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DESIGN AND EVALUTION MATRIX GASTRO RETENTIVE TABLETS OF BISOPROLOL

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ABSTRCT

The purpose of the present work was to develop an optimized floating tablet for Anti hypertensive drug. Bisoprolol was formulated as a floating layer using hydrophilic swellable polymer like HPMC K4M, HPMC K100M, sodium bicarbonate as a gas generating agent. Preformulation studies were carried out to optimize the ratios required for various grades of HPMC. Drug excipient interaction studies performed using techniques FTIR studies. Prepared floating tablets were subjected to various evaluation parameters like floating lag time, total floating duration, swelling index, in vitro drug release studies. The M3 formulation showed 99.67% drug release in 12 hours with floating lag time of 42 seconds maintain matrix integrity for 15 hours.

The M3 formulation were selected as optimized floating tablet which is further investigated for stability studies. The study revealed that the optimized floating tablet found to be stable for 1 month at 25^0C /75% RH. Hence, the present research work was to study systematically the effect of formulation variables on the release and floating properties of the drug.

Key words: Bisoprolol, sustained, matrix ,dissolution , floating, gastoretentive

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INTRODUCTION

Hypertension or high blood pressure is a condition in which the blood pressure in the arteries is chronically elevated. (1,2) Blood pressure is the force of blood that is pushing up against the walls of the blood vessels. If the pressure is too high, the heart has to work harder to pump, and this could lead to organ damage and several illnesses such as heart attack, stroke, heart failure, aneurysm, or renal failure. The definition (WHO, 1996) of hypertension is level of systolic blood pressure of 140 mm Hg or above, a level of diastolic pressure of 90 mm Hg. (3,4)

Bisoprolol is an anti h6ypertensive drug having short half life of 3-5 hrs with 38% of poor oral bioavailability So it needs gastro-retention to improve bioavailability and to avoid the fluctuations in the plasma drug levels these systems are been developed. In order to achieve patient compliance by controlling blood pressure for extended duration of time a floating tablet was suggested.

Bisoprolol is used in the treatment of hypertension and stable angina pectoris. Bisoprolol is selected as a model drug for this investigation because its absorption in stomach has short biological half-life(2-4hrs) and poor bioavailability(50-60%) due to extensive hepatic first pass metabolism (5,6). Bisoprolol has higher absorption in the distal region of the GI tract and poor absorption in colon, suggest it is an ideal candidate for a gastro retentive drug-delivery system that will increase the gastric residence time of the dosage form it was planned to formulate and evaluate floating controlled release tablets of Bisoprolol by using different polymers

MATERIALS AND METHODS

Bisoprolol was received as a gift sample from Dr.Reddys Pharmaceuticals Pvt ltd, Hyderabad. HPMC different grade, Micro crystalline Cellulose, Aerosil procured from SD fine chemiclas, Sodium Bicarbonate, Ethyl Cellulose were used along with diluents, binding agents and polishing agent are microcrystalline cellulose, Povidone. These all polymers are used in different ratios for different formulations. Isopropyl alcohol is used as solvent were obtained from sigma Aldrich Pvt ltd.

FORMULATION DESIGN:

Si. No.	**INGREDIENTS** (in milligrams)	M 1	M 2	M 3	M 4	M 5	M 6	M 7	M 8	M 9
1	Bisoprolol	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**
2	HPMC K 10M	**100**	**75**	**50**				**25**	**37.5**	**50**
3	HPMC K 100M				**100**	**75**	**50**	**50**	**37.5**	**25**
4	Carboxy methyl cellulose	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**
6	Poly vinyl pyrrolidine	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
7	Isopropyl Alcohol	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**
8	**Sodium Bicarbonate**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**
9	**Citric Acid**	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**

10	Aerosil	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
11	**MagnesiumStearate**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
12	MCC 102	**69**	**44**	**19**	**69**	**44**	**19**	**60**	**44**	**19**
13	Total	**240**	**240**	**240**	**240**	**240**	**240**	**240**	**240**	**240**

