GASTRO RETENTIVE FLOATING TABLETS OF PITAVASTATIN SODIUM FORMULATION AND TESTING

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Abstract:

The goal of this study was to develop and test a gastro retentive floating tablet of the antilipidemic medication Pitavastain sodium, as well as to look into the effects of both hydrophilic and hydrophobic retardants on in vitro release. Pitavastatin sodium is an antilipidemic drug that inhibits HMG-CoA reductase but has only a 51% oral bioavailability due to poor absorption from the lower gastrointestinal tract. Pitavastatin sodium floating tablets were developed to improve drug bioavailability by increasing stomach retention, extending drug release. Weight variation, hardness, friability, swelling index, floating lag time, total floating time, and Kinetic Analysis were all used to evaluate the manufactured tablets. The tablets were tested in vitro in 0.1N HCl as a dissolving medium. It may also be inferred that a floating drug delivery system for Pitavastatin sodium can be successfully designed as a method of increasing stomach residence duration and, as a result, increasing bioavailability.

Keyboards: *Pitavastatin Sodium, Gastrointestinal Retention, Bioavailability, weight variation, hardness, friability, swelling index, floating lag time, Kinetic Analysis.*

Abbreviations: *UV = Ultraviolet, HCl = hydrochloride, FTIR = Fourier transform infrared, W= weight.*

1. INTRODUCTION:

GI transit time, reduced drug absorption due to partial drug release from dosage forms, and too short residence duration of dosage forms in the absorption zone of the GI tract are all physiological constraints of orally administered dosage forms. Gastro-retentive systems can stay in the gastric region for several hours, considerably extending the duration medications spend in the stomach. Longer gastro retention of the therapeutic component may provide a number of benefits, including higher bioavailability, less drug waste, and improved solubility of medications that are less soluble in the small intestine's high pH environment. [1] It can also be utilized to deliver drugs to the stomach and proximal small intestine on a local level. [2]. To keep the dosage form in the stomach, various ways have been proposed. Development of a high-density dosage form, simultaneous delivery of medications or excipients, and preparation of a bio-adhesive or mucoadhesive dosage form are examples of these approaches. On and above the absorption window, [3-5] medication delivery system Because most absorption windows are in the proximal small intestine (duodenum), keeping the formulation in the stomach will be the most effective technique. [6]. A Hydrodynamically Balanced System is the name given to this floating dose type (HBS). [7]. To improve bioavailability of medications with a solubility or stability problem in the small intestinal fluid, drugs that are only efficacious locally in the stomach, and drugs with a short therapeutic window, it has been suggested that an active ingredient be made in the form of an HBS. Pitavastatin Sodium is an inhibitor of HMG-CoA reductase that is used to treat hyperlipidemia. [9] It also has a high rate of first-pass metabolism. The upper section of the GIT absorbs more of it. [10] As a result, increasing the drug's stomach retention duration can improve oral absorption. Pitavastatin was formulated as a floating drug delivery system in this study in order to optimize absorption and bioavailability. The goal of this study was to develop a sustained - release formulation that would deliver a once-daily, sustained-release dose form. To make Pitavastatin Sodium, multiple ratios of the hydrogel hydrophilic polymer HPMC K100M, HPMC K15M, and hydrophobic retardants including AVICEL PH102, sodium bicarbonate, and citric acid were explored.

2. MATERIALS AND METHODS:

Pitavastatin Sodium (Drug) was obtained from the Delhi Drug Centre. Zee Laboratories Limited provided HPMC K100M, HPMC K15M, AVICEL PH102, Sodium bi Carbonate, Citric acid, Lactose, Magnesium Stearate, and Talc. The rest of the excipients and compounds were of analytical quality.

2.1 Drug excipients interaction study and Identification

2.1.1 UV spectroscopy (determination of lambda max):

Pitavastatin Sodium stock solution (1000 mg/ml) was produced in distilled water. To achieve a concentration of 3 mg/ml, this solution was diluted adequately with distilled water. On a Shimadzu twin beam UV visible spectrophotometer, the UV spectrum was measured in the region of 200-400 nm. In 0.1 N HCl, the same technique was performed (hydrochloric acid, pH 1.2). The maximum absorption spectrum and wavelength were recorded.

2.1.2.1 Preparation of standard curve :

Aliquots ranging from 1 to 10 ml were pipetted out of the secondary stock solution (1000 mg/ml) and diluted to 10 ml with 0.1N HCL to obtain a concentration of 2 to 20 mcg/ml, after which absorbance was measured at 245 nm against a blank (0.1 N HCl). The line's correlation coefficient and equation are determined.

