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FORMULATION AND EVALUATION OF FLOATING TABLET OF ATENOLOL FOR THE TREATMENT OF HYPERTENSION

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Abstract: -

The current study set out to develop a gastro-retentive atenolol floating tablet. Angina pectoris and hypertension are both treated with this beta-blocker (beta-adrenoreceptor antagonist). When used orally, it is only partially absorbed from the digestive system and only 50% of the medication is accessible; the other 25% is excreted unchanged in faeces. This problem results from insufficient absorption in the lower gastrointestinal system. To improve the oral bioavailability and therapeutic effectiveness of atenolol, the gastro-retentive floating drug delivery system (GFDDS) growth was deemed useful. The direct compression technique was used to make floating pills of atenolol (F1-F5). To reduce the floating delay, a polymer like HPMC was used together with gas-producing chemicals such citric acid and sodium bicarbonate. Evaluations were done on the blends, compressibility index, bulk density, Hausner's ratio, angle of repose and tapped density. Additionally evaluated were the tablets' hardness, diameter, weight variation, homogeneity of the drug content, friability, floating and buoyancy lag times, impact of hardness, in vitro swelling behavior, and in vitro release of drug. The USP dissolving test apparatus-II was utilised to rotate 900 cc of a hydrochloric acid buffer with a pH of 1.2 at 50 rpm while maintaining a 37.5°C temperature for the in-vitro release of drug examination.

Keywords: Direct Compression Method, Floating Tablets, HPMC, Atenolol, Dissolution, Gastro-Retentive.

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. [4,5].

- Davis published the first description of floating drug delivery systems (FDDS) in 1968. These developments made it possible for drug delivery devices to stay longer in the stomach and other parts of the gastrointestinal tract (GRT). The transit rate of other drugs is unaffected by this prolonged holding time in the stomach. FDDS is especially beneficial for medications that operate locally in the stomach, have a constrained window of absorption in the upper small intestine, or have low solubility or stability in intestinal fluids. [6,7]
- A beta-blocker known as atenolol, it is frequently used to treat hypertension, arrhythmias, angina pectoris, myocardial infarction, and to prevent migraines. Atenolol absorbs quickly and consistently through the mouth, although not completely. A dose taken orally is absorbed from the digestive system in around 50% of cases, with the remaining 50% being expelled unchanged in faeces. Consequently, the atenolol gastroretentive drug delivery method would result in better therapeutic outcomes. [8]
- Any heart or circulatory system ailment is included in the category of cardiovascular disease.[9] The main risk factors for cardiovascular illnesses are smoking, high blood pressure, high cholesterol, drinking alcohol, and obesity.[10]
- Hypertension is responsible for approximately 9.4 million out of the 17 million annual fatalities caused by cardiovascular diseases worldwide.[11]
- Approximately 60% of people had hypertension and hypercholesterolemia during the third NHANES, and 55% of people with hypercholesterolemia also had hypertension. [12]
- To extend drug release and give matrix tablet formulations floating capabilities, the current effort will aim to synthesise GFDDS of atenolol using natural and synthetic polymers of various viscosity grades.[13]

MATERIAL & METHODS

Material:-Atenolol was obtained from Yarrow chem. Pvt.Ltd,Mumbai ,and Sodium bicarbonate was obtained from Modern labs Indore , Sodium alginate and Citric Acid was obtained from Merk Specialities Pvt., Ltd. Microcrysttaline cellulose (MCC),Eudragit RS 100,HPMC,Carbapol940 was obtained from SD.Fine Chem Pvt.Ltd, Mumbai.

Methods:- Utilising polymers such as HPMC, sodium bicarbonate, citric acid, carbapol 940, EUDRAGIT RS-100, and sodium alginate in a range of ratios (marked as F-1 to F-5 in the Table), all of the formulations were developed utilising the direct compression method. All materials, including the atenolol, were separately put through sieve number 40. By triturating for up to 15 minutes, all the materials were thoroughly combined. MCC was used to lubricate the powder mixture.