FORMULATION METHODOLGY:

Weighed quantity of Drug and excipients such as MCC 102, povidone K 30, HPMC were passed through # 40 mesh. The above powdered blend was Granulated with sufficient quantity of Isopropyl Alcohol. The granules were dried in the Oven at 40-45ºC, Till LOD of the granules reaches less than 2% w/w. The dried granules was passed through # 24 mesh. Weighed quantity of sodium Bicarbonate, Citric Acid and Aerosil was passed through # 40 mesh and mixed with the dried granules in polybag for 10 min. Weighed quantity of Magnesium Stearate was passed through # 60 mesh and mixed with the pre lubricated granules in polybag for 5 min. Finally, The lubricated mixture was then punched in to tablets using 9 mm flat-faced punches (4.7)

EVALUATION :

.Angle of Repose:

A funnel was kept vertically in stand at a specified height above a paper placed on horizontal surface. The bottom was closed and 10gm of sample powder was filled in funnel. The funnel was opened to release the powder on paper to form a smooth conical heap. The height of heap was measured using the scale. A border of heap was marked circularly and its diameter was measured at four points. The angle of repose was calculated using following formula:

$$\tan \theta = h / r$$

$$\theta = \tan^{-1} h / r$$

Where; h = height of the heap

r = radius of the heap

Bulk Density:

The powder to be tested was sized appropriately to break lumps during storage. This powder was then poured in to the measuring cylinder up to 3/4th capacity. The powder was leveled without tapping. The weight and height of powder was used to calculated bulk density by following equation:

$$\text{Bulk density (B.D)} = \frac{\text{Powder mass (gm)}}{\text{Initial volume (ml)}}$$

Tapped Density:

Now this cylinder was kept in the holder of USP tapped density apparatus, where it was tapped at an average rate of 300 drops / minute, for 500 taps. After 500 tapes volume of powder (v_0) was noted and again tapped for another 750 taps. This gave a new volume (v_f). If the difference between v_0 and v_f was more than 2% another 1250 taps are given repeatedly until the difference reduces to less than 2%.

Tapped density was found out from following equation:

$$\text{Tapped density (T.D)} = \frac{\text{Powder mass (gm)}}{\text{Tapped volume (ml)}}$$

Compressibility Index and Hausner's Ratio:

Compressibility of powder can be calculated using following formulas:

$$\text{Compressibility Index} = \frac{\text{Tapped Density - Bulk Density}}{\text{Tapped Density}} \text{x} 100$$

$$\text{Hausner's ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Correlation between compressibility of powder, compressibility index and Hausner's ratio has been depicted in following table.

Post-compression Parameters:

Thickness:

Thickness of the tablet was measured using Digital Vernier caliper. Ten tablets of the formulation were picked randomly and measured individually.

Hardness &Friability:

Hardness was measured using Monsanto Hardness Tester. It is expressed in kg.Twenty tablets were weighed and placed in the Electrolabfriabilator USP and apparatus was rotated at 25 rpm for 4 minutes. The tablets were dedusted and weighed again. The percentage friability is measured using the formula:

Friability = {1-(Wt/W)} ×100

Where,

F = Friability in percentage

W = Initial weight of tablets

Wt = Weight of tablets after friabilation

Weight variation:

Twenty tablets were randomly selected from each batch and individually weighed .The average weight and standard deviation of twenty tablets were calculated. The batch passes the test for weight variation if not more than two of the individual weight oftablet deviate fromthe average weight by more than the % shown in Table-2.

***in vitro* buoyancy time**

The *in vitro* buoyancy was determined, as per the method described by Rosa et al. The tablets were placed in a 100-mL beaker containing 0.1N Hcl. The time required for the tablet to rise to the surface and float was determined as floating lag time and duration of time, for which tablet constantly remain on surface of medium was recorded as total floating time.

