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DEVELOPMENT AND ASSESSMENT OF GASTRO RETENTIVE FLOATING TABLETS OF CELIPROLOL USING NATURAL POLYMERS

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Abstract

Gastro retentive floating tablets are a promising drug delivery system for improving the bioavailability and therapeutic efficacy of orally administered drugs, particularly those with a narrow absorption window in the gastrointestinal tract. In this study, we aimed to develop and evaluate gastro retentive floating tablets of Celiprolol using natural polymers. The tablets were formulated by incorporating a combination of natural polymers, including hydroxypropyl methylcellulose (HPMC) and sodium alginate, to achieve buoyancy and sustained drug release. Various formulation parameters, such as polymer concentration, drug-to-polymer ratio, and effervescent agents, were optimized to attain desired tablet characteristics. The prepared tablets were evaluated for their physical characteristics, floating behavior, drug release profile, and drug stability. The optimized formulation demonstrated excellent floating properties, with a floating lag time of less than 60 seconds and a floating duration of more than 12 hours. In vitro drug release studies revealed sustained release of Celiprolol from the tablets over a period of 12 hours. The drug release kinetics followed the Higuchi model, suggesting diffusion as the predominant mechanism. Stability studies indicated that the floating tablets maintained their physical and drug release characteristics over a period of six months under accelerated storage conditions. Overall, the developed gastro retentive floating tablets of Celiprolol using natural polymers showed promising characteristics in terms of floating behavior, sustained drug release, and stability. This formulation has the potential to improve the therapeutic outcomes of Celiprolol by enhancing its bioavailability and ensuring prolonged drug exposure in the gastrointestinal tract. Further in vivo studies are warranted to validate the efficacy and pharmacokinetic profile of these tablets for potential clinical applications in the treatment of hypertension and other cardiovascular condition.

Keywords: Gastro retentive floating tablets, Celiprolol, Natural polymers, Hydroxypropyl methylcellulose (HPMC), Sodium alginate.

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Introduction

Rapid gastrointestinal transit could result in incomplete drug release from the dosage form above the absorption zone leading to diminished efficacy of the administered dose. These considerate have led to the development of a controlled or sustained delivery system [1]. The main purpose for developing these systems was to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for long time [2]. Gastroretentive drug delivery is an approach to prolong gastric retention time, thereby targeting site- specific drug release in the upper GIT for local and systemic effect [3].Therefore, different approaches have been proposed to retain the dosage form in the stomach. These include bioadhesive systems, swelling and expanding systems and floating systems [4].

Floating drug delivery or hydrodynamically balanced systems have a sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolong period [5]. Celiprolol is indicated for the management of mild to moderate hypertension and effort-induced angina pectoris. It is simultaneously a selective β1 receptor antagonist, a β2 receptor partial agonist and a weak α2 receptor antagonist that works specifically on the heart. It

works by slowing down the heart rate and makes the heart more efficient at pumping blood around the body [6]. A majority of the investigations on natural excipients in drug delivery systems have centered on proteins and polysaccharides due to their ability to produce a wide range of materials and properties according to molecular structural alterations.

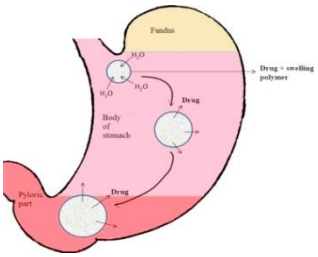

Fig. 1. Gastro-retentive drug delivery system based on polymer swelling [7]

In recent years, plant gums and mucilages have evoked tremendous interest due to their diverse pharmaceutical applications such as diluents, binders, disintegrates in tablets, thickeners in oral liquids, protective colloids in suspensions, gelling agents in gels and bases in suppository, thus making them attractive substitutes for costly semisynthetic and synthetic excipients [8]. India, due to its geographical and environmental positioning, has traditionally been a good source for such products among the Asian countries [9]. With an aim to improve the absorption and oral bioavailability we took an attempt to formulate floating drug delivery systems using Celiprolol as the drug candidate employing natural polymers, including hydroxypropyl methylcellulose (HPMC) and sodium alginate, to achieve buoyancy and sustained drug release [10].