2.1.3 I.R spectrum for Pitavastatin Sodium (12):

Using a SHIMADZU FTIR Spectrophotometer, an infrared spectrum of pure drug, mixing of drug with each retardant, and physical mixture of optimal formulation was recorded. The IR spectra of the samples were acquired using the KBr disc method, and the scanning range was 500- 4000 cm-1. To find any chemical interactions, any change in the drug's spectrum pattern due to the presence of polymers was studied.

2.1.4 Differential Scanning calorimetry (DSC): (12)

Differential scanning calorimetry was used to look into the likelihood of a drug-excipient interaction. DSC analysis was carried out using a Pyris 6 DSC (Perkin Elmer, CT, USA) in an inert environment maintained by nitrogen purging. The sample was placed in an aluminum pan and firmly sealed. As a guide, an empty aluminum pan was employed. Thermograms were recorded as samples were heated at a rate of 10 C/min over a temperature range of 40-250°C.

2.2 Preparation of floating tablet of Pitavastatin Sodium:

2.2.1 Method of Preparation (13):

Melt granulation was used to make effervescent floating tablets containing 4 mg Pitavastatin Sodium apiece. Table 1 shows the composition of several formulations. Except for Magnesium stearate and talc, all of the components were sieved 40 times. Magnesium stearate and talc were both processed through # 60 mesh and collected separately in a double-lined poly bag. Extra granular talc was used to lubricate the grains. The lubricated granules were then compacted into a tablet in 16 station compression machines utilizing 7mm standard flat-round shaped punches plain on both sides.

Table 1: Formulation of floating tablet of Pitavastatin Sodium

S.No.	Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
1.	Pitavastatin Sodium	4	4	4	4	4	4
2.	HPMC K100M	40	50	60	-	-	-
3.	HPMC K15M	-	-	-	40	50	60
4.	Microcrystalline cellulose	50	45	40	50	45	40
5.	Sod. Bicarbonate	35	30	25	20	30	25
6.	Citric acid	10	10	10	10	10	10
7.	Lactose	5	5	5	5	5	5
8.	Magnesium stearate	5	5	5	5	5	5
9.	Talc	5	5	5	5	5	5

2.3 Pre-compression evaluation (14, 15, 16):

Standard protocols were used to test the granules for flow properties such as angle of repose, bulk density, tapped density, compressibility index (Carr's index), and Hausner's ratio.

2.4 Post compression parameter:

Physical properties such as hardness, thickness, weight variation, friability, and drug content were assessed in the produced tablets.

Twenty pills of each formulation were weighed using an electronic scale and the test was conducted to investigate weight variation. If no more than two tablets go outside the % restriction and none of the tablets differ by more than double the percentage limit, the tablet passes the test. A Vernier caliper was used to measure the thickness and diameter of the tablets. The average values of ten tablets from each batch were calculated. The mean and standard deviation were calculated using the information gathered. The hardness of 10 produced tablets of each formulation was measured using a Monsanto hardness tester and given in kilograms per square centimeter.

The Roche friabilator was used to test the friability of twenty produced tablets. Using a plastic chamber that circles at a speed of 25 rpm and drops the tablets to a distance of 6 inches in each revolution, this test subjects a number of tablets to the combined effects of shock and abrasion. A sample of pre-weighed tablets was placed in the Roche friabilator, which was then run for 4 minutes at 100 revolutions. After that, the tablets were dusted and reweighed. (17-21)

Ten Pitavastatin Sodium tablets were crushed into a fine powder. A amount of Pitavastatin Sodium equivalent to 100 mg was added to a 100 ml volumetric flask and dissolved in 0.1 N HCl (pH 1.2). The absorbance was measured against a blank using a UV spectrophotometer (Shimadzu) at 246 nm after appropriate dilutions. A calibration curve was used to calculate the drug content (22).

Randomly selected tablets from each formulation were placed in a 100-ml beaker containing 0.1 N HCl for in vitro buoyancy testing (pH 1.2). The time it takes for the tablet to rise to the surface and float was calculated as the floating lag time (FLT), and the time it takes for the tablet to stay afloat on the medium's surface was calculated as the duration of floating. Placing the tablets in the basket of a dissolution apparatus with dissolution medium pH 6.8 buffers at 370.5o C was used to evaluate the swelling index of the tablets. Each dissolution basket containing a tablet was extracted and blotted with tissue paper to remove excess water before being weighed on the analytical balance after 0.5, one, two, three, four, five, six, seven, and up to twelve hours. For each time point, the experiment was repeated three times, and the swelling index was computed using the formula below (25).

