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Optimization of Formulation of Gastroretentive Drug Delivery System Containing Atenelol

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ABSTRACT

Floating dosage form is an oral dosage form that is designed to prolong the residence time of dosage form within the GI tract. It is formulation of a drug and gel forming hydrocolloids meant to remain buoyant on stomach contents. The purpose of this investigation was to optimize the formulation of gastroretentive drug delivery system of Atenelol. Atenelol is a drug of choice for the treatment of hypertension and it is a ß-1 cardio selective adrenergic receptor blocker. Optimization of formulation of floating tablets of Atenelol was done depending upon three different factors such as controlled drug release of drug, floating characteristics and hardness of tablets. This was carried out by studying the effect of different proportions of the polymers, effervescent and different compression pressure. Semi-synthetic polymers HPMC-K100M and a natural polymer, Xanthan gum were used to assess the effect on the release of drug. Dicalcium phosphate was used as a channeling agent. Sodium bicarbonate was used as a gas generating agent. Evaluation of powder blends like angle of repose, bulk density, Carr's index and Hausner's ratio was evaluated. Atenelol floating tablets were evaluated for *In vitro* dissolution and floating lag time. Evaluation of tablets i.e. diameter, thickness, friability, hardness, average weight and content uniformity were performed. Drug release from the tablets was sufficiently sustained.

Key-words: Atenelol, Floating tablet, optimization, *In vitro* study

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INTRODUCTION:

Gastroretentive drug delivery system is one of the oral controlled dosage forms in which the dosage forms are retained in the stomach or small intetstine. These dosage forms remain in the gastric region for several hours and prolong the gastric residence time of drugs. Prolonged gastric retention improves the absorption of drug in gastrointenstinal tract. Floating dosage form is an oral dosage form that is designed to prolong the residence time of dosage form within the GI tract. It is formulation of a drug and gel forming hydrocolloids meant to remain buoyant on stomach contents. This not only prolongs GI residence time but also does so in an area of the GI tract that would maximize drug reaching its absorption site in solution and hence ready for absorption. Gas generating system utilize effervescent reaction between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2 which gets entrapped in the jellified hydrochloride layer of the system, thus decreasing its specific gravity and making it float over chyme. Floating drug delivery system offers several applications for drugs having poor bioavailability because of narrow absorption window in the upper part of GI tract. It retains the dosage form at the site of absorption and then enhances the bioavailability. Atenelol is a drug of choice for the treatment of hypertension. It is a ß-1 cardio selective adrenergic receptor blocker. Atenelol is a good rationale for floating drug delivery system because of identical physicochemical parameters required to the gastroretentive drug delivery system such as it is having oral bioavailability 50%, short half life, does not undergo first pass metabolism and poorly absorbed from stomach.

MATERIALS AND METHODS:

Materials:

Atenelol , HPMC- K100M and Xanthan gum (Rheo gel 120) were obtained as gift samples. Microcystalline cellulose, Dicalcium phosphate, Sodium bicarbonate were procured from Sahyadri Scientific Suppliers, Islampur.

Methods:

Selection of drug

Atenelol , a ß-1 cardio selective adrenergic receptor blocker is used as a drug of a choice in the treatment of hypertension. It is formulated in gastorenentove dosage forms because it does not undergo first pass metabolism, it has short half-life (6-8h), has a narrow absorption window and has less oral bioavailability (50-60%). In gastroretentive dosage forms, the bioavailability of Atenelol can be improved.

Selection of polymers and excipients

Semi-synthetic polymers HPMC-K100M and a natural polymer, Xanthan gum were used to assess the effect on the release of drug. These polymers are hydrophilic in nature and have good gelling properties. These are compatible with drug, non-toxic, cheap and easily available. Dicalcium phosphate was used as a channeling agent. It forms a small pores or channels through which drug is released slowly. Sodium bicarbonate was used as a gas generating agent. Microcrystalline cellulose was used a filler. Talc and Magnesium stearate were used as glidant.

Preformulation studies

The flow properties of powder (before compression) were characterized in terms of angle of repose, Bulk density, Tapped density , Carr's index and Hausner's ratio. Angle of repose for blend of each formulation was determined by fixed funnel method. The fixed funnel method employs a funnel that is secured with its tip at given height, h, which was kept 2 cm, above graph paper that was placed on a flat horizontal surface. With r, being the radius of base of conical pile, angle of repose can be determined using $\tan^{-1}$ (height of pile/radius of base). Bulk density, Tapped density , Carr's index and Hausner's ratio were calculated. An accurately weighed 20 gm powder was allowed to flow in a fine stream into a graduated cylinder and final volume was noted. Thin layer chromatography was performed to chek the compatibility of excipients with drug. The solvent system used was Dioxane, Acetonitrile, Methanol and Concentrated ammonia solution.The glass plates coated with silica gel-G 60 were use to perform TLC. 100mg sample of each formulation and standard pure atenelol was dissolved in 10ml Methanol in a separate container and a drop of each solution was spotted on glass plates. The plates were placed in iodine chamber to locate the spots. R_f value was calculated using formula distance traveled by sample of formulations/distance

traveled by standard (Atenelol). Solvent systems composed of solvents Dioxane 60% (v/v), Acetonitrile 36% (v/v), Methanol 5%(v/v) and Concentrated ammonia solution (25%) 4%(v/v).

