 phosphate buffer has better Solubility.

The drug excipints compatibility study was done by using IR the characteristics Peaks of Metoprolol Succinate with polymers & other excipients was identified.

The preliminary Evaluation was done. The Wavelenth was found to be at 224nm, the calibration curve was plotted in 6.8 phosphate buffer with r^2 value 0.99

The pre-formulation study of raw material and powder blend were carried out and drug and all excipients showed optimum result.

The Tablet of Metoprolol Succinate was prepared by using various synthetic with varying Concentration, evaluated for necessary parameters including Weight variation, friability, Hardness & drug content. It was observed that the results were in considerably good range.

The buoyancy study was carried out and it was observed that all batches showed floating time more than 16hours and floating lag time was found in between 40 to 69sec.

The percentage swelling index of all formulation was determined and it was observed that combination batches of polymer showed better swelling than single polymer formulation.

The In-vitro drug release study was carried out in dissolution medium PH 6.8 Phosphate Buffer, the percentage drug release obtained in formulation S1,S2,S3 are decreased while in formulation S4 is increased in which concentration of Sodium Alginate to HPMC K100 is 1:2 ratio. The drug release of polymer combined formulation showed synergistically better result than formulation with single polymer. The combination in 1:2 ratio showed better release profile.

The drug kinetic study was carried out, most of the formulation best fited with korsmeyer-peppas model while few formulation showed different type of drug release kinetics and S4 formulation shows best model. So there is increase in floating with 1: 2 ratio of polymers.

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