(Wt -W0/ W0)*100 = SI (percentage)

Where Wt is the weight of the tablet at time t, and W0 is the initial weight of the tablet

2.5 *In vitro* dissolution studies:

Using the USP Type II Apparatus, the release rate of Pitavastatin Sodium from floating tablets was determined (Paddle Type). The dissolution test was carried out using 900 ml of 0.1 N HCl for 12 hours at 37 0.5 _C and 50 rpm. After a predetermined time interval, aliquots of sample were removed from the dissolution medium and replaced with an equal amount of new medium

to keep the volume constant. The samples were filtered, diluted to an appropriate concentration with dissolving medium, and absorbances were measured using a UV/Visible spectrophotometer at 245 nm for Pitavastatin Sodium (Shimadzu, Japan). An equation derived from a standard curve was used to compute cumulative percentage medication release (22).

2.6 Kinetic analysis of release data (26-28):

The in-vitro release profiles obtained for all formulations were plotted in the following modes of data treatment: -

1. Cumulative percent medication released vs time in a zero-order kinetic model.
2. Log cumulative percent drug left vs time in a first-order kinetic model.
3. Higuchi's model: Cumulative percent medication released vs. square root of time
4. Log cumulative percent medication released vs log time – Korsmeyer equation / Peppa's model.

2.7 Stability study

The optimized formulation (F3) was packed in silver foil and submitted to stability testing at 40 _C ± 2 _C/75 ± 5 percent RH. At specified intervals of 0 (initial), 30, 60, and 90 days, samples were withdrawn. Different physicochemical criteria, such as appearance, weight variation, thickness, hardness, friability, drug content, and in vitro release, were assessed.

3. Result and Discussion

3.1. Drug excipients interaction and identification:

The maximum absorption wavelength was found to be 245 nm (Fig 3.1). The calibration curve was found to be linear in the range of 2-10 mg/ml, and a straight line equation with a regression coefficient of 0.996 was derived, indicating that the results were accurate (Fig 3.2)