Fig.1: Formulated floating tablet

S.NO	INGREDIENTS	measured in milligrammes				
		F1	F2	F3	F4	F5
1.	Atenolol	50	50	50	50	50
2.	HPMC	80	70	60	50	40
3.	NaHCO3	30	30	30	30	30
4.	Citric acid	50	50	50	50	50
5.	Carbapol 940	40	40	40	40	40
6.	Eudragit RS-100	30	35	40	45	50
7.	Sodium alginate	40	50	50	50	50
8.	MCC	30	35	40	45	50
	Total weight	350	350	350	350	350

Table-1: Atenolol floating tablets formulation composition (F1 – F5)

Evaluation of powder blend (pre-compression parameter)

Repose Angle [14]

The powder's repose angle was measured with the help of the funnel method. Carefully weighed grains of powder were poured into a funnel. The funnel was lifted to about 2.0 cm above the solid surface, where its tip just barely touched the top of the powder mound. The funnel was then left unlocked, letting the powder descend to the ground without restriction. The diameter of the powder cone and the diameter of the cone were used to determine the angle of repose using the given equation.

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

Consequently, = Tanθ-1h/r

Where θ is the cone's repose angle, r is radius of its base, and h is its height.
The results are shown in Table 2.

Bulk Density (Db) [15]

It measures the bulk volume to total mass ratio of the powder. It was calculated by weighing the powder and then adding it to a measuring cylinder after passing it through a standard sieve no. 20. The bulk volume was the initial volume. Using this data, the following formula was used to get the same. It is measured by this formula.
Db = M/ Vb and is represented in gm/ml.
Where M and Vb, respectively, stand for the powder's mass and bulk volume.
Table 3 presents the outcomes.

Tapped Density (Dt) [15]

By separating the entire mass of the powder by the size of the tap, one can get the bulk density. Any change in volume below 2% was observed after 750 taps. Additional 1250 taps were performed, recording the volume after each tap, if the difference was greater than 2%. The tapping process was repeated until the volume difference between each tap was under 2%. The unit of bulk density is grammes per millilitre (g/mL).
Dt = M/ Vt

Compressibility index and Hausner's ratio[16]

The assessment of tapped and bulk density yields the measurement of compressibility index. The compressibility of a substance decreases as its flowability increases. The material is regarded as having free-flowing properties when the compressibility index is between 20 and 30 percent. Compressibility index (CI) is calculated as (Dt - Db) / Dt.
The following formula is used to determine the Hausner ratio, which is an indirect index for assessing the powder flow.
Hausner's ratio: bulk density divided by tapped density

Evaluation of tablets

Post compression parameters [17]

Tablets were inserted between the movable jaw and the stationary jaw of the Vernier callipers, which are used to measure thickness. The screw was then turned to accommodate the tablet between the jaws, and the values are recorded.

Hardness: When pressure is applied along a tablet's diameter, the amount of force necessary to fracture it is referred to as tablet hardness. The tablet's resistance to breaking, chipping, or wearing during handling before usage and storage depends on this crucial feature. Each formulation's tablet hardness is evaluated with the help of the Monsanto Hardness tester.

Friability: The mechanical strength of medicines is measured by their friability. Friability is assessed using the Roche friabilator. Placed inside a revolving plastic container, tablets are dropped from a height of six inches. Tablets are dusted, reweighed, and the % weight loss is used to determine friability after four minutes of rotation.

Friability [%] = (Initial weight - Final weight) / (Initial weight x 100)

Variation of Weight: The weight average of the twenty pills was measured after measuring the weight of each one separately. The average weight was then calculated and compared to the weight of each pill. Each tablet must adhere to the test requirements in order to meet the criteria, with a maximum of two tablets being allowed to depart from the average weight by up to 2%. Furthermore, it's crucial to make sure that no tablet exceeds the maximum %.

Drug content uniformity: To determine the medication content, three pills are randomly selected from each batch. The appropriate medium is then added to 100 ml volumetric flasks containing these tablets. 1 ml is taken from each volumetric flask after a 48-hour incubation period and put into test tubes. The samples are properly diluted before being examined by means of a spectrophotometer UV of the right wavelength. The linear equation derived from the tuning curve is used to compute the content of drug. [18,19].

Dimensions of Tablet: A vernier calliper can be used to measure the thickness and tablets diameter. Next, the sizes of the three randomly selected tablets from each formulation are determined. The dimensions are given in millimetres. [19]

Swelling study: - Each pill can be put in a different glass beaker that has a pH 1.2 HCl buffer in it so that the swelling index (SI) can be calculated. The incubation period for the tablets should be predetermined, ranging from one hour to a maximum of 24 hours. Any extra liquid on the surface should be carefully drained after the floating pills have been taken out of the beaker. The suggested method can then be used to calculate the swelling index (SI). [20, 21:]

Index of Swelling (SI%) = - 100

Time spent floating and duration of floating: The USP-II paddle equipment was used to test the developed formulations' buoyant properties while the tablets were submerged in water. The study's medium, 900 millilitres of hydrochloric acid buffer with a pH of 1.2, was kept at a constant 37 0.5 °C temp during the experiment. The duration and lag time of floating, as well as how long it took for the pills to start floating in the stomach fluid after insertion, were all measured. Throughout the trial, the integrity of the test tablets was regularly checked. The results for the floating duration and floating lag time of the various formulations are shown in Fig 1 and Table 4, respectively.

