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FORMULATION AND ASSESSMENT OF A FLAOTING PHARMACEUTICAL DELIVERY SYSTEM FOR AN ANTIARRYTHMIC AGENT UTILIZING VARIOUS NATURAL AND SYNTHETIC POLYMERS

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Abstract: An effervescent floating tablet formulation of Acebutolol hydrochloride was developed to enhance bioavailability by improving stomach retention. Using a direct compression method, various synthetic and natural polymers were evaluated. Effervescent agents, sodium bicarbonate and citric acid, were incorporated with polymers to lower the dosage form's density below that of gastric fluid, thereby extending gastric residence time. FTIR analysis was employed for drug identification, followed by the creation of floating tablets to assess polymer effects on swelling and buoyancy. Drug-excipient compatibility studies and FTIR comparisons with pure drug indicated no interactions in the optimal formulation. Stability tests confirmed unchanged post-compression parameters. The most effective combination of sodium bicarbonate, citric acid, and karaya gum (FA7) resulted in a floating lag time of 1 second, total floating time of 590 minutes, and 98.91% release after 600 minutes. Release kinetics analysis revealed adherence to a zero-order non-fickian diffusion-controlled system. The study found no drug-excipient interactions and demonstrated that Acebutolol hydrochloride floating tablets with karaya gum (FA7) mitigate plasma concentration fluctuations associated with frequent dosing of conventional immediate-release forms by prolonging gastric residence time.

Index Terms **-** Floating, gastrointestinal, gastro retentive system, antiarrythmic agent.

1. Introduction

Drug administration by oral delivery is recommended over other conventional routes like intravenous and intramuscular injection because it is more natural and less invasive. Numerous strategies are developed to ensure optimal bioavailability, and one of them is the use of gastro-retentive dosage forms. The system could be low-density or high-density, increasing the gastric residence time, floating, swelling, inflation, adhesion.[1] Gastroretentive devices are employed to advance the drugs bioavailability using a constrained absorption window, those with a decreased water solubility in the small intestine's alkaline pH, or those with a least stability in the colonic or intestinal environment.[2,3].These consist of expandable classifications, floating drug delivery systems (FDDS), expandable systems, expandable systems, High density systems and ultra

porous hydrogels. They are more suitable for medications with localised effects in the stomach or with strong effects in the duodenum and upper jejunum segment, where absorption is good.

Floating Drug Delivery Systems

Davis first described the floating drug delivery system (FDDS) in 1968. FDDS is a useful technique for extending the gastric residence period to increase the drug's bioavailability. FDDS, which bulk density initially is less than that of gastric juice (1.004 g/cm3) or falls to the appropriate value after being consumed for a predetermined amount of time.[4] Due to this ability, the medicine can stay on the surface of the stomach's contents rather than being evacuated to the stomach's deeper portions, preventing damage to the mucous membranes and the rate of emptying. Flotation gives the system the ability to deliver drugs specifically to the right places at the right times for the right therapeutic needs. When it comes to drugs with low intestinal fluid solubility and stability, these devices are helpful. The idea of FDDS is to make the dosage form less dense than the stomach juices so that it can float on them. [5] With enough buoyancy to float over the contents of the stomach and remain buoyant there without noticeably slowing down the process of gastric emptying, FDDS are hydrodynamically regulated low-density devices. The residual system in the stomach is emptied with the drug's release. This results in an extended period of stomach occupancy and more effective management of variations in plasma drug concentration. The idea of buoyant preparation provides a simple and practical way to increase stomach capacity. In some cases, it makes sense to extend a delivery system's stomach retention in order to boost the pharmacological component's therapeutic efficacy.[6] For example, drugs that are poorly soluble or that break down at an alkaline pH are good at prolonging stomach retention. Additionally, there is increased absorption of these medications at the proximal portion of the gastrointestinal tract. Furthermore, in the treatment of certain ulcerative disorders, prolonged gastric retention of the therapeutic moiety permits sustained drug administration to the stomach and proximal small intestine. Numerous advantages result from this, such as increased bioavailability and therapeutic efficacy with fewer dose requirements [7-14].