Optimization of Formula

Optimization of formulation was carried out for different parameters as controlled drug release of drug, floating characteristics and hardness of tablets. This was carried out by studying the effect of different proportions of the polymers, effervescent and different compression pressure. The trial preparations were prepared by using 10 and 20% concentration of the polymers to study the drug release whereas 8 to 12% sodium bicarbonate was used to optimize the concentration of effervescent. Hardness was optimized from 4.0 to 4.5 kg/cm^2 .

Preparation of floating tablets

After optimization of formula the floating tablets were prepared by direct compression method. The concentration of above ingredients were optimized on the basis of trial preparation of the tablets. On the basis of flow characteristics and compressibility index, Direct compression method was preferred for the preparation of floating tablets. All the ingredients including drug and excipients were accurately weighed. The drug was mixed with release retarding polymers and other excipients in ascending order of their weights. The powder mix was blended for 20mins so as to have uniform distribution of drug in the formulation. 350mg of the powder mix was weighed accurately and fed into the die of single punch machinery and compressed at 3N compression force using 10mm concave punches. Formulation of floating matrix tablets of Atenelol is shown in Table no. 1

Table No.1 : Formulation of floating matrix tablets of Atenelol

Ingredients/ Formulation	**F1 (1:1)**	**F2 (1:2)**	**F3 (2:1)**	**F4 (1:1)**	**F5 (1:2)**	**F6 (2:1)**	**F7 (1:1)**	**F8 (1:2)**	**F9 (2:1)**
Atenelol	50	50	50	50	50	50	50	50	50
HPMC-K100M	35	35	70	35	35	70	35	35	70
Xanthan gum	35	70	35	35	70	35	35	70	35
Sodium bicarbonate	28	28	28	35	35	35	42	42	42
Dicalcium phosphate	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5
Magnesium stearate	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75
Microcrystalline cellulose	181	146	146	174	139	139	167	132	132
Talc	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75
Total	350	350	350	350	350	350	350	350	350

*All quantities are in mg.

**Formula for one chewing gum is shown in table.

Floating characteristics

Floating characteristics of the prepared tablets were determined by using USPXXIII paddle apparatus (Electrolab, TDT- 06P, Mumbai, India). The dissolution medium was 900ml of 0.1N HCl (pH 1.2) at 37±0.5^{0}C throughout the study. Floating lag time was determined by measuring the time between the introduction of tablet and its buoyancy on the 0.1N HCl and floating time was determined by measuring time during which dosage form remain buoyant.

RESULT:

Optimization of formula

Optimization of concentration of polymers

% Drug release for different concentration is given in Table no.2

Table No.2 : Cumulative % Drug release for different concentration

Time (h)	Cumulative % Drug Release								
	F1 (1:1)	F2 (1:2)	F3 (2:1)	F4 (1:1)	F5 (1:2)	F6 (2:1)	F7 (1:1)	F8 (1:2)	F9 (2:1)
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
0.5	2.28± 0.58	5.12± 0.35	8.89± 0.31	66.57± 0.28	61.54± 0.64	47.28± 0.61	38.15± 0.39	34.99± 0.63	35.02± 0.61
1	14.66± 0.67	17.46± 0.19	15.44± 0.52	92.26± 0.64	74.40± 0.37	58.92± 0.53	42.70± 0.17	38.58± 0.45	37.90± 0.31
2	19.87± 0.39	19.13± 0.25	19.03± 0.93	62.48± 0.38	75.91± 0.29	59.59± 0.47	45.46± 0.61	44.47± 0.54	40.23± 0.43
3	24.98± 0.85	19.37± 0.94	24.56± 0.27	71.31± 0.27	76.41± 0.71	61.05± 0.63	55.00± 0.73	51.45± 0.19	55.93± 0.70
4	46.38± 0.64	36.27± 0.64	45.96± 0.71	82.57± 0.81	78.76± 0.39	75.95± 0.13	78.73± 0.64	60.32± 0.64	66.52± 0.63
5	51.60± 0.28	46.27± 0.46	51.22± 0.16	93.52± 0.71	99.48± 0.27	85.61± 0.74	79.93± 0.28	80.18± 0.81	81.78± 0.34
6	79.52± 0.67	51.96± 0.72	79.75± 0.42	100.69 ±0.36	102.6± 0.38	85.44± 0.52	82.99± 0.63	94.23± 0.31	96.65± 0.40
7	87.89± 0.64	79.03± 0.51	97.57± 0.17	128.79 ±0.29	111.7± 0.52	208.28 ±0.41	147.53 ±0.82	100.1± 0.43	144.1± 0.87
8	91.81± 0.12	98.34± 0.93	98.59± 0.27	179.67 ±0.45	150.0± 0.52	214.30 ±0.85	207.83 ±0.47	145.8± 0.52	160.4± 0.61