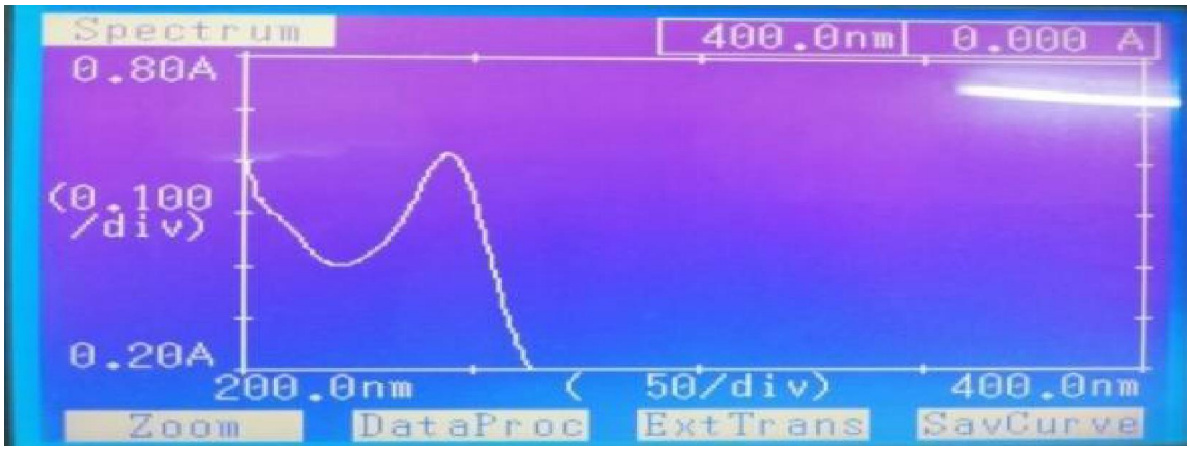


Figure 3.1. UV- Spectrum Analysis of Drug

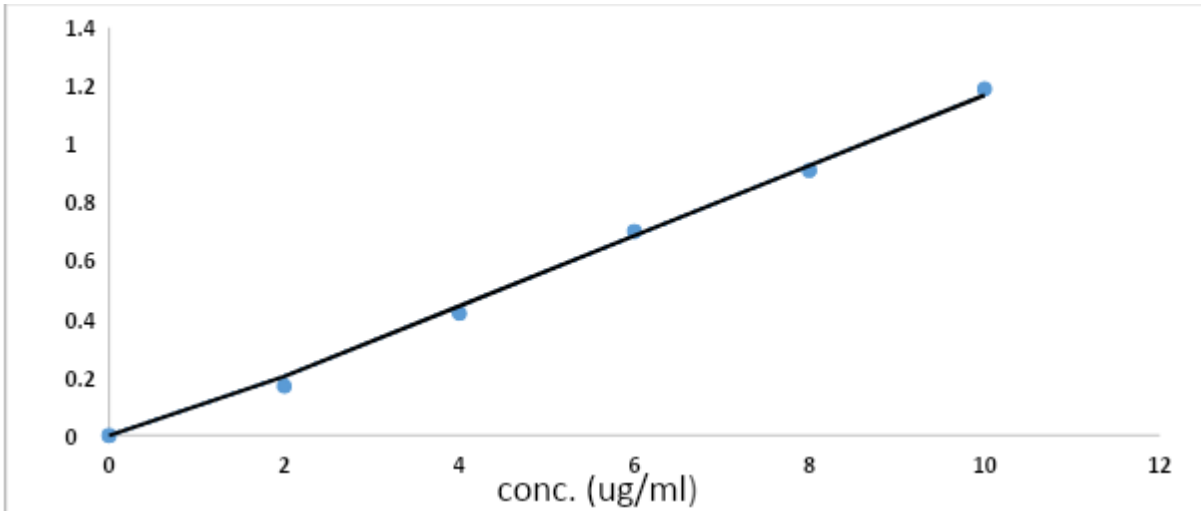


Figure 3.2 Calibration curve of Pitavastatin sodium

Pitavastatin sodium and polymers such as hydroxyl propylmethyl cellulose and Avicel PH102 were identified by the frequency of the observed peaks using the FTIR technique. The infrared spectra of the medicament and polymers is interpreted as follows. (Figures 3.3.3 and 3.4)