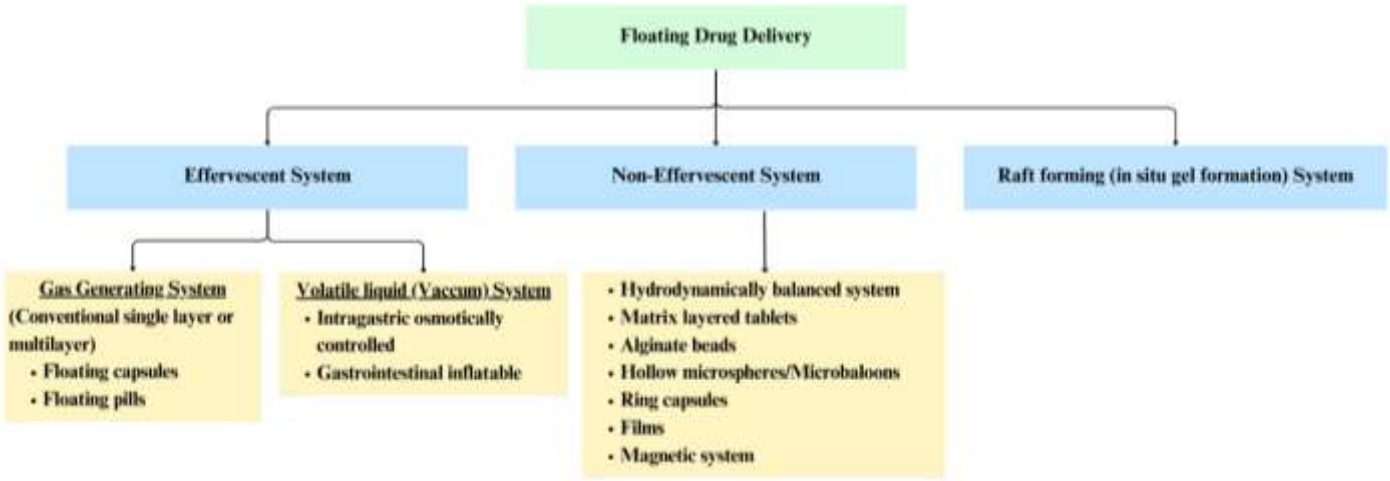

Fig 1: Classification for FDDS

MATERIAL & METHODS

Material:

Acebutolol hydrochloride was obtained from Luna Chemical Industries Pvt Ltd, and PGA (Banka Bioloo Ltd, Telangana), Ethyl cellulose (N R Life Care, Gujrat), HPMC K 15 & E15 (Deepen Drugs Pvt Ltd, Gujrat), Xanthan gum & Guar gum (Hemadri Chemicals Ltd, Mumbai), Sodium alginate & Karaya gum (Sage Herbals Pvt Ltd, Hyderabad), Chitosan (Ranbaxy Research Laboratories, Gurgaon), Sodium bicarbonate, Citric acid & Microcrystalline cellulose (Green Pharma Pvt Ltd, Hyderabad). All other chemicals and reagents used were of analytical grade.

Method:

The preparation of floating tablets was carried out using the direct compression method, with modifications made to the formula based on different parameters. The specific details can be found in the tables below. An acebutolol hydrochloride floating tablet was formulated according to the specifications stated in Table 1. The measured quantity of the medicine was combined with the remaining excipients, which had already been individually sieved through a number 60 sieve, in a specific sequence, excluding talc and magnesium stearate. Finally, an 8-station tablet compression machine was used to compress the mixture of talc and magnesium stearate into tablets using a flat round punch. [15-19]

Fig 2: Formulated floating tablet

Table 1: Development of floating tablets of Acebutolol hydrochloride

Name of the ingredients in a tablet	FA1 (mg)	FA2 (mg)	FA3 (mg)	FA4 (mg)	FA5 (mg)	FA6 (mg)	FA7 (mg)	FA8 (mg)
Acebutolol hydrochloride	443.2	443.2	443.2	443.2	443.2	443.2	443.2	443.2
PLG	60	-	-	-	-	-	-	-
Carbopol 940	-	60	-	-	-	-	-	-
HPMC K15	-	-	60	-	-	-	-	-
HPMC E 15	-	-	-	60	-	-	-	-
Xanthan gum	-	-	-	-	60	-	-	-
Guar gum	-	-	-	-	-	60	-	-
Karaya gum	-	-	-	-	-	-	60	-
Chitosan	-	-	-	-	-	-	-	60
Sodium bicarbonate	30	30	30	30	30	30	30	30
Citric acid	6	6	6	6	6	6	6	6
Magnesium stearate	6	6	6	6	6	6	6	6
Talc	12	12	12	12	12	12	12	12
Microcrystalline cellulose	42.8	42.8	42.8	42.8	42.8	42.8	42.8	42.8
Total	600	600	600	600	600	600	600	600

Evaluation of the granules

Before compression step into tablets, the granules were evaluated for some evaluation properties such as angle of repose which done by funnel method, bulk density, tapped density, compressibility index (CI), and Hauser's ratio as shown in Table 4. Tapped bulk density (TD), bulk density (BD), and CI were calculated by using the following equations:

Tapped density = Weight of powder /Bulk volume of powder

Carr's Index = Bulk density×100/ Taped density

Bulk density = weight of the sample / bulk volume of the powder

Hausner 's ratio = Tapped density /Bulk density

Evaluation of tablets

The prepared tablets were evaluated for weight variation, drug content, friability, hardness, and thickness as shown in Table 5 and and in vitro dissolution test.