In vitro drug release studies: - Using the authorised process and tools, in vitro release of drug tests were performed on the tablets. The USP Type-II dissolution device held the pills together with sinkers in six compartments. The dissolution medium was 900 cc of degassed 0.1N HCl, with a 100 rpm

paddle speed and a 37 0.5 °C temp. At 1, 3-, 6-, 9- and 20-hour intervals Samples were collected and pooled for UV spectrometer analysis at 261 nm.[23]

Rapidly conducted stability tests

Atenolol floating tablets were tested for accelerated stability at 40 degrees Celsius and 75% relative humidity for four weeks. The removed trials were examined for physical characteristics and put through in vitro release of drug assays.[24]

Analysis of in-vitro drug release

The following mathematical models for characterising the drug release pattern were fitted with the outcomes of the in-vitro data release:

Zero order kinetics

The following equation can be used to forecast a zero-order release:

At = AO - KO * t

In this equation, At stands for the release of drug at time t, AO for the starting concentration of drug, and KO for the zero-order rate constant (hr-1). When charting the cumulative percent of release of drug versus time, a linear relationship with a gradient equal to KO indicates zero-order release kinetics.

First order kinetics

The following equation would predict a first release order:

C=log in log CO - Kt /2.303

The equation includes variables C (remaining drug at time t), CO (initial drug amount), and K (first-order rate constant, hr-1). Plotting cumulative percent of remaining drug against time shows a linear relationship, indicating first-order kinetics. The constant "K" can be determined by multiplying the line's slope by 2.303, confirming first-order kinetics. The slope of the line can also be multiplied by 2.303 to obtain the constant "K".

Higuchi's Model

Drugs released from matrix devices by diffusion have been described using Higuchi's conventional diffusion equation.

Ft = Q = A D (2C – Cs) Cs t

Where D is the drug's coefficient of diffusion in the matrix, and Q is the medicine amount released at time t.

A is the full dosage contained in a single matrix volume.

The drug's solubility in the diffusion medium is denoted by Cs.

Matrix porosity is equal to Time (hrs) at which 'Q' released quantity of medication, which is provided by t = tortuosity.

If D, CS, and A are considered constants, this equation could be made simpler. Equation therefore becomes: Q = K (t) 12.

The results of utilising the equation previously indicated to plot the cumulative release of drug against the square root of time reveal a linear connection, proving that the release of drug mechanism is diffusion-based. This line's slope is denoted by the letter "K." To describe the release rates from controlled release polymeric matrices, Korsmeyer et al. developed the Korsmeyer and Peppas' model equation.

Q = K1t n

Where K = Kinetic constant including the geometric and structural properties of the pills and Q = Percentage of medication released at time t and diffusional exponent n serves as an indicator of the release mechanism.

n is equal to 0.45 for Fickian release, but it can vary from 0.45 to 0.89 for anomalous (non-Fickian) transport; it is equal to 0.89 for zero order release (case II transport). For n 0.89, super case II transport is advised.

Fourier Transforms Infra-Red (FTIR) Spectroscopy

FTIR was used to analyse the IR spectra of the medication found in KBr pellets while scanning slowly between 4000 and 400 cm-1. Peak values (wave numbers) and potential functional groups are displayed in spectra in proportion to a standard value. These findings demonstrate that the material was pure atenolol when compared to atenolol's chemical structure. To determine whether a medicine was compatible with polymers, an FTIR research was conducted.

Stability studies of the most satisfactory formulation

The best formulation's stability studies were finished in accordance with ICH criteria. After achieving encouraging results, the ideal formulation was stored for two months in an aluminum-packaged humidity chamber at temperatures of 30°C/65°RH and 40°C/75°RH. Trials were examined for content of drug, in vitro dissolution, a variety of other physicochemical properties once the research was finished and floating behaviour. Tables 10 and 11 list the corresponding results.