Graphical representation of cumulative % drug release of optimized formulations F1, F2 and F3 is shown in Figure no.1

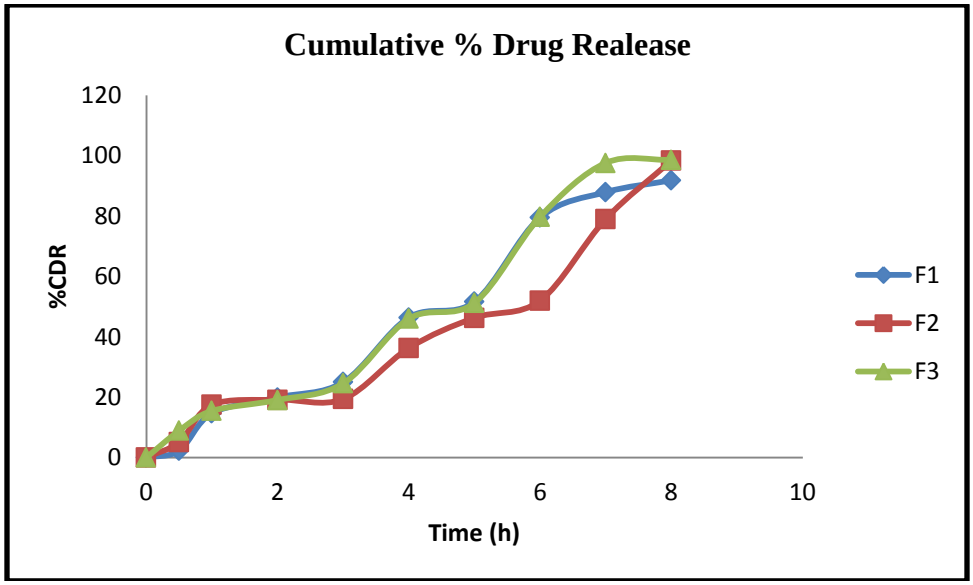

Figure No. 1: Comparative % cumulative drug release profile of formulations F1-F3

Optimization of concentration of sodium bicarbonate

The effect of different concentration of sodium bicarbonate on floating lag time is shown in Table No. 3

Table No.3: Effect of different concentration of sodium bicarbonate on floating lag time

Concentration of Sodium bicarbonate (%)	Floating Lag time (mins)		
	1:1	1:2	2:1
8	7	8	7
10	5	5	5
12	4	5	5

Optimization of appropriate hardness of tablets

The effect of different hardness of tablets on floating lag time is shown in Table No. 4

Table No.4: Effect of different hardness of tablets on floating lag time

Hardness of tablet (Kg/cm^2)	Floating Lag time (mins)		
	1:1	1:2	2:1
5.5	45	50	52
5.0	20	25	27
4.5	11	10	11
4.0	8	9	8

Preformulation studies

Powder blends of matrix tablets showed the bulk density from 0.314 to 427g/cc, angle of repose from 21.11 to 35.75^0 , Carr's index from 11.99 to 17.79% and Hausner's ratio 1.13 to 1.21. which showed good flow properties. The R_f value of standard Atenelol is 0.3 and that of powder blends was forund to in the range of 0.2727-0.5178. Evaluation of powder blends is given in Table no.5

Table no.5: Evaluation of powder blends

Batch	Bulk Density (g/cc)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (θ^o)	R_f Value
F1	0.314 ±0.002	11.99 ± 0.763	1.13 ± 0.01	23.67 ± 0.30	0.3090± 0.05
F2	0.327 ±0.002	16.68 ± 0.955	1.20 ± 0.01	22.61 ± 0.05	0.3454± 0.01
F3	0.314 ±0.010	13.99 ±2.389	1.16 ± 0.03	21.11 ± 0.10	0.3148± 0.03
F4	0.427 ±0.004	17.79 ± 3.884	1.21 ± 0.06	29.24 ± 0.14	0.5178± 0.03
F5	0.405 ±0.002	13.17 ± 2.899	1.15 ± 0.03	30.96 ± 0.08	0.3818± 0.05
F6	0.385 ±0.008	16.02± 1.778	1.19 ± 0.02	30.96 ± 0.07	0.3833± 0.08
F7	0.334 ±0.002	13.93± 0.754	1.16 ± 0.01	35.37 ± 0.12	0.2727±0 .03
F8	0.320 ±0.011	15.01± 1.312	1.17 ± 0.05	35.75 ± 0.08	0.3454± 0.06
F9	0.334 ±0.003	17.41± 0.581	1.21 ±0 .03	32.61 ± 0.06	0.2790± 0.01