Water Uptake Study:

The swelling of the polymers can be measured by their ability to absorb water and swell. Three tablets from each formulation were kept in a petridish containing 0.1N Hcl. After a selected time intervals the tablets were withdrawn blotted to remove excess of liquid and weighed. Swelling characteristics of the tablets is expressed in terms of water uptake (WU) which is calculated by using following equation.

$$\textbf{\%Water Uptake} = \frac{\text{weight of swollen tablet - Initial weight of tablet}}{\text{Initial weight of tablet}} \text{x}\,100$$

***In Vitro* Dissolution Studies:**

Dissolution of the tablets was carried out by using USP type I apparatus. The tablets were placed in the jars containing 900 ml of dissolution medium and the medium was stirred at 75 rpm and the temperature of the medium was maintained at 37 ± 0.5ºC. Samples of 5 ml were collected at predetermined time intervals for 24hrs (7,8). The withdrawn samples were diluted to 50ml with 0.1N Hcl, filtered and analyzed on UV spectrophotometer at 225.8 nm using 0.1N Hcl as a blank.

RESULTS AND DISCUSSION

In this case, nine formulations for floating tablets (B1 to B9) were prepared using polymer Hydroxy propyl methylcellulose in various grades and in combination with different ratios. In total nine formulations were prepared using hydrophilic swellable polymer HPMC with different viscosity grades (K4M, K100M).Wet granulation method was employed for all formulations was found to be satisfactory as the physicochemical evaluation parameters were within the permissible limits. Sodium bicarbonate (NaHCO3) was incorporated in the formulation in such a way that when in contact with the acidic gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage form.

The grade of micro crystalline cellulose responsible for retardation of the drug release without compromising floating behavior of the formulations.

Formulation code	Evaluation parameters				
	Thickness ± S.D. (mm) (n = 5)	Hardness ± S.D. (kg/cm^2) (n = 5)	Friability (%)	Average weight variation (n=10)	Drug content (%)
B1	3.242±0.093	5.2±0.4	0.291	0.302±0.011	97.2
B2	3.108±0.046	5.4±0.2	0.308	0.298±0.010	98.4
B3	3.234±0.035	4.8±0.2	0.415	0.305±0.018	96.16
B4	3.267±0.044	5.6±0.1	0.152	0.304±0.013	103.1
B5	3.262±0.048	5.8±0.6	0.419	0.295±0.014	96.17
B6	3.256±0.039	5.5±0.3	0.244	0.304±0.009	97.24
B7	3.288±0.051	5.2±0.2	0.298	0.299±0.021	99.92
B8	3.228±0.025	5.5±0.3	0.205	0.308±0.011	100.5
B9	3.264±0.058	5.4±0.4	0.393	0.304±0.015	105.2

Table 12:Evaluation parameters for floating tablets of the drug

Preliminary Trials with selected excipients: The preliminary trials of influence of HPMC and sodium bi carbonate on drug release and floating time was conduted. The selection of 20% of the polymer ie HPMC K4M has shown good drug release, good floating lag time and the floating time when compared to higher percentages of HPMC which has shown very less drug release when used in the percentages of 30% and 40%.

Floating property study of a floating tablet:

At 0 seconds At 10 seconds At 40 seconds At 42 seconds

Figure 1: floating tablet buoyancy time study

The criteria for selection of optimum floating tablet were floating lag time, total floating duration and in vitro drug release. All the nine formulations were prepared using different concentration of HPMC K4M, HPMC K100M.

As the concentration of polymer is getting increased, the amount of drug release is getting decreased and tablet will take more time to float on to the surface as the viscosity of the polymer increases. Taking into consideration of floating lag time M3 formulation showed less lag time that is about42sec which is more for other formulations, which took nearly 100sec for the tablet to float on to the surface.