RESULTS AND DISCUSSION

Drug-polymer combination and drug's individual FTIR spectra were both captured, The infrared spectra make it plainly evident that the medication did not interact with any polymers.

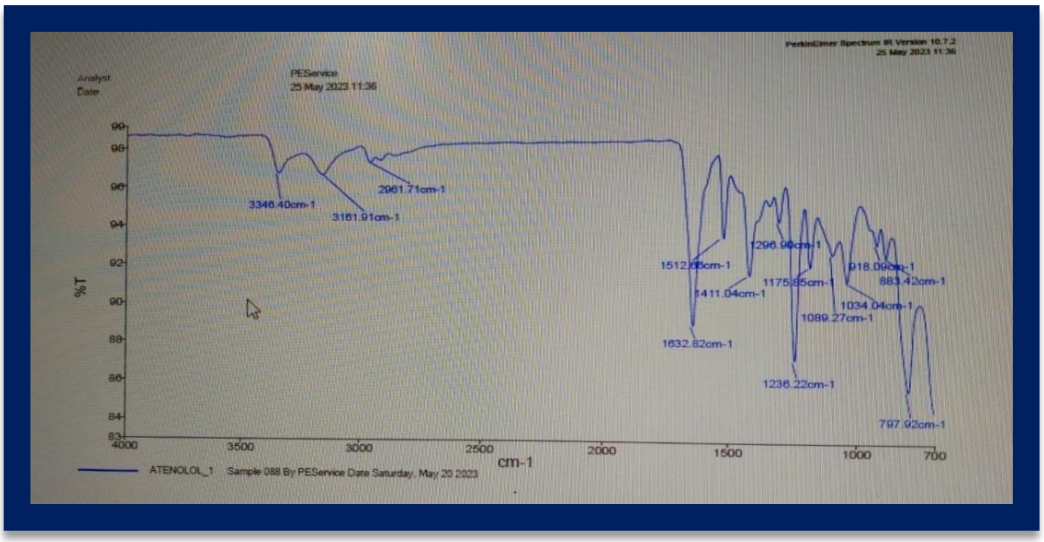


Fig.2: Pure ATENOLOL FTIR spectra

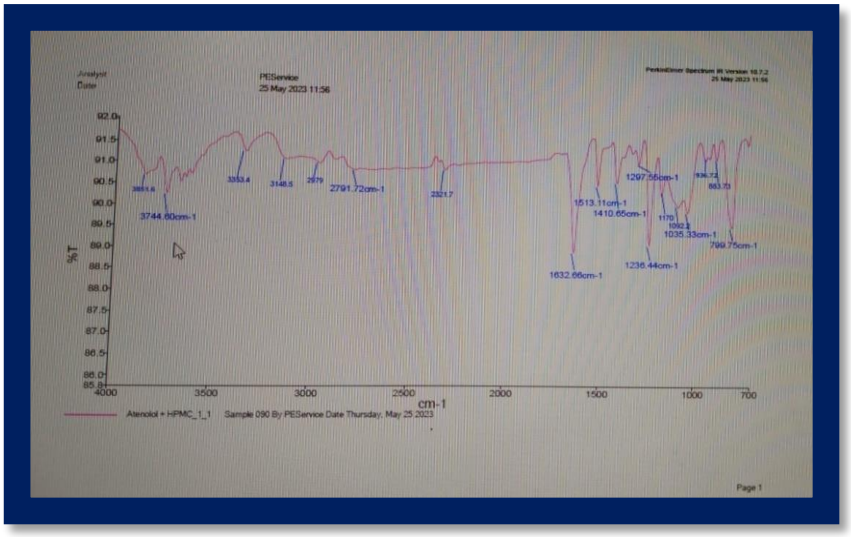


Fig.3: ATENOLOL FTIR spectra and HPMC physical mixture

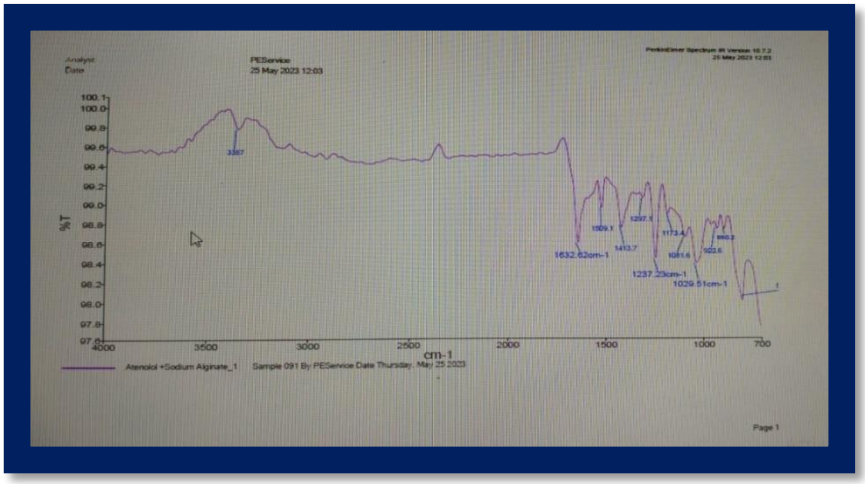


Fig.4: SODIUM ALGINATE and ATENOLOL FTIR spectra and mixture physically

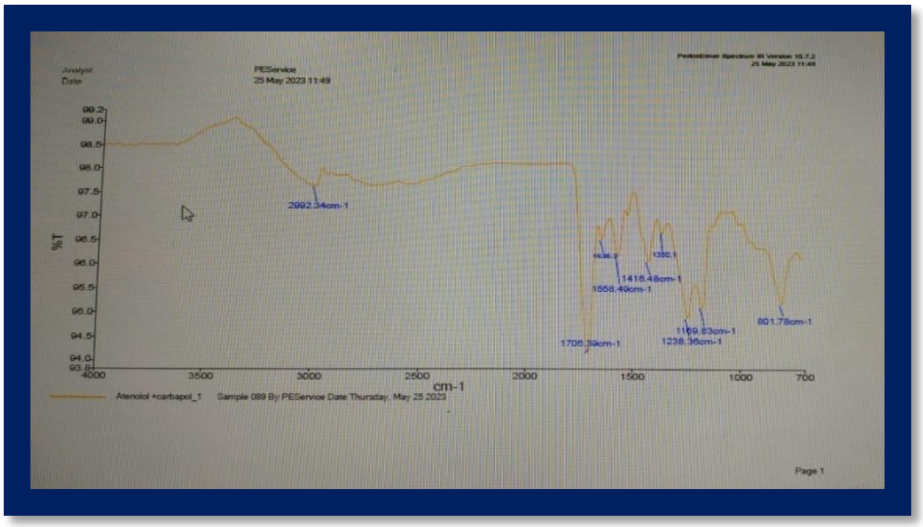


Fig.5: CARBAPOL and ATENOLOL FTIR spectra mixture physically