Materials and Methods

Materials

Celiprolol were obtained as pure sample from Sun Pharmaceutical Industries Ltd as gift samples along with their analytical reports. Xanthan gum, guar Gum, Sodium bicarbonate, lactose and Magnesium stearate were purchased from Bross Chem. Limited, Tirupati. Double distilled water was prepared freshly and used whenever required. All other chemicals used in this study including those stated were of analytical reagent (A.R.) grade.

Methods

Determination of absorption maxima

Celiprolol solution containing the concentration 10µg/ml was prepared in 0.1N HCl. UV spectrum was taken using Double beam UV/VIS spectrophotometer (Labindia-3000+). The solution was scanned in the range of 200-400nm [11].

Preparation calibration curve

10ml of stock solution-2 was extracted and its volume was adjusted to 100ml using 0.1N HCl, resulting in a concentration of 10 µg/ml. From this solution, 2ml, 4ml, 6ml, 8ml, and 10ml were withdrawn into separate 10ml volumetric flasks. Each of these withdrawn portions was then brought up to a final volume of 10ml using 0.1N HCl, yielding concentrations of 2, 4, 6, 8, and 10 µg/ml, respectively [12].

Pre compression evaluation

Flow properties and compressibility properties of powder mixture were evaluated by measurement of angle of repose, bulk density, tapped density, carr's index and hausner's ratio.

Angle of repose (θ)

The angle of repose was determined by using fixed funnel method. The physical mixtures of drug with different excipients were prepared and the accurately weighed drug powder or its physical mixture was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the drug powder. The powder was allowed to flow through the funnel freely onto surface. The angle of repose was calculated using the following equation [13].

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

Where, h and r are the height and radius of the powder cone respectively.

Bulk density

Both loose bulk density (LBD) and tapped density (TBD) were determined were calculated using the following formulas [14].

LBD = Powder weight/volume of the packing

TBD = Powder weight /tapped volume of the packing

Compressibility index

The compressibility index of the granules was determined by Carr's compressibility index [15].

$$\text{Carr's index (\%)} = [(TBD - LBD)/TBD] \times 100$$

Hausner's ratio

Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula [16].

Hausner's ratio = Tapped density/Bulk density

Drug Excipients Compatibility Study

Compatibility studies were done to recognize the possible interactions between drug Captopril and excipients utilized in the formulation. Physical mixtures of drug and excipients in the proportion1:1 was set up to study the compatibility. Drug polymer compatibility studies were completed utilizing FTIR spectroscopy. The IR Spectra's were recorded in the middle of 500 –4000 cm^{-1} [17].

Formulation development of tablets

Direct compression method Different tablets formulations (F1-F9) were prepared by direct compression technique. Floating controlled release tablets were prepared by direct compression method. Celiprolol was mixed with the required quantities of polymers (xanthan gum, guar gum) sodium bicarbonate (12%), and lactose by geometric mixing. The powder blend was then lubricated with magnesium stearate (2%) and mixed for about 3 minutes. Finally this mixture was compressed on a 16-station rotary tablet machine [18].

Table 1: Quantity of Raw materials Per Tablet (In mg)

S.NO	INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Celiprolol	200	200	200	200	200	200	200	200	200
2	Xanthum gum	5	10	-	10	20	-	15	30	-
3	Guargum	5	-	10	10	-	20	15	-	30
4	Sodium bicarbonate	12	12	12	12	12	12	12	12	12
5	Lactose	26	26	26	16	16	16	6	6	6
6	Magnesium stearate	2	2	2	2	2	2	2	2	2
7	Total weight	250	250	250	250	250	250	250	250	250

Evaluation of floating tablets of Celiprolol

All the tablets were evaluated for following different parameters which includes;

General Appearance

Five tablets from different batches were randomly selected and organoleptic properties such as color, odor, taste, shape were evaluated. Appearance was judged visually.

Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach).

Friability

The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated [19].

Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 100mg of drug was transferred to 100ml standard flask. The powder was dissolved in 50 ml of 0.1 N HCl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and analyzed for drug content by UV spectrophotometer at a λmax of 246 nm using of 0.1 N HCl as blank [20].

In vitro buoyancy studies

In vitro buoyancy was determined by floating lag time as per the method described by Rosa et al [21]. The tablets were separately in a 100 ml glass beaker containing simulated gastric fluid (SGF), pH 1.2 as per USP. The time necessary for the tablet to increase to the outside and float was determined as floating lag time. The experiments were conducted in triplicate. Total floating times were measured during in vitro dissolution studies.

In-Vitro Dissolution Studies

In vitro dissolution studies of all the fabricated tablets and the pure drug was carried out USP paddle method at 50 rpm in 900 ml of Phosphate Buffer pH 5.8, maintained at 37 + 0.5 °C. 5 ml of aliquots withdrawn at specified intervals and for filtration passed through whatmann filter paper. The dissolution was carried out for 12 hours. The absorbance of the samples at different time intervals were carried out using UV - visible spectrophotometer at λ max of 243 nm [22].

Results and Discussion

Solubility of Celiprolol was freely soluble in methanol and ethanol, slightly soluble in 0.1N NaOH, soluble in water, 0.1N HCL and 6.8 pH phosphate buffers. The melting point of Celiprolol was 110-112° C and λ max of Celiprolol was found to be 232 nm by using U.V. spectrophotometer (Labindia-3000+) in linearity range 5-25 µg/ml. Tablet powder blend was subjected to various pre-compression parameters Table 2. The angle of repose values indicates that the powder blend has good flow

properties. The bulk density and tapped density of all the formulations was found to be in the range of 0.260 to 0.347 (gm/ml) and 0.320 to 0.391 showing that the powder has good flow properties. The Carr's index and Hauser's ratio of all the formulations was found to be ranging between 13.12 to 16.31 and 1.08 to 1.19 which show that the powder has good flow properties. In Drug-Excipients Compatibility Studies the peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. It does not show any well-defined interaction between Celiprolol and excipients. This indicates that the drug is compatible with the excipients. The spectra for pure drug, drug-excipients mixture are shown in Figures 3-6 respectively. Celiprolol tablet quality control tests such as weight variation, hardness and friability, thickness, drug content and drug release studies in different media were performed on the compression tablet. All the parameters such as weight variation, hardness, friability, thickness and drug content were found to be within limits Table 3. F4 formulation had the shortest buoyancy lag time of all the formulations, with a period of 45 seconds. The total floating time for all formulations was more than 12 hours. Swelling was greater in xanthan gum-containing formulations than in those containing both xanthan and guar gum or guar gum alone table 4, the improved formulation, F4, demonstrated outstanding buoyancy qualities with a 45-second buoyancy lag time and achieved 99.65% drug release in 14 hours table 5.