Formulation code	Floating lag time (sec)	Total floating time (hr)
B1	91±0.8	13.25
B2	87±0.9	14.40
B3	40±0.5	15.20
B4	36±0.4	12.50
B5	156±0.5	16.00
B6	21±0.4	14.00
B7	130±0.6	16.20
B8	110±0.5	16.80
B9	106±0.4	17.20

Table 1: Results of floating property of the floating tablets.

Time in hour	Formulation Code									
	B1	B2	B3	B4	B5	B6	B7	B8	B9	
1	98.2	94.2	88.3	86.2	79.4	76.2	74.8	70.3	65.4	
2	103.2	100.7	97.4	92.3	86.2	82.4	80.2	75.4	69.7	
3	109.6	108.6	105.2	99.8	95.4	88.6	87.3	82.4	78.9	
4	116.9	115.8	110.4	106.2	102.3	96.4	95.2	89.9	84.4	
5	125.9	121.9	117.6	112.4	109.4	102.3	99.8	93.4	89.2	
6	140.3	138.5	132.9	127.6	116.3	107.4	105.3	99.7	94.6	
7	132.4	129.7	125.9	134.8	121.4	114.6	111.3	106.4	100.6	
8	121.4	119.6	115.2	129.7	118.3	122.4	119.8	114.3	110.4	
9	104.8	101.9	109.4	121.2	115.4	129.6	128.6	123.4	109.6	
10	96.3	95.8	102.6	116.4	110.2	134.6	133.9	128.6	106.3	
11	89.3	87.3	96.4	109.2	109.4	124.2	126.4	126.4	105.2	
12	79.4	79.2	89.3	102.9	108.6	120.6	122.4	124.9	104.6	

Table 2:Percent water uptake study for floating tablets of the drug

2. Water uptake study (Swelling index):

All the nine formulations showed increases in weight indicating that, the polymer employed inthe present investigation were having a capacity to swell the tablets. The order of swelling nature of formulations are represented as follows:B1>B2>B3>B4>B5>B6>B7>B8>B9 .

***In vitro* dissolution rates for floating tablets:**

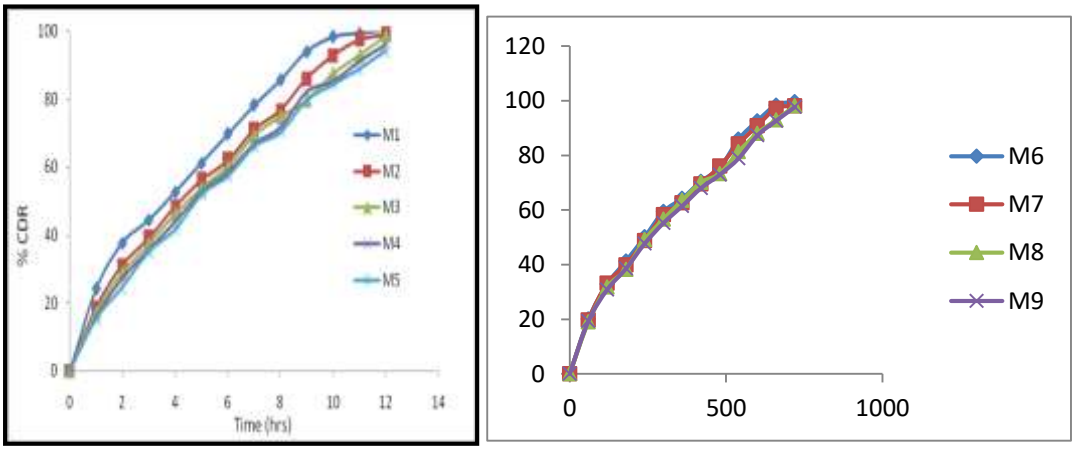

Figure 1: *In vitro* cumulative percent drug release versus time for formulations M1 to M9

In vitro drug release:

B3 formulation has 20% of HPMC K4M as the formulation contains less amount of drug, the %of drug release was 99.67% which was comparatively high and the tablet was able to float for 15.5hrs, whereas in M2 formulation as the amount of HPMC K4M was high(30%), the percentage of drug release was found to comparatively less(99.17%) and the tablet was able to float for 14 hrs. M1 formulation contains 40% of the polymer and the percentage of drug release was found to be 98.91% and the floating time was found to be 13hrs.As the amount of the polymer increased the percentage of drug release decreased and the floating time also decreased.

