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Development and evaluation of floating tablets of atenolol using hydrophilic and hydrophobic polymers

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INTRODUCTION

Today's formulations are consumed orally in excess of 90% of the time. This indicates that the researcher's primary focus is on this path and that this type of formulation is the most popular globally. Additionally, because oral medication delivery is the most popular method, it is the most economical, patient-complies, and has flexible formulation options. It is also very simple to administer. Furthermore, a therapeutic dose of the medication can be administered via this drug delivery system to the intended spot in the body, allowing for the quick achievement and maintenance of the intended drug concentration [1][2]. Due to its less invasiveness and greater naturalness, oral drug delivery is preferred over other traditional methods such as intravenous and intramuscular injection. The employment of gastro-retentive dosage forms is one of the many techniques established to guarantee optimum bioavailability. Increasing the stomach residence time, adhesion, swelling, inflating, and floating are all possible effects of a low-density or high-density system [3][4].

The process of gastric emptying is complex and very variable, affecting the in vivo administration of medication. Long-term stomach retention improves bioavailability, reduces medication waste, and improves the solubility of medications that are less soluble in high pH solutions. Several experiments have been conducted to increase the retention duration by preserving the dose form in the stomach [5][6]. Floating dosage forms (gas-generating and swelling/expanding systems), mucoadhesive, high-density, modified-shape, gastric-emptying delaying devices, and co-administration of gastric-emptying delaying medications are all part of these trials. Floating dose forms are the least commonly utilized system among these. With a limited absorption window, those with less water solubility in the alkaline pH of the small intestine, or those with the least stability in the colonic or intestinal environment, gastro retentive devices are used to increase the bioavailability of the medicine [7][8].

The concept of floating tablets is based mostly on the matrix type drug delivery method, wherein the medication is implanted in the matrix and gradually erodes without the tablet disintegrating when it comes into contact with stomach juice. These drug delivery systems include a precise mixing of the medication and the gel-forming hydrocolloid. Following oral administration, this dosage form expands and reaches a bulk density of less than one when it comes into contact with stomach juices. The dose form is floated by the trapped air inside the inflated matrix pickup [9][10].

As a result, the intended gel-like structure swells, transforms into a barrage, and allows the medicine to release gradually over the gelatinous mass. The establishment of a hydrated viscous layer surrounding hydrophilic matrix tablets controls drug release by preventing water from penetrating the tablet and the flow of dissolved solutes out of the matrix tablets [11].

A beta-blocker often used to treat hypertension, arrhythmias, angina pectoris, myocardial infarction, and migraine prevention is called atenolol. Through the lips, atenolol is rapidly and reliably absorbed, but not entirely. About half of an oral dosage is absorbed from the digestive tract, with the other half being unchanged excreted in faeces. Thus, superior therapeutic effects would emerge from the atenolol gastro retentive drug administration strategy [12].

Cardiovascular disease encompasses any condition involving the heart or circulatory system. The primary risk factors for cardiovascular diseases are alcohol use, smoking, high blood pressure, high cholesterol, and obesity. Approximately 9.4 million of the 17 million yearly deaths globally from cardiovascular illnesses are attributable to hypertension. In the third NHANES, around 60% of participants had both hypertension and hypercholesterolemia, and 55% of those with hypercholesterolemia also had hypertension. The current endeavor will try to synthesize GFDDS of atenolol utilizing natural and synthetic polymers of varied viscosity grades in order to extend drug release and give matrix tablet formulations floating capabilities [13][10].