Table-2: Result of pre-compression properties of Celiprolol FGR tablets

S.No.	Formulation code	Angle of repose (±SD)	Bulk Density (gm/ml) ±SD	Tapped Density (gm/ml) ±SD	Carr's Index (%) (±SD)	Hausner'sratio (±SD)
1	**F1**	26.12±0.04	0.317±0.01	0.367±0.02	14.65±0.06	1.08±0.05
2	**F2**	27.07±0.01	0.327±0.03	0.389±0.04	15.21±0.07	1.09±0.04
3	**F3**	26.04±0.03	0.337±0.06	0.381±0.01	13.63±0.04	1.11±0.02
4	**F4**	29.0i±0.07	0.347±0.04	0.391±0.07	16.52±0.01	1.19±0.06
5	**F5**	26.97±0.09	0.296±0.03	0.320±0.03	13.12±0.03	1.16±0.03
6	**F6**	25.71±0.06	0.260±0.01	0.336±0.01	15.27±0.01	1.15±0.01
7	**F7**	26.16±0.03	0.266±0.04	0.372±0.02	14.56±0.04	1.16±0.03
8	**F8**	27.11±0.09	0.307±0.05	0.332±0.03	13.41±0.07	1.17±0.05
9	**F9**	26.16±0.04	0.312±0.02	0.356±0.01	16.31±0.05	1.18±0.04

Table-3: Results of post compression properties of Celiprolol GRF tablets

S.No.	Formulationcode	Weight variation in mg (±SD)	Hardness in kg/cm² (±SD)	Friability (%)	Drug content (±SD)	Thickness in mm (±SD)
1	**F1**	251±2.89	4.5±0.34	0.47	98.76±0.19	1.3±0.12
2	**F2**	250±1.88	4.2±0.73	0.68	99.16±0.27	1.2±0.21
3	**F3**	249±3.6	4.4±1.92	0.47	100.87±0.41	1.3±0.53
4	**F4**	250±6.4	4.3±0.34	0.46	99.32±1.23	1.3±0.16
5	**F5**	250±1.4	4.6±0.28	0.72	98.48±0.26	1.3±0.42
6	**F6**	249±6.58	4.3±0.37	0.74	99.67±0.17	1.2±0.53
7	**F7**	251±1.59	4.4±0.89	0.63	99.87±0.32	1.3±0.24
8	**F8**	249±3.07	4.3±0.42	0.45	99.28±0.33	1.2±0.16
9	**F9**	250±3.89	4.4±0.56	0.83	98.87±0.16	1.2±0.29

Table 4: Results of in-vitro buoyancy study of Celiprolol

S. No	Batch No	Buoyancy lag time (sec)	Floating duration (h)
1	F_1	47	>12h
2	F_2	60	>12h
3	F_3	50	>12h
4	F_4	45	>12h
5	F_5	70	>12h
6	F_6	90	>12h
7	F_7	48	>12h
8	F_8	50	>12h
9	F_9	55	>12h

Table 5: In-vitro drug release study of Celiprolol tablets

TIME (H)	CUMULATIVE PERCENTAGE DRUG RELEASE (%)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	15.68	21.98	20.18	10.23	20.16	9.31	8.14	15.27	8.00
2	26.22	44.03	31.77	14.76	31.52	13.16	11.56	25.32	10.02
3	37.04	60.07	41.91	17.86	39.23	16.56	15.12	36.59	14.56
4	48.09	72.17	52.76	21.97	50.36	20.96	17.56	45.62	16.23
5	55.71	79.46	58.82	26.53	56.51	25.43	22.16	50.06	20.58
6	62.05	85.18	63.11	31.65	61.68	30.62	26.28	54.42	24.12
7	69.16	92.71	67.99	38.15	66.79	36.25	34.47	58.69	30.16
8	76.96	94.51	72.34	44.87	71.24	40.17	37.52	63.16	46.19
9	88.34	95.65	81.19	56.01	85.11	59.21	58.75	70.28	68.78
10	90.11	97.90	94.76	70.03	94.16	78.75	64.89	78.44	71.85
11	93.26	99.14	98.42	77.36	98.14	94.23	78.13	87.59	86.16
12	95.89	99.56	99.12	84.06	99.18	99.11	96.14	98.16	97.36
13	98.08	99.67	99.38	97.02	99.62	99.51	98.78	99.34	99.26
14	98.67	99.87	99.83	99.64	99.78	99.89	99.25	99.87	99.89