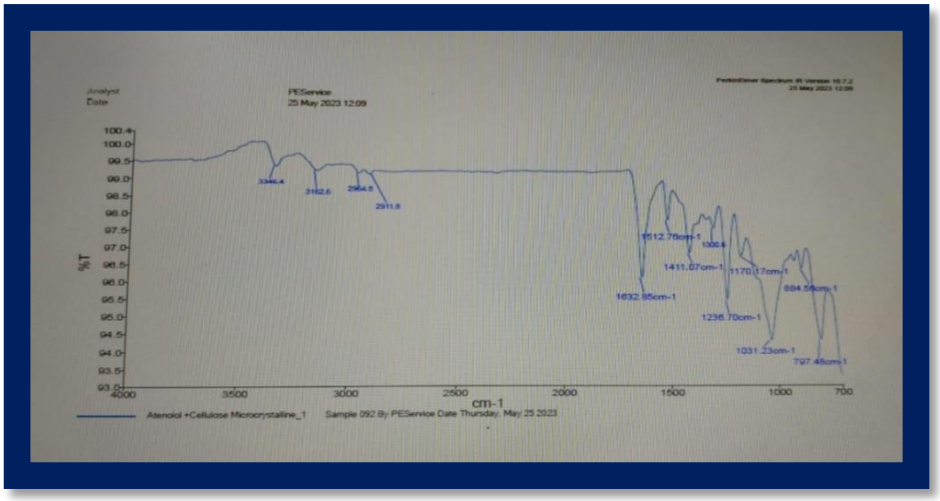


Fig.6: CELLULOSE MICROCRYSTALLINE and ATENOLOL FTIR spectra mixture physically

In the current study, an effort has been made to create floating atenolol tablets that are gastro-retentive. Atenolol floating tablets in various batches were created utilising chosen excipients based on preformulation experiments. Testing powders were assessed. Tablets were examined for bulk density, Hausner's ratio and tapped density before being punched as a compressibility index. The overall results of these research are shown in the following tables:

Table No. 2: Precompression evaluation of the Atenolol Powder Blend (F1-F5)

Code of Formulation (F)	Density of Bulk (G/Cm2)	Density Tapped (G/Cm2)	Angular Repose (Ø)	Index Carr (%)	Ratio of Hausner
1	0.34	0.44	24.74	17.20	1.20
2	0.37	0.41	37.59	18.18	1.25
3	0.35	0.47	24.38	20.72	1.26
4	0.36	0.44	32.96	17.17	1.22
5	0.34	0.41	37.52	17.06	1.20

Table No.3: formulations Post compression parameters (F1-F5)

Code of Formulation (F)	Length (mm)	Diameter (mm)	Hardness (Kg/Cm2)	Friability (%)	Change in Weight (mg)	Uniformity of content (%)
1	3.45± 0.2	8.80± 0.2	4.80	0.704	252± 0.09	99.30
2	3.50± 0.2	8.80± 0.2	4.30	0.672	250± 0.10	97.82
3	3.66± 0.20	8.80± 0.2	5.10	0.558	251± 0.26	98.65
4	3.49± 0.20	8.80± 0.2	4.70	0.661	250± 0.19	98.55
5	3.75± 0.20	8.80± 0.2	4.60	0.672	252± 0.14	99.13

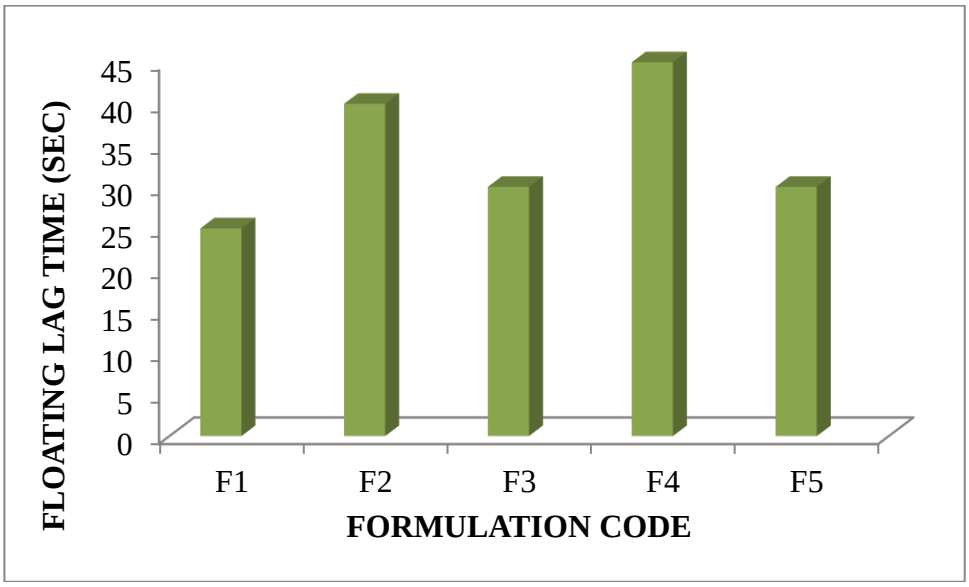
Evaluation of floating properties

A 100ml beaker of 0.1N HCl was filled with the pills. The necessary time for the pills to raise their surface and float was known as the lag time of floating. The stomach retentive floating tablets of atenolol's in vitro buoyancy properties were shown in table no. 4.

Table No.4: Floating property evaluation

Code of Formulation	floating lag in minutes	Hours of total floating time	Swelling index (%)
F1	25	>24	33.15
F2	40	>24	35.67
F4	30	>24	32.18
F4	45	>24	35.12
F5	30	>24	38.17