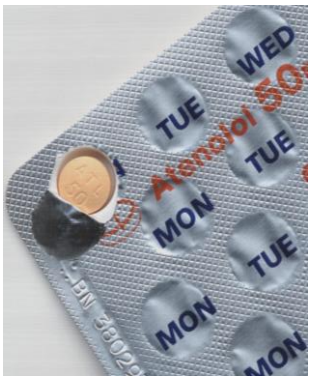

Fig.1: Atenolol 50mg floating tablet

MATERIAL AND METHOD

Material: Atenolol was obtained from Actiza Pharmaceutical Pvt. Ltd. Surat, Gujarat and Sodium bicarbonate was obtained from Tirkuta Chemicals Private Limited, Ghaziabad, Uttar Pradesh, Sodium Alginate and citric acid was obtained from Goel Chem Associates, Trinagar, Delhi. Microcrystalline cellulose (MCC), Eudragit RS 100, Carbapol 940, HPMC was obtained from OLL Chem Inc, Ahemdabad.

Methods: All of the formulations were created utilizing the direct compression method and a variety of ratios (shown as F-1 to F-5 in the Table) of polymers, including sodium bicarbonate, citric acid, carbapol 940, EUDRAGIT RS-100, and sodium alginate. Each component—including the atenolol—was separately run through sieve number 40. Following a maximum of fifteen minutes of trituration, every component had been well blended. MCC was used to lubricate the powder mixture.

Preparing floating atenolol pills

Amlodipine floating tablets were prepared using the direct compression method and the formulae provided in Table 1. The floating pills had a combination of Atenolol, HPMC, NaHCO3, Citric acid, Carbapol 940, Eudragit RS-100, Sodium alginate, and MCC. All of the components were correctly weighed and passed through mesh #60. To fully combine the materials, the medicine and polymer were combined geometrically in a mortar and pestle for 15 minutes before adding sodium bicarbonate, talc, and aerosol one at a time. After carefully combining these materials, the powder mixture was sieved through # 44 meshes. Powder mix was compacted using a rotary tablet punching machine (IIMT University, Meerut). Compressed pills were evaluated using both official standards and unauthorized testing. Tablets were packed in tightly sealed light-resistant and moisture-proof containers.

Table 1: Formulation and content of atenolol floating tablets (F1–F5)

S. No.	Ingredients	Measured in Milligrams				
		F1	**F2**	**F3**	**F4**	**F5**
1.	Atenolol	50	50	50	50	50
2.	HPMC	75	70	60	50	40
3.	NaHCO3	20	20	20	20	20
4.	Citric acid	40	40	40	40	40
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	30	40	42	50
	Total weight	325	335	340	337	340

Assessment of the pre-compression parameter for the powder blend

1. Angle of Repose:

The funnel method was used to measure the powder's angle of repose. Powdered grains that had been carefully weighed were put into a funnel. The tip of the funnel was raised to a height of approximately 2.0 cm above the solid surface, just barely touching the top of the powder pile. After then, the funnel was left open, allowing the powder to freely fall to the ground. Using the provided equation, the angle of repose was ascertained using the diameters of the powder cone and the cone [14].

$\tan\theta = h/r$---------- (1)
Consequently, = $\tan\theta$-1h/r

Where r is the cone's base radius, h is its height, and θ is its repose angle.

2. Density of Bulk (Db):

It calculates the powder's bulk volume to total mass ratio. It was computed by weighing the powder and then transferring it through a standard sieve no. 20 before adding it to a measuring cylinder. The starting volume was the bulk volume. The following formula was used to this data in order to obtain the same. This formula is used to measure it [15].

Db is expressed in gm/ml and is equal to M/Vb .where M and Vb are the mass and bulk volume of the powder, respectively.

3. Density Tapped (Dt):

The bulk density may be obtained by dividing the whole powder mass by the tap's diameter. After 750 taps, any variation in volume less than 2% was noted. If the difference was more than 2%,

1250 more taps were made, with the loudness being recorded after each tap. Until there was less than a 2% variation in volume between each tap, the tapping procedure was repeated [16]. Bulk density is measured in grams per millilitre, or g/mL.