Friability, hardness, and thickness

The tablets were subjected to abrasion and stress in a Roche friabilator to determine their friability. To do this, we spin a plastic chamber containing the pills at a rate of 25 revolutions per minute. With each revolution, the tablets are dropped from a height of six inches. A full tablet sample weighing about 6.5 g is required for analysis of tablets with a unit weight of 650 mg or less. The intact pill sample that was measured was rinsed, put into the friabilator, and then spun 100 times. After the rotation, the pills were given one last dusting and then weighed. [18-23]

The thickness of each set of tablets was measured with a vernier caliper. The thickness of the tablet shouldn't exceed ± 5% of the given standard value.

10 tablets were taken randomly for hardness test from each formula. The hardness was measured using Monsanto manual hardness tester, and the average value for the tablets was measured [24].

Weight variation

20 tablets were randomly selected from each formula (FA1 to FA8), and the average weight of these tablets was measured. According to the Indian Pharmacopeia (IP), not more than 2 of individual weights of tablets were out of the average by more than the percentage deviation and none deviate twice the percentage.[25]

Table 3: Weight variation data

S.no	Average weight of tablet in mg	Percentage Deviation
1.	80 mg or less	± 10%
2.	More than 80 mg and less than 250 mg	± 7.5%
3.	250 mg or more	± 5%

Uniformity of drug content

The following method was used to ascertain the drug concentration in every formulation. A hundred milliliters of simulated gastric fluid (SGF) with a pH of 1.2 was used to dissolve the about twenty pills that were crushed to obtain the powder. The weight of the powder was average. The solution underwent filtration using Whatman filter paper no.41. The solution was subsequently diluted to the correct concentration, and its absorbance at 233 nm for Acebutolol hydrochloride was measured with a spectrophotometer. The blank used for comparison was SGF pH 1.2. [26-27]

In vitro dissolution test:

To assess the rate of release of Acebutolol hydrochloride from floating tablets, the USP Dissolution Testing Apparatus II (Paddle type) was utilised. The dissolve test required heating 900 cc of pH 1.2 simulated stomach fluid to 37 ± 0.5°C and spinning it at 50 rpm. For 10 hours, at regular intervals, a small amount of the sample was taken out of the dissolving apparatus. Another batch of dissolving agent was added to the extracted fraction. Whatman filter paper no. 41 was used for the filtration process of the samples. A wavelength of 233

nm was used to measure the solutions' absorbance. The cumulative percentage of medication release was determined after an equation was generated using a standard curve. [28]

In vitro drug release kinetics

The solubility of a medicine in solid dosage forms can be characterised by the kinetic model, in which the drug's dissolution rate is proportional to the duration of the test. To study the precise mechanism of drug release from the tablets, the data on drug release was analysed using the following models: first order, zero order, Korsmeyer - Peppas, and Higuchi square root. A goodness of fit test determined which model was most appropriate. Statistical functions in MS Excel were used to do regression analysis on the collected data. [29-30]

Result:

Evaluation of granules for all formulas (FA1 to FA8) was done and the results showed in Table 4. Bulk Density, Tapped Density, Carr's Compressibility and Hausner's ratio for each formula was measured, and results showed excellent and good flow for all the formulas.

Table 4: Pre-compression parameters of powder blend of Acebutolol hydrochloride

Formulation code	Bilk Density (g/ml)	Tapped Density (g/ml)	Carr's Compressibility	Hausner's Ratio
FA1	0.68	0.72	5.59	1.06
FA2	0.74	0.81	9.14	1.10
FA3	0.72	0.79	8.97	1.10
FA4	0.47	0.51	7.99	1.09
FA5	0.44	0.48	7.65	1.08
FA6	0.67	0.71	5.49	1.06
FA7	0.71	0.79	9.50	1.11
FA8	0.45	0.49	7.9	1.09

CI which was calculated by equation 3 showed most of the formulas was having good compressibility, which they were showed good CI. Results showed that Hausner ratio values were of 1.09 indicates excellent flow, in which Hausner ratio is a measure of the interparticulate friction. Lower CI or lower Hausner ratios of granules indicates better flow properties than higher values as shown in Table 4.