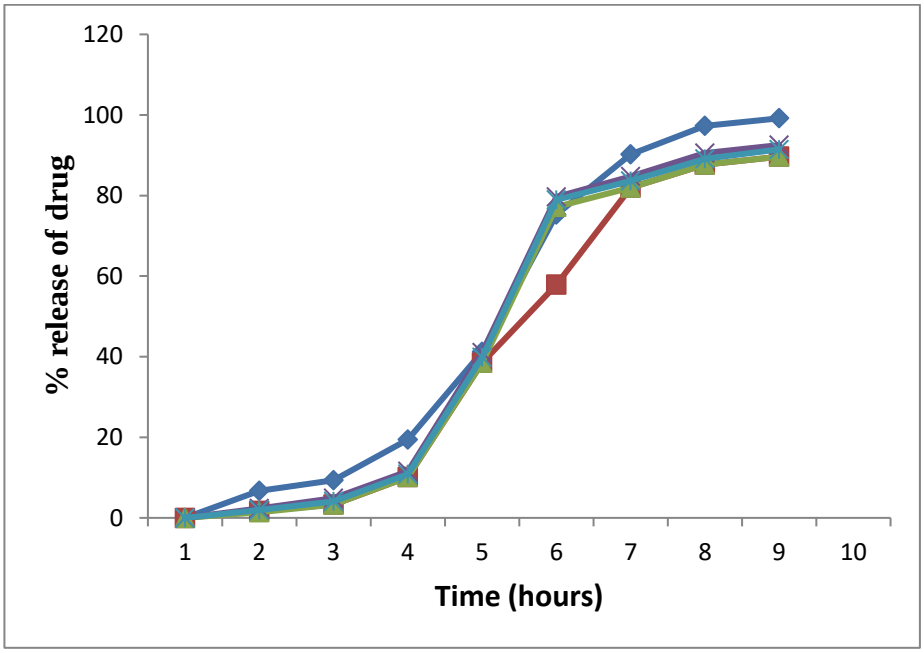
Initial time After 25 sec



Release Cumulative Percentage of Drug of All the Formulations

Table No.5: Release Cumulative Percentage of Drug (F1-F5)

TIME(h)	% DRUG RELEASE CUMULATIVE				
Formulations	1	2	3	4	5
0	0	0	0	0	0
1	6.691±0.000	1.672±0.099	1.409±0.150	2.327±0.159	1.967±0.099
2	9.351±0.197	3.313±0.150	3.313±0.150	4.920±0.421	4.133±0.098
4	19.392±0.000	10.106±0.057	10.106±0.057	11.550±0.372	10.861±0.150
8	41.165±0.150	38.527±0.057	38.527±0.057	41.009±0.398	39.873±0.098
12	75.275±0.038	57.920±0.114	77.223±0.057	79.621±0.569	78.897±0.114
16	90.199±0.057	81.987±0.057	81.987±0.057	84.744±0.151	83.628±0.057
20	97.275±0.038	87.697±0.113	87.697±0.113	90.520±0.542	89.076±0.114
24	99.165±0.140	89.638±0.150	89.638±0.150	92.526±0.317	91.443±0.150



Kinetic Modeling and Mechanism of Drug Release:
Following are the conclusions reached after applying kinetic equations to the dissolving characteristics of each batch of tablets from F1 to F5.

Table.No.6: Kinetic values from various formulation plots (F1-F5)

Code of Formulation (F)	Zero-order	First-order	Higuchi	kosermeyer-peppas	
	Coefficient of Regression (r2)	Coefficient of Regression (r2)	Coefficient of Regression (r2)	Slope (n)	Coefficient of Regression (r2)
1	0.8927	0.9538	0.9255	2.562	0.9148
2	0.8938	0.9456	0.9235	2.6487	0.916
3	0.8925	0.9487	0.9231	2.6966	0.9127
4	0.8923	0.9547	0.9255	2.562	0.9148
5	0.8927	0.9693	0.9230	2.7586	0.9106

STABILITY STUDIES:-
Since there were no changes in the in vitro drug release trials, floating lag time, or percentage drug content after 6 months of storage, it was decided that the optimised formulation F1 was stable.

CONCLUSION
As a selective 1-adrenoreceptor blocking medication, atenolol is used to treat hypertension. The polymers HPMC, sodium bicarbonate, citric acid, carbapol 940, EUDRAGIT RS-100, sodium alginate, and MCC were used to make the atenolol tablets used in this investigation. Atenolol floating tablet formulations in five different forms were created using the direct compression method. Of all the experiments, the F1 formulation was determined to be the best. Based on assessment data, the optimised formulation F1 may be administered once day for the treatment of angina pectoris and hypertension.The floating tablets may prolong the time the medicine spends in the stomach, control variations in plasma drug concentration, and eventually improve the drug's bioavailability. Based on the results of the FTIR testing, we determine that there are no drug-excipient interactions.