Dt = M/ Vt

4. Index of compressibility and Hausner's ratio:

The compressibility index is measured as a result of the evaluation of bulk and tapped density. A substance's compressibility diminishes as its flow ability rises. When the compressibility index falls between 20 and 30 percent, the material is said to have free-flowing qualities [17]. The formula for the compressibility index (CI) is (Dt -Db) / Dt.

The Hausner ratio, an indirect metric for evaluating the powder flow, may be calculated using the formula below.

An analysis of tablets:

1. Parameters after compression: The Vernier callipers, which measure thickness, had tablets placed between their moveable and stationary jaws. The data are then recorded after the screw was adjusted to fit the tablet between the jaws.

2. Hardness: Tablet hardness is the term used to describe the force required to shatter a tablet when pressure is applied along its diameter. This important attribute determines the tablet's resistance to shattering, chipping, or wearing during handling prior to usage and storage. The Monsanto Hardness tester is used to assess the tablet hardness of each formulation [18].

3. Friability: Friability is a measure of a medicine's mechanical strength. The Roche friabilator is used to evaluate friability. Dropped from six inches above the surface, tablets are placed within a rotating plastic container. After four minutes of spinning, the tablets are crushed, reweighed, and the percentage weight loss is used to measure friability.

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

4. Variation of Weight: After weighing each tablet individually, the weight average of the twenty was determined. Next, the weight of each tablet was compared to the average weight. To satisfy the standards, every tablet must comply with the test specifications; deviations from the average weight of up to 2% are permitted for a maximum of two tablets. Additionally, it's vital to guarantee that no pill surpasses the limit percentage [19].

5. Uniformity of drug content: From each batch, three pills are chosen at random to ascertain the pharmaceutical content. These tablets are then placed in 100 ml volumetric flasks along with the appropriate media. Following a 48-hour incubation period, 1 ml is extracted from each volumetric flask and transferred into test tubes. Before the samples are analyzed using a spectrophotometer

with the appropriate UV wavelength, they are appropriately diluted. The drug's content is calculated using the linear equation that was obtained from the tuning curve [20][6].

6. Tablet dimensions: Tablet diameter and thickness may be measured with a vernier calliper. The three tablets that were chosen at random from each formulation are then measured to ascertain their sizes. The measurements are expressed in millimetres.

7. Studying swelling: To determine the swelling index (SI), each tablet can be placed in a separate glass beaker filled with a pH 1.2 HCl buffer. The pills should be allowed to incubate for a specific amount of time, up to and including 24 hours. After removing the floating tablets from the beaker, any excess liquid on the surface has to be carefully drained. The swelling index (SI) can then be determined using the recommended methodology. Index of Swelling (SI%) = -100 [21][22].

8. Duration and amount of time spent floating: The buoyant qualities of the produced formulations were tested while the tablets were immersed in water using the USP-II paddle apparatus. Throughout the experiment, the study's medium—900 millilitres of pH 1.2 hydrochloric acid buffer—was maintained at a steady 37 0.5 °C. Measures were taken of the length of time the pills floated and the lag time before they began to float in the stomach fluid following insertion. The integrity of the test tablets was routinely examined during the experiment.

9. Drug release investigations conducted in vitro: The pills were subjected to in vitro drug testing using the approved procedure and instruments. The tablets were kept together with sinkers in six compartments by the USP Type-II dissolving mechanism. With a speed of 100 rpm, 900 cc of degassed 0.1N HCl served as the dissolving media paddle velocities well as 37 0.5 °C. Samples were collected and pooled for UV spectrometer examination at 261 nm at 1, 3, 6, 9, and 20-hour intervals [23].

10. Swiftly carried out stability tests: For duration of four weeks, atenolol floating tablets were subjected to accelerated stability testing at 40 degrees Celsius and 75% relative humidity. The trials that were eliminated underwent physical examinations and underwent in vitro drug release testing [24].