Table 5: Post-compression parameters of floating tablets of Acebutolol hydrochloride

Formulation Code	Thickness (mm) (n = 6) Avg ± S.D	Hardness (kg/cm^2) (n=6) Avg ±S.D	Friability (%) (n = 20)	Weight variation (g) (n=20) Avg ± S.D	Floating lag time (FLT) (sec)	Total floating time (TFT) (min)	Drug content (%)
FA1	2.97±0.005	4.76±0.12	0.56	0.597±0.004	1	275	**96.52**
FA2	2.72±0.004	4.90±0.11	0.23	0.604±0.003	1	365	**101.54**
FA3	3.03±0.008	5.06±0.21	0.16	0.602±0.005	1	320	**95.16**
FA4	2.8 ± 0.004	4.86±0.14	0.19	0.595±0.008	1	280	**98.52**
FA5	3 ± 0	4.84±0.18	0.32	0.594±0.008	1	335	**98.74**
FA6	2.72±0.004	4.76±0.12	0.55	0.606±0.004	1	400	**102.97**
FA7	**2.78±0.004**	**4.90±0.11**	**0.51**	**0.598±0.005**	**1**	**590**	**97.84**
FA8	**2.97±0.005**	**4.84±0.18**	**0.39**	**0.605±0.008**	**1**	**465**	**91.68**

Results for the evaluation of tablets were shown in Table 5; weight variation study was considered within the accepted range as stated by the USP for all the formulas.

Drug content measurements were within the accepted values. Friability measurements were accepted for all formulas because the values obtained were <1% as stated by the USP. Hardness values were within the range of sustained or controlled release tablet type. Thickness values showed acceptable properties and complied with pharmacopeia specifications.

FTIR

Acebutolol hydrochloride's FTIR spectrum is displayed in Figure 3. The NH stretching peak was seen at 3398 cm-1. The carboxylic acid peak was seen at 2993 cm-1. The C=C aromatic stretching peak was observed at 1616 cm-1. The methyl and methylene peaks were found at 1475 cm1. The C-O peak was seen at 1276 cm-1. The secondary alcohol peak could be seen at 1114 cm-1. An aromatic unsaturated C=C signal was detected at 843 cm-1. The positions of the primary peaks did not significantly alter when comparing the spectra of the best formulation of Acebutolol hydrochloride with those of pure Acebutolol hydrochloride in Figure 3. This shows that there was no chemical interaction between the medicine and the excipients.