As the B4 formulation contains more amount of polymer (40%) and the high viscous

Polymer (HPMC K 100M), the amount of drug released was comparatively very less (94%) and the floating time was found to be 12hrs.

As the B5 formulation contained 30% of polymer it has shown comparatively more percentage of drug release (96%) and the floating time was found to be 16hrs, but the floating lag time was very high, the tablet took more time to come on to the surface.

As the M6 formulation contains 20% of polymer, the percentage of drug release was found to be (97%) which is comparatively high when compared to M4 and M5.

As B9, B8, B7 contains both the different grades of polymers the percentage of drug release was intermediate between that of the low viscous and the high viscous polymers. As the B3 formulation is having less amount of polymer the percentage of drug release was higher i.e (99.67%) when compared to that of other formulations which slightly showed variations in the amount of drug release as the amount of polymer concentration was increased. In the B2 formulation as the concentration of polymer increased from 20% to 32% the %drug release was effected and showed the release of only ie (99.37%)

So, as the concentration of polymer increases the amount of drug release decreases and the high viscous polymer shows comparatively less amount of drug release when compared with that of less viscous polymer.

IR data:

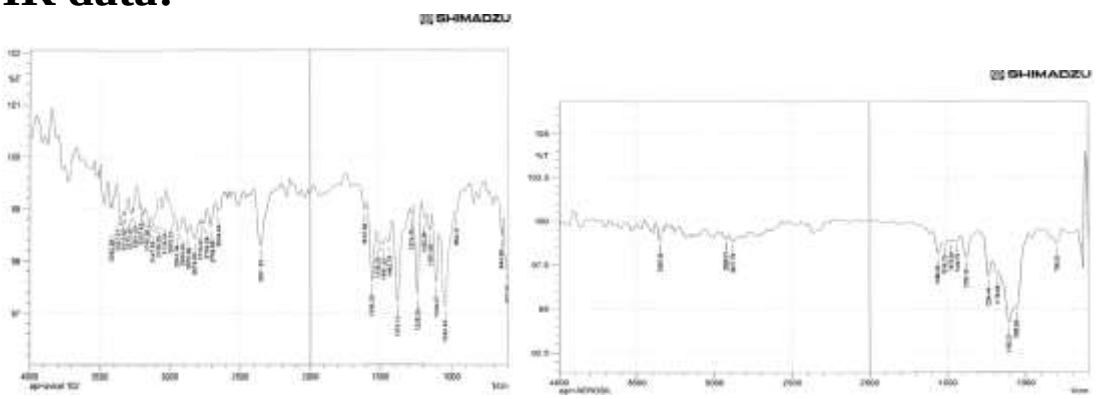

FIGURE 2: FTIR OF API AND AVICEL

FIGURE 3: DRUG AND AEROSIL

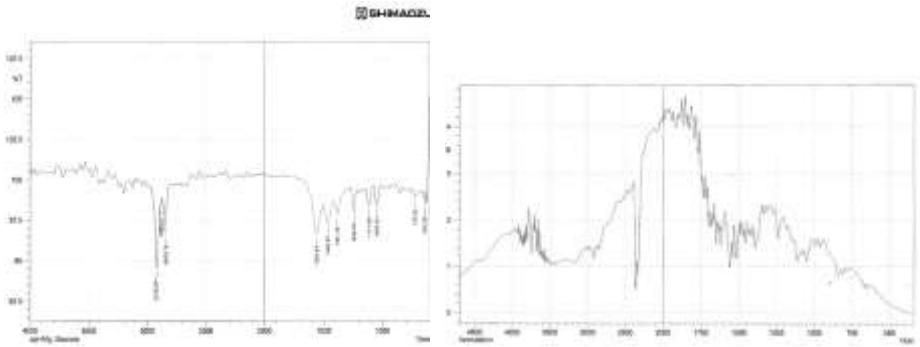

FIGURE 4: DRUG AND MAGNESIUM STEARATE

FIGURE 5: FTIR OF FORMULATION

FT IR STUDIES:

Physical mixture of drug and polymer were characterized by FTIR spectral analysis for any physical as well as chemical alteration of the drug. From the results, it was concluded that there was no interference in the functional groups as the principle peaks of the drug was found to be unaltered, indicating they were compatible chemically. The presence of aromatic ring, secondary amine, alcohol, carboxylic acid and the carbonyl groups in the formulation FT IR graph indicated that there is no interaction between the drug and the excipients and indicates the drug is compatible with the excipients. The formulation floating tablet showed the superimposed spectra and additive. The spectra does not showed the shifting of peaks which indicates that the drug does not showed any interaction with excipients.