11. Infrared Fourier Transforms (FTIR) Spectroscopy: The drug contained in KBr pellets was analyzed using FTIR, which scanned slowly between 4000 and 400 cm-1. In spectra, peak values (wave numbers) and possible functional groups are shown in relation to a standard value. When compared to the chemical structure of atenolol, these results show that the substance was pure atenolol. An FTIR study was done to find out if a medication was compatible with polymers.

12. Studies on the most suitable formulation's stability: Stability studies for the optimal formulation were completed in compliance with ICH guidelines. The optimal formulation was kept for two months at 30°C/65°RH and 40°C/75°RH in an aluminum-packaged humidity chamber following the attainment of favorable findings. Trials were analyzed for drug content, in vitro

dissolution, floating behavior, and a range of other physicochemical characteristics once the study was completed.

RESULTS AND DISCUSSION

Features of floating tablets containing atenolol

Pre-compression parameters

Pre-compression parameters are essential for enhancing pharmaceutical flow characteristics, especially when it comes to tablet formation. These include the Hausner ratio, Carr's index, bulk density, tapped density, and angle of repose.

The angle of repose

The angle of repose might be used to adjust the flow qualities of the powder as well as the resistance of particles to movement. This measurement provides a qualitative and quantitative estimate of internal cohesive and frictional force at low levels of external stress, which might be used in mixing and tablet compression. Table 2 shows values for the angle of repose, which ranged from 24.42 to 37.56, demonstrating excellent flow qualities.

The compressibility index of Carr

Carr's Index is used to measure the stability and strength of powder bridges. As a result, as Table 2 illustrates, the compressibility index values range from 17:00 to 20.68%, indicating good powder mix flow ability and low cohesiveness, this is sufficient for the key tableting technical parameters.

Hausner’s ratio

The inter-particulate friction and consolidation were calculated using Hausner's ratio. These data demonstrated that the powder blend had acceptable flow qualities. The Hausner ratio for the majority of formulations in the powder blend is less than 1.28, as shown in Table 2, indicating satisfactory flow capabilities.

The Bulk density

Bulk density, often referred to as apparent density in materials science, is a characteristic of a material that is calculated by dividing its mass by its bulk volume. The overall volume occupied by the particles, including the internal pore volume, inter-particle void space, and the particle's own volume, is referred to as bulk volume. The tapped density readings fall within the range of 0.33 to 0.37 g/cm2.

The Tapped density

The higher bulk density that results from mechanically tapping a container holding the powder sample is known as the "tapped density." A graduated measuring cylinder or vessel containing the

powder sample is mechanically tapped to determine the tapped density. A graduated cylinder containing a weighed amount of powder was tapped for a predetermined number of times (100) at a height of two centimeters. It is the ratio of the sample's weight to its tapped volume. As seen in (table 2), the tapped density values vary from 1.21 to 1.25 g/cm2.

Table No. 2: Assessment of the Atenolol Powder Blend prior to compression

Formula code	**Angle of repose** (θ)	**Carr's compressibility index (%)**	**Hausner's ratio**	**Bulk density (g/cm^2)**	**Tapped density (g/cm^2)**
F1	24.70	17.23	1.22	0.33	1.22
F2	37.56	18.20	1.23	0.35	1.21
F3	24.42	20.68	1.20	0.36	1.23
F4	32.97	17.20	1.25	0.34	1.25
F5	37.50	17.00	1.28	0.37	1.24

Post-compression parameters

Uniformity of content

Each tablet's medication content ranged from 97.90% to 99.25% of the relevant average content, according to Table 3's content uniformity test findings, which are within an acceptable range and show that all tablets meet the conditions set by the manufacturer (BP).

Tablet dimensions

The tablets' thickness, which ranged from 4.22 to 4.35 mm, was displayed in Table 3. According to these findings, batches with lower polymer concentrations produced tablets that were thinner overall. Additionally, tablets with greater polymer content are thicker and less dense.