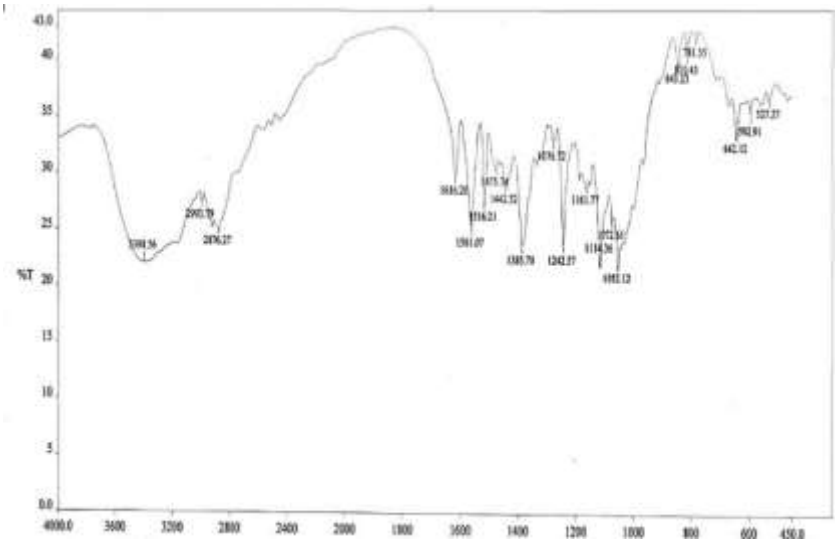

Fig. 3: FTIR spectrum of Acebutolol hydrochloride

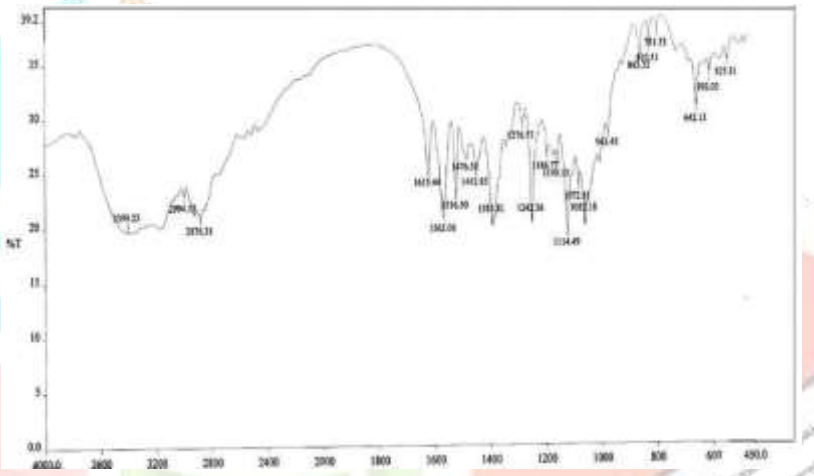

Fig. 4: FTIR spectrum of best formulation of Acebutolol hydrochloride

In vitro dissolution studies data

To make a floating tablet containing acebutolol hydrochloride (FA1–FA8), an effervescent agent with the highest ratio was mixed with natural polymers (Chitosan, Xanthan gum, Karaya gum, and Guar gum) and synthetic polymers HPMC (K15 and E15), Carbopol 940, and PGA. The tablet weighed ten percent in total. According to the information in table 4.2, the tablets' thickness varied from 2.72 to 3.03 mm, and they all appeared to be in good condition with no evidence of breakage. Hardness ranged from 4.76 to 5.06 kg/cm2, weight fluctuated within a 5% w/w variable, and friability was between 0.16 and 0.56% w/w. Every formulation had a floating lag time of one second, and the total floating time varied from 274 to 590 minutes.

Table 6: In vitro dissolution studies data for floating tablets of Acebutolol hydrochloride

Time (min)	% Amount of Drug released							
	FA1	**FA2**	**FA3**	**FA4**	**FA5**	**FA6**	**FA7**	**FA8**
0	0	0	0	0	0	0	0	0
5	14.48	15.54	13.48	16.54	13.28	14.45	3.25	5.38
10	25.84	25.15	25.54	25.29	28.68	26.25	6.54	14.21
30	32.84	33.98	36.87	39.35	36.64	32.49	12.45	22.51
60	46.45	39.46	52.15	58.48	41.38	41.57	21.49	31.67
90	52.15	46.38	61.68	66.68	46.59	49.24	29.57	44.18
120	61.64	55.19	69.18	75.27	58.49	56.49	36.16	55.91
180	68.87	61.65	78.29	83.15	66.67	69.15	42.98	62.24
240	79.57	76.58	82.67	87.98	79.48	77.28	55.46	69.43
300	88.74	84.82	87.49	90.54	87.24	83.84	62.32	76.57
360		88.84	90.35		91.37	89.45	70.42	82.19
420		92.45				93.48	77.29	88.73
480							81.37	93.82
540							88.61	
570							94.42	
600							98.81	

Table 6 of the in vitro dissolution research reveals that all of the formulations containing Karaya gum (FA7) remained afloat longer in the simulated stomach fluid pH 1.2 than other formulations, with a drug content ranging from 91.68% to 102.97%. This is because, when compared to other polymers, karaya gum has the biggest swelling index, which stimulates the creation of porous gel. The in vitro dissolving investigations displayed in table 6 and figure 5 indicate that the drug was continually released from the floating tablet for 600 minutes. A plausible reason for the dosage form's ongoing floating could be that the gel's increased swelling and viscosity slow down the drug's release from the matrix. The exceptionally high degree of swelling of the polymer is caused by its improved ability to absorb water from its surroundings. Figures 6-8 provide kinetic plots of the dissolution data, which further illustrated how the release kinetics followed zero-order non-fickian diffusion control.