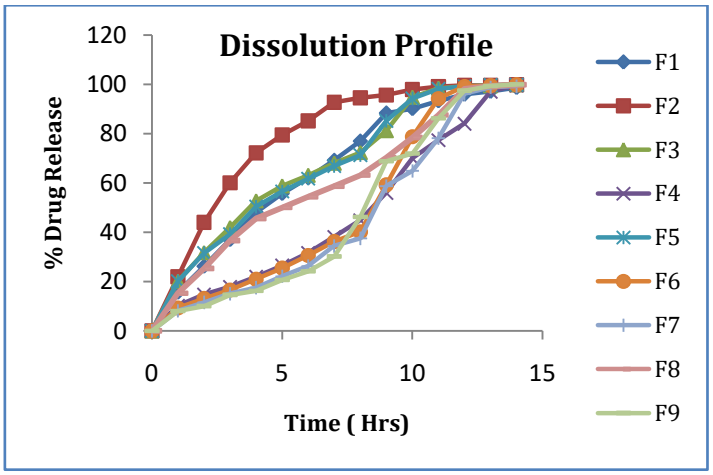

Fig.2: In-vitro drug release study

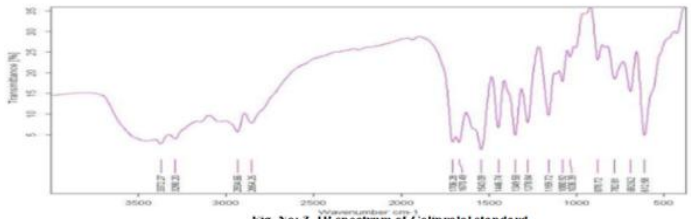

Fig. No: 3 IR spectrum of Celiprolol standard

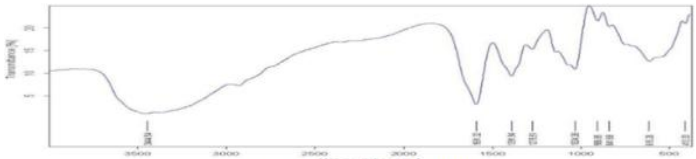

Fig. No: 4 IR spectrum of guar gum

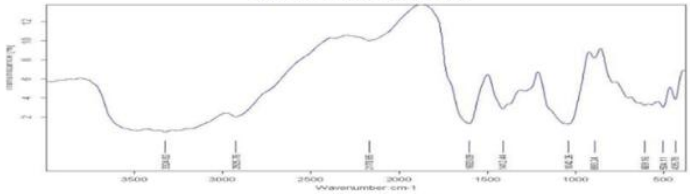

Fig. No: 5 IR spectrum of Xanthan gum

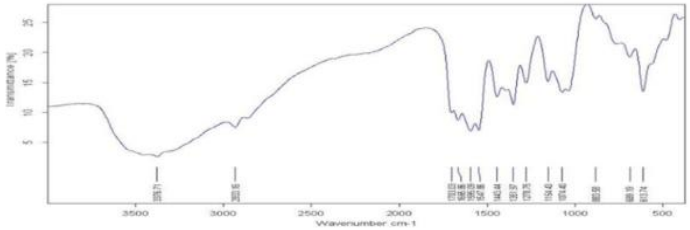

Fig. No: 6 IR Spectrum of Celiprolol and polymers

Conclusion

Celiprolol floating tablets were successfully formulated by floating technique. The optimized formulation (F4) was selected on the basis of in vitro buoyancy and in vitro drug release. The addition of gel forming agent and gas generating agent was essential to achieve in vitro buoyancy. The results of the in vitro drug release and in vitro buoyancy study showed that the optimized formulation (F4) sustained the drug release (99.64) up to 14 hrs. And remained buoyant for >12 hrs. Optimized formulation (F4) does not show any significant change in physical appearance, floating properties and drug release after storage at 40°C/75% RH and stable for 6 months.

Conflicts of Interest: The authors declare no conflicts of interest.

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Conflict of interest

Authors are declared that no conflict of interest

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Not Applicable

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