The Hardness test

In table 3 the hardness of the tablets was between (4.70 to 520) kg/cm2 and this confirms best characteristics of handling for all the batches. The study shows a slight increase in the hardness of tablet containing the largest quantity of ethyl cellulose (EC) as shown in (F9), this may be due to the increase in density of powders blend and a reasonable increase in the number of interaction points or the bonding surface area that governs the tablet more hardness which is confirmed by the increase in thickness of tablet as shown in F9.

The Friability test

As seen in (table 3), the friability of the tablets functioned as planned and regularly. Every formula's outcome fell between (0.599 and 0.790)% . This observation seems to indicate that ethyl cellulose's (EC) flexibility improves the tablet's cohesive strength. This indicates that the recorded

friability values for the designated formulations were less than 1%, which is often thought to indicate a good level of tablet mechanical resistance.

Variations in weight

Weight is compendial standard to assess the quality of tablets, and thus the weight variation test must indicate that all the tablets were uniform with low standard deviation values. In case of amlodipine floating tablets; (tablet 3) demonstrate that weight variation of all formulas was in the range of (249± 0.19 to 253± 0.10). The prepared matrix tablets demonstrated good weight consistency by meeting the required pharmacopeia range (>0.5%).

Table 3: Characteristics of the manufactured atenolol floating pills after compression

Formula code	Tablet thickness	Tablet Hardness	Diameter (mm)	Friability test	Weight variation	Content uniformity
F1	4.30	4.70	8.80± 0.2	0.704	251± 0.09	99.25
F2	4.22	4.90	8.80± 0.2	0.672	253± 0.10	97.90
F3	4.27	5.10	8.80± 0.2	0.790	252± 0.26	98.55
F4	4.35	5.20	8.80± 0.2	0.680	249± 0.19	99.15
F5	4.25	4.70	8.80± 0.2	0.599	252± 0.14	98.67

Tablets' floating behavior

When floating tablets made with hydrocolloid gelling agent hydroxyl propyl methylcellulose (HPMC) E50 come into touch with an aqueous media (0.1 N HCl, pH 1.2), they absorb water and swell, delaying the release of the medication. Additionally, the impact of raising the hydroxyl propyl methylcellulose (HPMC) E50 concentration was assessed by analyzing the floating characteristic of these produced tablets. It was discovered that this polymer could preserve the matrix integrity for the intended amount of time, reduce floating lag time, and sustain total floatation duration for more than twenty-four hours. This might be explained by the fact that the systems began to float when the volume increased more than the mass increased during swelling, causing the density to drop.

Table 4: The overall floating time and floating lag time of the formulas

Formula code	Floating Lag Time (min)	Total Floating Time (h)	Swelling index (%)
F1	30	>24	32.40
F2	40	>24	35.20
F3	35	>24	34.60
F4	45	>24	36.30
F5	40	>24	38.10