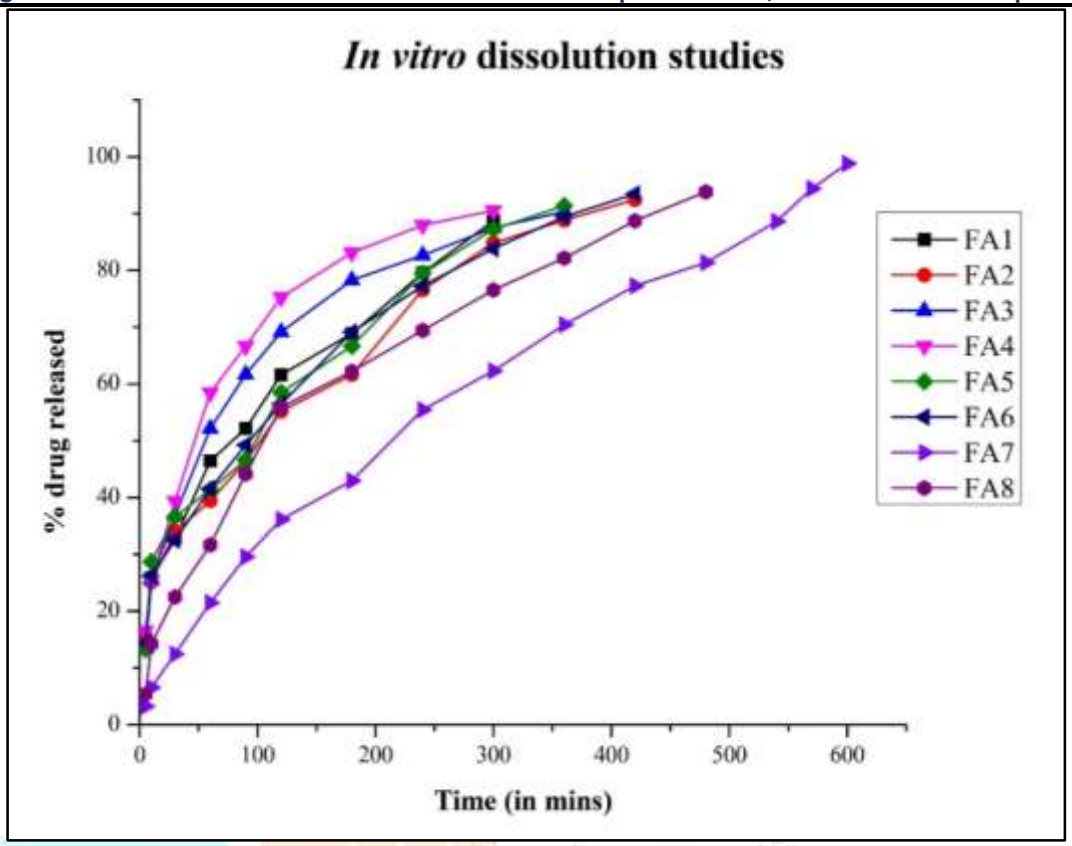

Fig. 5*: In vitro* dissolution profile for floating tablet of Acebutolol hydrochloride