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References

1. Hwang S. J, Park.H & Park.K, Drug carrier system. 1998, 15 (3), 243–284.
2. Fukuda M, Peppas NA, McGinity JW. Floating hotmelt extruded tablets for gastroretentive controlled drug release system. J Control Release. 2006;115(2):121-129.
3. Khan F, Ibn Razzak SM, Khan ZR, Azad MA, Chowdhury JA, Reza S. Theophylline loaded gastroretentive floating tablets based on hydrophilic polymers: preparation and in vitro evaluation. Pak J Pharm Sci. 2009;22(2):155-161.
4. Tamizharasi S, Rathi V, Rathi JC. Floating drug delivery system. Syst Rev Pharm. 2011;2(1):19-29.
5. Wanjari D. A review on floating drug delivery system. Int J Bioassays. 2014;3(8):10.21746.
6. Soppimath, K.S,; Kulkarni, A.R,; Rudzinski, W.E,; Aminabhavi, T.M. Microspheres as floating drug delivery system to increase the gastric residence of drugs. Drug Metab Rev., Vol. 33: 2001; pg 149-160.
7. Garg, R.; Gupta, G.D. Progress in controlled gastroretentive delivery systems. Trop. J. Pharm. Res., Vol. 7(3): 2008; pg 1055-66.
8. Anlar S, Capan Y and Hincal AA. Physico-chemical and bioadhesive properties of polyacrylic acid polymers. Pharmazie 1993; 48(4): 285-287.
9. Fox CS. Cardiovascular disease risk factors, Type 2 diabetes mellitus, and the Framingham heart study. Trends Cardiovasc Med 2010;20:90-95.
10. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease risk factor, paradox, and impact of weight loss. J Am Coll Cardiol 2009;53:1925-32.
11. Department of Health Statistics and Informatics. Causes of death 2008: data sources and methods. Geneva: World Health Organization; 2008.
12. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Rohani HA, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: A systematic analysis for the global burden of disease study 2010. Lancet 2012;380:2224-60.
13. Martindale. The complete drug reference. 33 rd ed. London: Pharmaceutical Press 2002:841.
14. Lachman, L.; Lieberman, H.A.; Lachman, kaling, J.L. The theory and practice of industrial pharmacy, 3rd ed., Varghese Publishing House, Bombay, 1987; pg 67-71.
15. Lee JW, Park JH, Robinson JR. Bioadhesive- based dosage forms: the next generation. J Pharm Sci.2000; 89: 850-866.
16. M.Purushothaman, C.Saravanan. Formulation and Evaluation of Metaprolol Succinate Floating Tablets Using Peanut Husk Powder as Natural Polymer. International Journal of Chem Tech Research.2017;10(10):169-77.
17. Lachman L, Liberman HA, Kang JL. The theory and practice of industrial pharmacy. 3rd ed. Mumbai: Varghese Publishing house; 1987.p. 296-303
18. Sarfaraz Md, LingaReddy B, Doddayya H, Rajagopal UH., Design and in-Vitro Evaluation of Gastro Retentive Floating Tablets of Repaglinide. International journal of drug delivery and research, 5(3):322-332,(2013)
19. Patil H, Prashar B, Chandel A, Thakur V., Formulation and Evaluation of Floating Tablet of Pantoprazole Sodium Sequihydrate. Journal of Pharmacy Research, 5(9):4659- 4662,(2012)
20. Reddy VS, Badarinath AV, Prakash KG., Formulation and evaluation of floating tablets of ciprofloxacin hydrochloride. Asian Journal of Pharmaceutics , 12(2): 106-113,(2018)
21. Pierce MW., Transdermal delivery of sumatriptan for the treatment of acute migraine. The Journal of the American Society for Experimental Neuro Therapeutics, 7: 159- 163,(2010)
22. Srivastava, A. K.; Wadhwa, S.; Ridhurkar, D.; Mishra, B. Oral sustained delivery of atenolol from floating matrix tablets formulation and in-vitro evaluation. Drug Dev. Ind. Pharm., 2005; Vol. 31: pg 367–374.

23. Tiwari SB, Murthy TK, Pai MR, Mehta PR, Chowdary PB. Controlled release formulation of tramadol hydrochloride using hydrophilic and hydrophobic matrix system. AAPS PharmSciTech 2003;4:E31.
24. ICH guidelines for accelerated stability studies. Available from: http//www.ikev.org/haber/stabilite/kitap/29%201.1%20Stability%20 Workshop%20ICH%20Q1AR2%20C.pdf. [Last accessed on 2011 Oct 15]