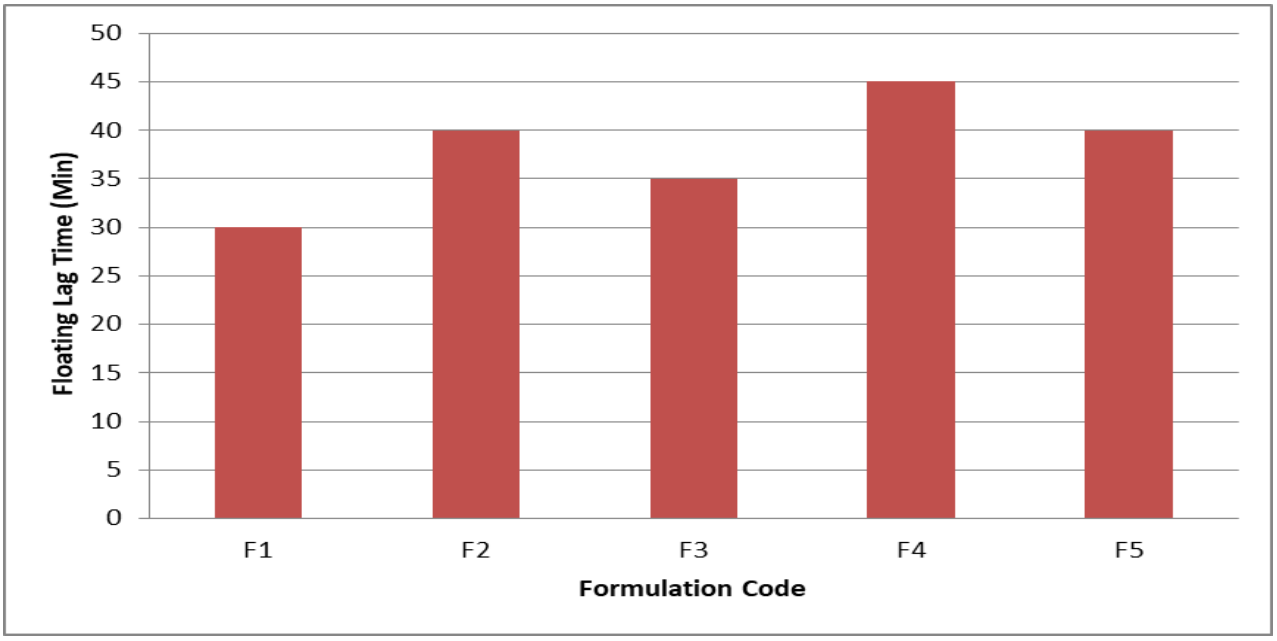

Fig 2: Floating property evaluation

***In vitro* dissolution study**

Figure shows that formulations (F1-F3) had quick release within 7 hours, but formulations (F4 and F5) had a delay in drug release of 8 and 11 hours, respectively. The release rate was strongly impacted ($p<0.05$) by the concentration of hydroxyl propyl methylcellulose (HPMC) E50. As the concentration rose, the release rate decreased [40]. As a result, it might be attributed to an increase in the polymer's molecular weight, resulting in higher macromolecule entanglement. As a result, the mobility of polymer concatenations diminished, reducing the free space available for diffusion. As a result, the ability of a drug molecule to jump from one cavity to another is reduced, resulting in a slower mass transfer rate.

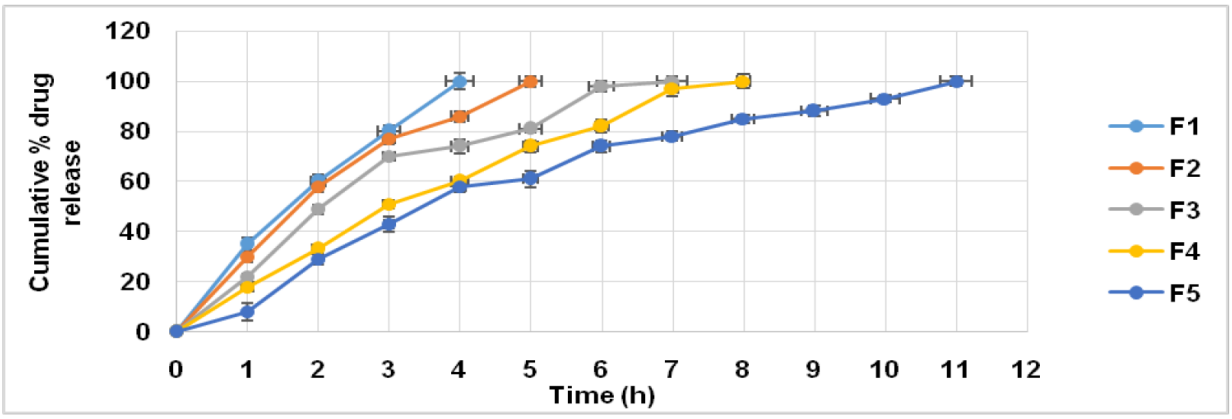

Fig. 3: Dissolution profile of amlodipine from floating tablets containing different concentrations of HPMC E50 (F1-F5), data given in mean ± SD, n=3

Release Cumulative Percentage of Drug of All the Formulations

1. Determine the amount of drug released from each formulation at different time intervals. This is usually done through dissolution testing.