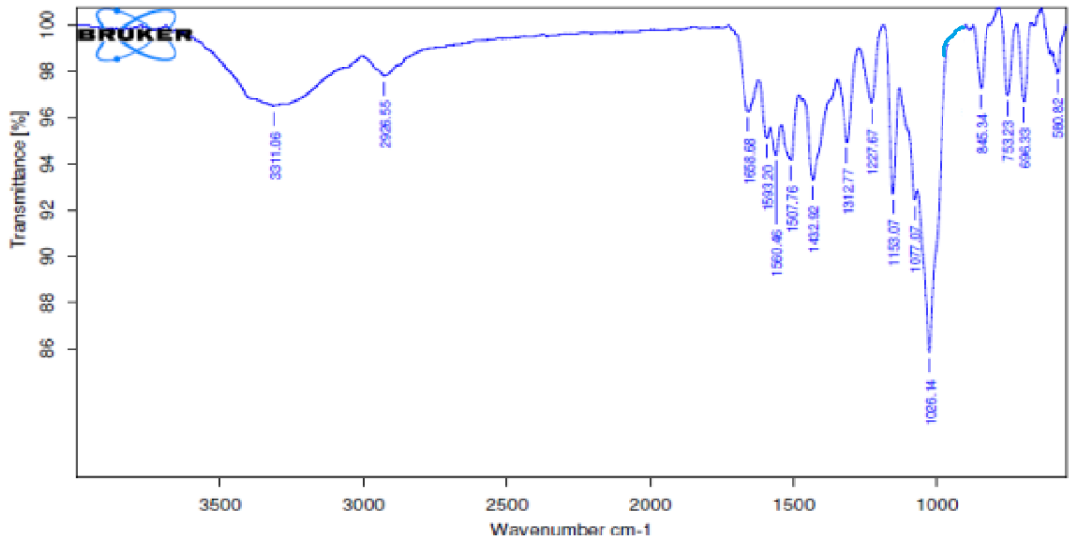


Figure 3.3 FTIR OF DRUG

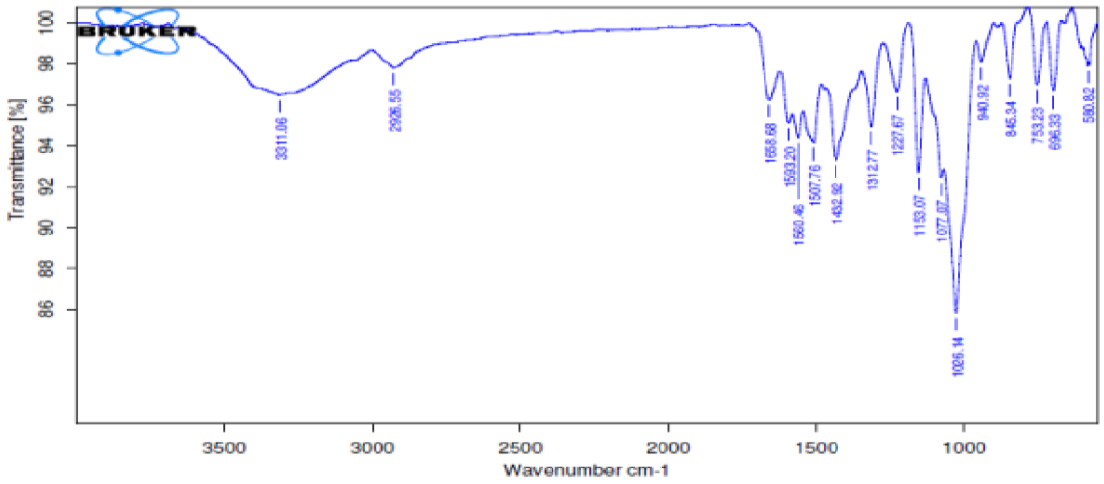


Figure 3.4 FTIR OF DRUG+EXCIPIENTS

Pitavastatin sodium had a characteristic stretching band of O-H at 3311.56 cm-1, Aliphatic C-H stretching at 2926.55 cm-1, C-O stretching at 1026.14 cm-1, C-H bending at 1432.19 cm-1, and C-H out of plane bending at 753.23 cm-1 wavenumber in the FTIR spectrum. After a pre-formulation investigation, these characteristic stretching bands were marginally altered, indicating that there was no chemical interaction between the active components of Pitavastatin sodium and excipients. The DSC thermogram revealed a pronounced endothermic peak at 229°C, which corresponds to the drug's melting point (fig.3.5). Due to the melting impact of hydrophilic polymers and hydrophobic retardants, a pre-formulation analysis revealed a small broadening and shifting of the endothermic peak. As demonstrated in fig.3.6, there was no significant change in the endothermic peak, which indicates the drug's melting point when mixed with excipients.