*All values are expressed as mean ± SD; n = 3

Evaluation of floating tablets

Data of evaluation of physical characteristics of floating tablets is shown in Table No.6

Table No. 6: Evaluation of floating tablets

Formulation	Uniformity of Weight * (mg) (± SD)	Thickness (mm)	Hardness (kg/cm²)	Friability* (%)	Uniformity content (%)
F1	340.55 ± 5.86	3.00 ± 0.00	4.0 ± 0.11	0.82 ± 0.02	98.09 ± 0.83
F2	336.89± 7.22	3.00 ± 0.05	4.1 ± 0.05	0.78 ± 0.01	96.97 ± 0.57
F3	342.01 ±5.69	2.99 ± 0.4	4.1 ± 0.11	0.91 ± 0.02	98.91 ± 0.65
F4	331.51 ± 6.00	2.97 ± 0.03	4.3 ± 0.05	0.82 ± 0.03	96.65 ± 1.27
F5	341.65± 2.09	2.98 ± 0.02	4.4 ± 0.10	0.85 ± 0.02	97.17 ± 0.69
F6	342.15± 5.23	2.98 ± 0.04	4.5 ± 0.10	0.73 ± 0.02	95.95 ± 0.98
F7	332.6± 4.83	2.97 ± 0.03	4.5 ± 0.10	0.93 ± 0.01	98.50 ± 1.06
F8	346.5 ± 5.06	3.01 ± 0.01	4.2 ± 0.05	0.94 ± 0.01	96.33 ± 0.92
F9	343.82 ± 2.10	3.02 ± 0.00	4.2 ± 0.11	0.80 ± 0.01	97.58 ± 0.64

None of the chewing gum tablet was found to deviate from the mean weight of the tablets. Thickness of the tablets was found to be in the range of 2.97- 3.02mm. Friability was found to be less than 1% which indicates the strength of tablets and also exhibit that these tablets can withstand the shocks during shipping, transportation and handling. Uniform drug content was observed for all the formulations (95.95± 0.98% to 98.91± 0.65%). The values for these parameters are given in Table No.5.

DISCUSSION:

The present work was aimed to develop the gastroretentive formulation of Atenelol to increase the bioavailability of Atenelol. The proportions of polymers HPMC-K100M and Xanthan gum were optimized on the basis of trial preparations of the tablets. Initially tablets were prepared by using 10% polymers. At low concentration these polymers showed the rapid release at lower concentration the polymers have low ability to form gel. Further increase in the concentration of polymers upto 20% retarded the release of drug and the floating time was increased upto 24h that was obsereved visually. 1:1, 1:2 and 2:1 proportions were selected and those proportions were used for the preparations of the tablets. Formulations having 8% of sodium bicarbonate showed the sustained release of drug upto 8h and as the concentration increases 10 and12% burst release of drug was found at 30 mins. When concentration of sodium bicarbonate increases from 8-12%, floating lag time decreases from 8-4mins. This is because formation CO_2 takes place immediately due to more availability of Sodium bicarbonate. But Formulations having 8% of sodium bicarbonate showed the sustained release of drug upto 8h and as the concentration increases 10 and12% burst release of drug was found at 30 mins. So optimized concentration of sodium bicarbonate was found to be 8%. Then as hardness increases from 4.0-5.5, tablet becomes more compact so it increases floating lag time from 8-52mins. , so optimized hardness was found to be 4.0Kg/cm² , as it showed floating lag time 8mins. The R_f value of the representative formulations and standard were forund to be same, which indicated that the drug and excipients are compatible with each other. The flow properties of powder blends and evaluation tests of tablets were complied with standard and showed good results.

CONCLUSION:

In present work optimization of formulation of floating tablets containing Atenelol was done by studying different parameters as concentration of polymers, floating characteristics and hardness of tablets. 10% concentration of polymers HPMC-K100M and Xanthan gum was found to be optimized because it gave the sustained release of Atenelol upto 8h. 8% concentration of Sodium bicarbonate and 4.0 Kg/cm² hardness was found to be optimized. This optimized formulation sufficiently sustained the drug release and remained buoyant in stomach fluid upto several hours. Floating tablets so prepared can be promising for increasing the bioavailability of drug by prolonging the presence of drug in absorption area.

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