2. Calculate Cumulative Percentage: Sum up the amount of drug released at each time point and divide by the total amount of drug in the formulation. Multiply by 100 to get the percentage.

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	6.692	1.622	1.402	2.321	1.876
2	9.35	3.401	3.313	4.024	4.122
4	19.34	11.11	11.106	12.333	10.555
8	40.255	38.402	39.111	42.246	40.873
12	75.3	56.999	76.222	78.928	77.999
16	90.2	81.657	82.111	84.561	84.11
20	97.145	86.999	87.123	90.402	89.111
24	98.775	88.638	89.111	91.526	92.301

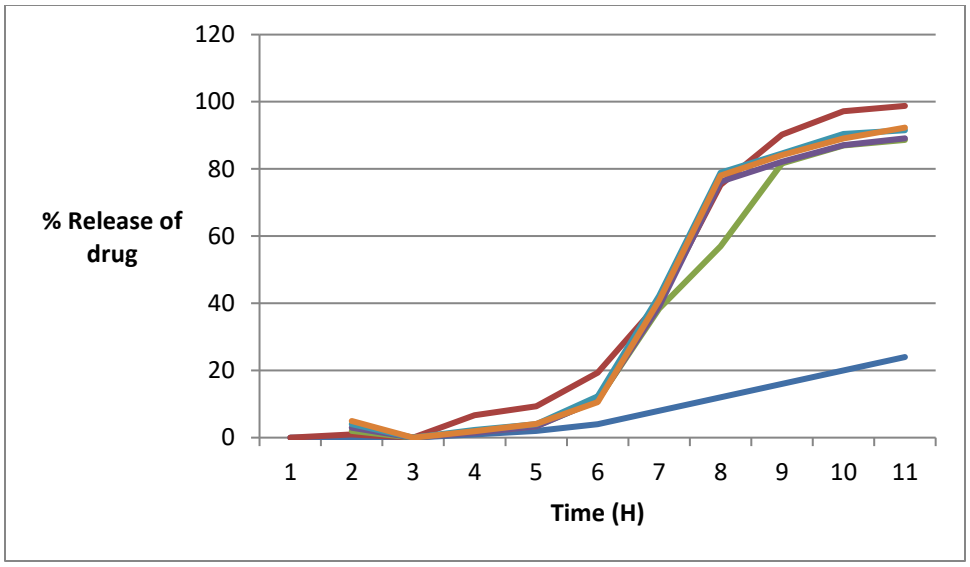

Fig 4: % Drug release Cumulative

Studies of Stability

After storing the optimized formulation F1 for six months, no alterations were seen in the floating lag time, % drug content, or in vitro drug release studies. This led to the conclusion that the formulation stable.

CONCLUSION

Atenolol is a selective 1-adrenoreceptor blocker that is used to treat hypertension. The atenolol tablets employed in this study were made of the polymers HPMC, sodium bicarbonate, citric acid, carbapol 940, EUDRAGIT RS-100, sodium alginate, and MCC. The direct compression approach was used to manufacture five distinct formulations of atenolol floating tablets. The F1 formulation was found to be the best of all the experiments. The optimized formulation F1 may be used once daily to treat angina pectoris and hypertension, according to evaluation results.

The floating tablets have the potential to extend the duration of the medication in the stomach, regulate fluctuations in the drug's plasma concentration, and ultimately enhance the drug's bioavailability. We conclude that there are no interactions between the medicine and the excipient based on the findings of the FTIR tests.

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