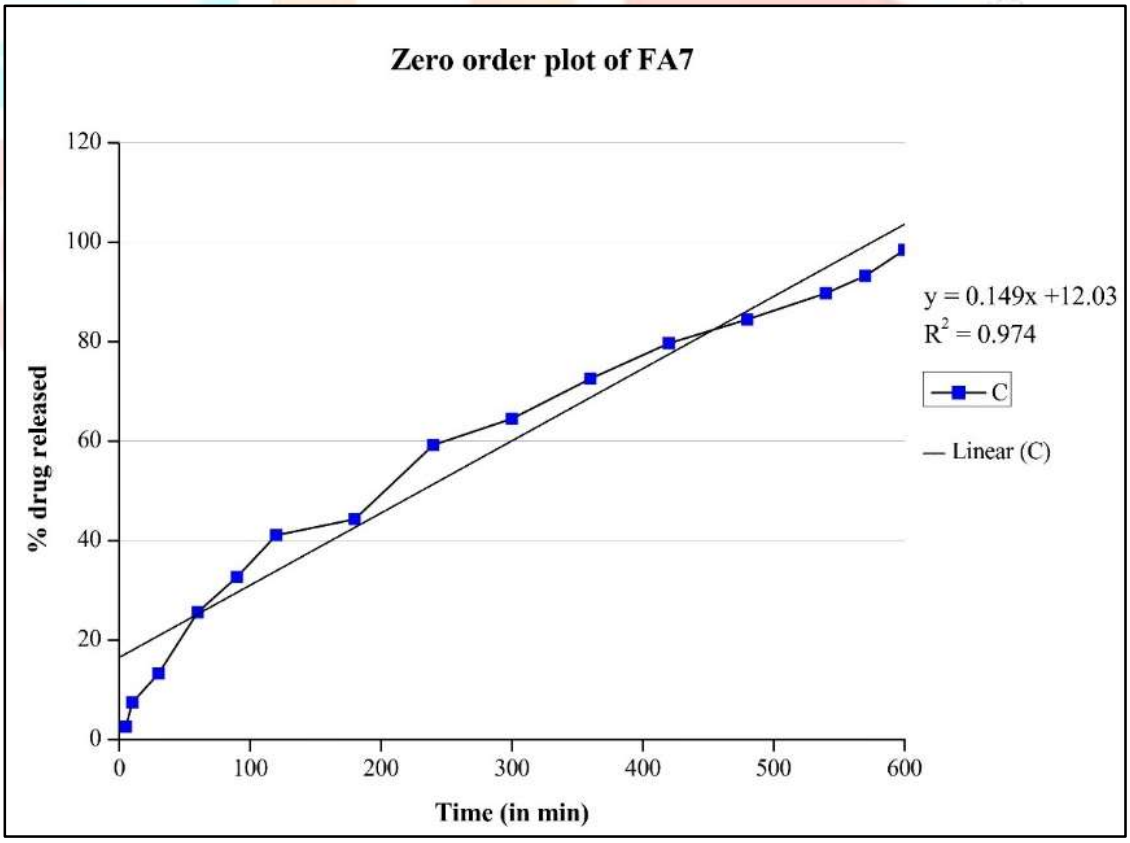

Fig 6: Zero order plot for best formulation of floating tablet of Acebutolol hydrochloride (A7)

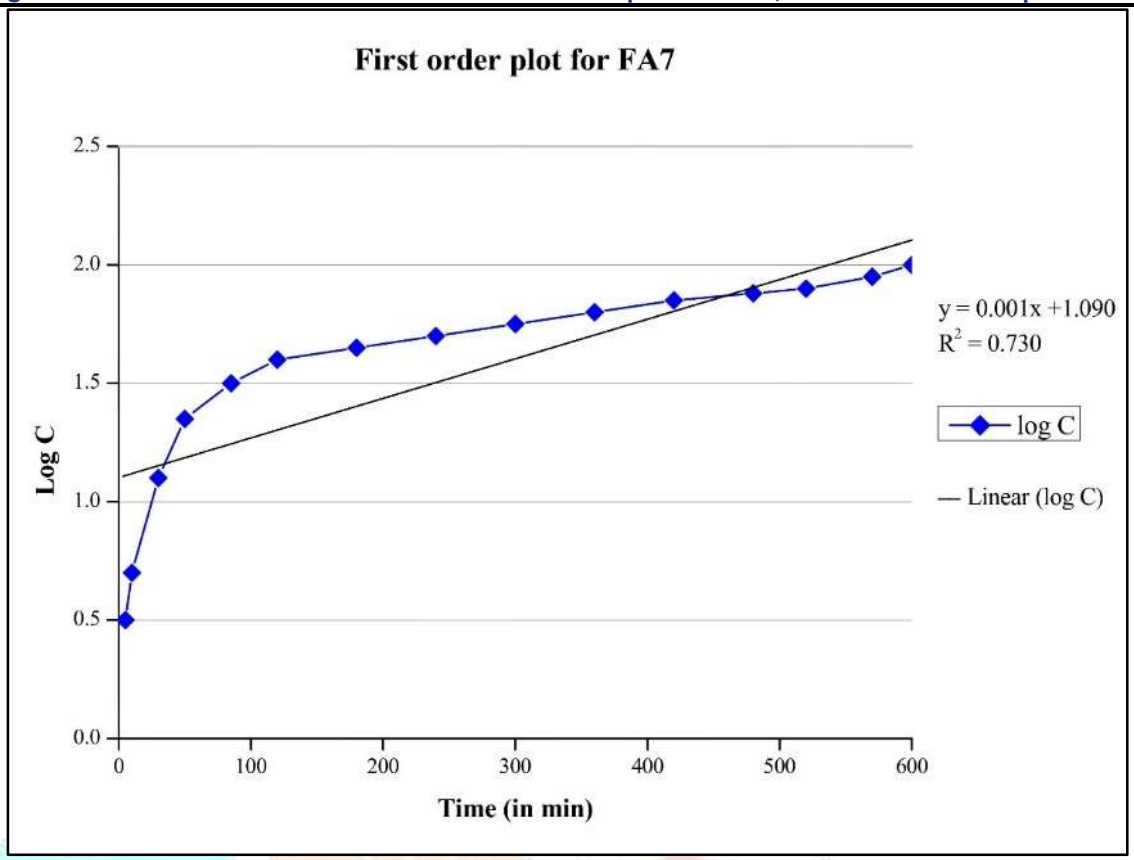

Fig. 7: First order plot for best formulation of floating tablet of Acebutolol hydrochloride (A7)