Model										
		B1	B2	B3	B4	B5	B6	B7	B8	B9
Krosmyer – peppas	k	21.934	16.8911	15.6257	14.284	13.2443	18.5994	18.3065	17.5624	17.5043
	n	0.6506	0.7361	0.7536	0.7821	0.8073	0.6910	0.6939	0.7018	0.6941
	r	0.9979	0.9993	0.9993	0.9990	0.9989	0.9987	18.3065	0.9985	0.9996
Zero order	k	10.9882	9.7230	9.0963	8.8294	8.6346	9.4753	9.3772	9.1454	8.9956
	r	0.9644	0.9786	0.9769	0.9808	0.9832	0.9626	0.9623	0.9645	0.9675
First order	k	-0.3018	-0.2441	-0.2457	-0.2052	-0.1883	-0.2589	-0.2637	-0.2367	-0.2228
	r	0.8800	0.8973	0.8459	0.9320	0.9505	0.9120	0.8976	0.8946	0.8994
Matrix	k	29.1887	26.9000	26.2466	25.433	24.8408	27.4615	27.1819	26.4955	26.0423
	r	0.9841	0.9748	0.9748	0.9710	0.9680	0.9825	0.9831	0.9824	0.9816
Hixson Crowel	k	-0.0652	-0.055	-0.0533	-0.048	-0.0463	-0.0650	-0.0565	-0.0529	-0.0510
	r	0.9699	0.9717	0.9668	0.9836	0.9888	0.9115	0.9751	0.9751	0.9746
Best fit model		Peppas	Peppas	Peppas	Peppas	Peppas	Peppas	Peppas	Peppas	Peppas

Release kinetic modelling of floating tablets:

Table 4:Release kinetic modelling of floating tablets:

The curve fitting results of the release rate profiles for the designed formulations confirmed that, the release mechanism for floating tablet by diffusion mechanism followed by non-fickian transport where n value lies between 0.4 to 0.9 for all formulations. The n value increases as the polymer content of the formulations increases.

CONCLUSION

In floating layer HPMC K4M and HPMC K100M has predominant effect on total floating time and drug release. Microcrystalline cellulose also shows significant effect on drug release.

Optimized floating tablet was found to be stable at room temperature for a period of month. From the study it is evident that a promising controlled release floating tablets of an antihypertensive drug can be developed. Based on various evaluation parameters formulation B3 was selected as composition for floating tablet and was further subjected to stability study. The optimized floating tablet showed good stability and values were within permissible limits.

From the study it is evident that a promising controlled release floating tablets of an antihypertensive drug can be developed. Further detailed investigations are required to establish efficacy of these formulations.

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