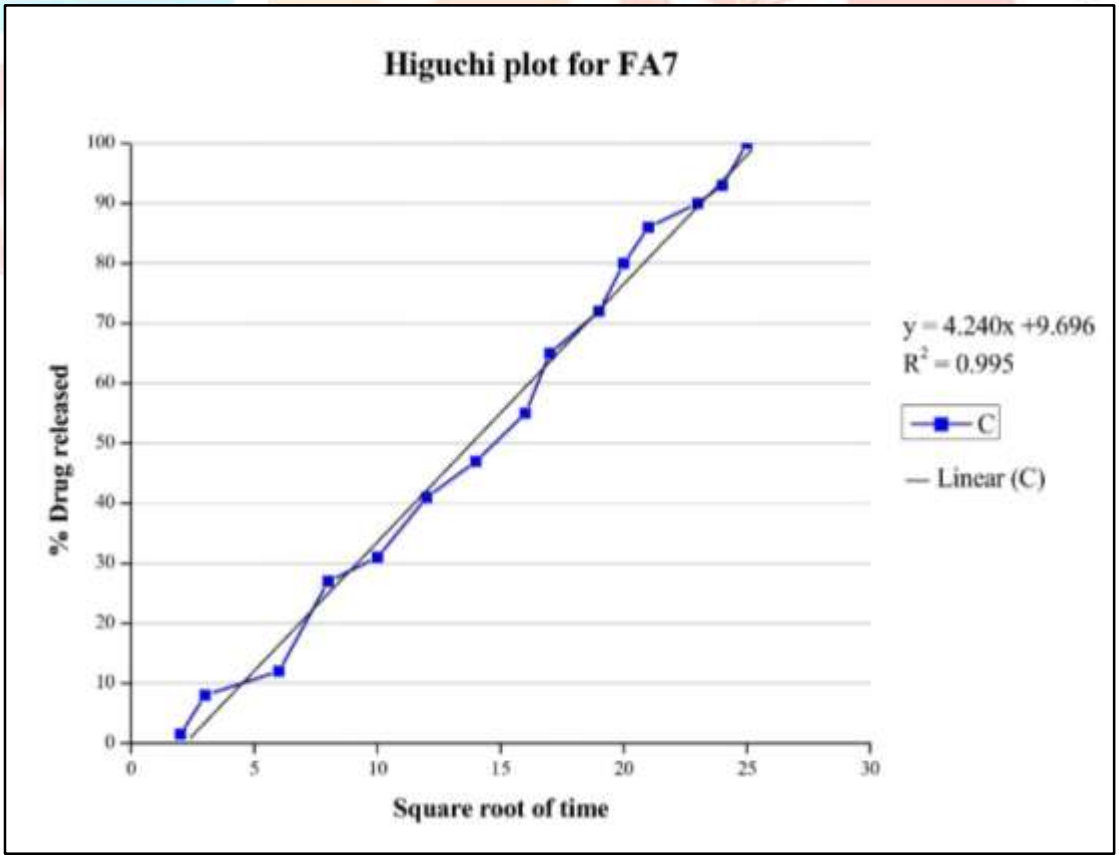

Fig. 8: Higuchi plot for best formulation of floating tablet ofAcebutolol hydrochloride (A7)

Stability studies

Table 7 indicates that there was no significant change in post-compression before and after the stability period for the optimized Acebutolol hydrochloride (FA7) formulation.

Table 7: Stability studies data for best floating tablet of Acebutolol hydrochloride

Parameter	Initial	After 3 months
Hardness (kg/cm^2)	4.90	5.1
Friability (%)	0.51	0.58
Floating lag time (sec)	1	1
Total floating time (min)	590	592
Drug content (%)	97.84	97.28

Conclusion:

An effervescent floating tablet formulation of Acebutolol hydrochloride was developed to increase the drug's bioavailability. Using a direct compression method, the study compared synthetic and natural polymers to enhance stomach retention. Effervescent agents like sodium bicarbonate and citric acid were combined with various polymers to create a gastro-retentive dosage form with a lower density than stomach fluid, thereby increasing gastric residence time. FTIR was used to identify the retrieved medications, and floating tablets were made to test polymer effects on the swelling index and buoyancy. The ideal formulation showed no drug-excipient interactions and exhibited stable post-compression parameters. The most effective combination included sodium bicarbonate, citric acid, and karaya gum (FA7), resulting in a floating lag time of 1 second, total floating time of 590 minutes, and 98.91% release after 600 minutes. The release kinetics indicated a zero-order non-fickian diffusion-controlled system, reducing plasma concentration fluctuations by extending gastric residence time.

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