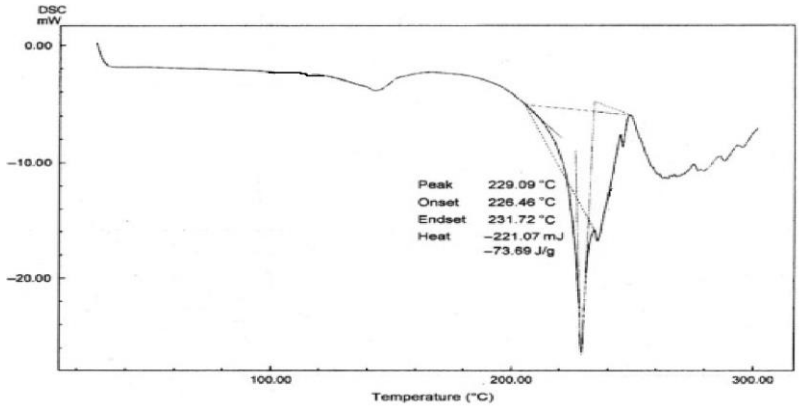


Figure 3.5 DSC of Pitavastatin sodium

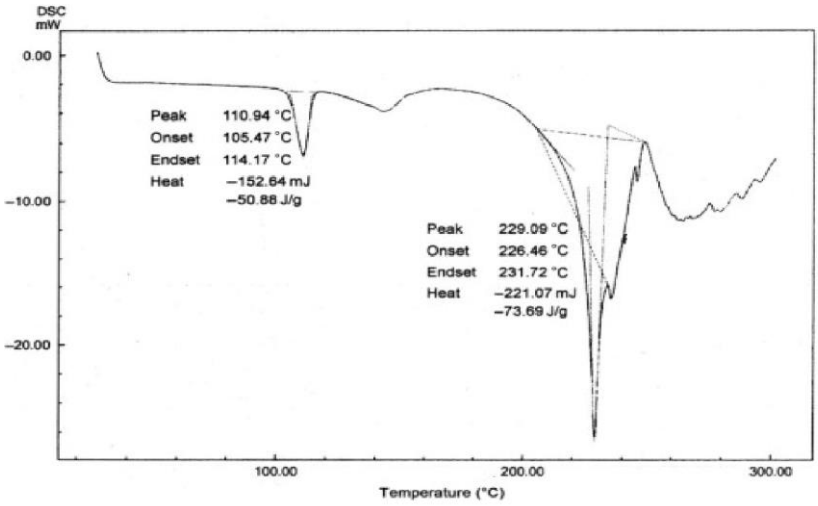


Figure 3.6 DSC of Pitavastatin Sodium+ Excipients

3.2. Formulation development:

Trial and error was used to determine the concentrations of the three hydrophilic polymers and hydrophobic retardants (HPMC K100M, HPMC K15M, and MCC). As a gas-generating agent, sodium bicarbonate was used. The trial batches were used to determine the sodium bicarbonate content. To increase the flow of the granules, talc was employed as a glidant. All of the retardants/ excipients utilized were found to be compatible with Pitavastatin sodium in an FTIR investigation.

Table 2 Precompression Evaluation:

Formulation code	Angle of Repose (o)	Bulk density	Tapped density	Hausner ratio	Carr's Index
F1	29.1±0.1	0.63±0.2	0.77±0.7	1.11 ± 0.03	17.9±0.9
F2	27.3±0.6	0.61±1.0	0.76±0.5	1.10 ± 0.02	18.12 ± 0.02
F3	31.3±0.5	0.59±0.5	0.73±0.5	1.06 ± 0.04	17.10 ± 0.04
F4	28.3±1.0	0.65±0.6	0.75±0.4	1.15 ± 0.06	22.32 ± 0.04
F5	26.8±0.7	0.68±0.1	0.78±0.9	1.05 ± 0.03	21.78 ± 0.03
F6	30.3±0.8	0.64±1.0	0.72±0.4	1.17 ± 0.05	18.45 ± 0.01

Table 3 Post Compression Evaluation

Formulation Code	Thickness (mm)±S.D	Diameter (mm) ±S.D	Hardness (Kg/cm2) ±S.D	Weight variation (mg) ± S.D	Friability (%) ±S.D	Content uniformity ± S.D
F1	1.99±0.19	7.0 ± 0.038	5.8 ± 0.223	152 ± 1.09	0.31 ± 0.002	99.01 ± 0.11
F2	2.38 ±0.31	7.2 ± 0.065	6.4 ± 0.251	151± 1.14	0.26 ± 0.004	98.12 ± 1.00
F3	2.19±0.36	6.7 ± 0.087	6.3 ± 0.244	150± 1.04	0.34 ± 0.003	99.16 ± 0.10
F4	2.31 ± 0.14	6.9 ± 0.018	6.7 ± 0.271	152 ± 0.41	0.34 ± 0.014	98.06 ± 0.03
F5	2.58 ± 0.16	7.4 ± 0.053	6.5 ± 0.048	151 ± 1.51	0.30 ± 0.009	98.15 ± 0.20
F6	2.11 ± 0.74	6.8 ± 0.036	6.2 ± 0.214	150 ± 3.17	0.39 ± 0.011	98.96 ± 0.17

3.3 Physical Characteristics:

The angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio were measured on the granules of six formulations (F1-F6), revealing that the pre-compressed blend has good flow properties, as given in table 3.1. Physical parameters such as hardness, thickness, diameter, weight variation, friability, drug content, and swelling index were examined for formulated matrix tablets, and the findings are displayed in Table 3.2. All of the granules were found to have good flow properties, with angle of repose values ranging from 26 to 30. This indicates that they have good flow properties. Except for formulations F4 and F6, the Carr's index value was determined to be less than 20, indicating outstanding properties. Except for formulations F4 and F6, which showed 1.15 and 1.17, Hausner's ratio was determined to be less than 1.11, indicating excellent flow properties.

Each formulation's total weight was kept consistent, and the weight fluctuations of the tablets were within acceptable ranges. According to IP specifications, the weight of tablets in each formulation was within the allowed range. The majority of the time, the variation was less than 5%. Tablet hardness varied depending on the hydrophobic retardant utilized, ranging from 5.8 0.24 kg/cm2 to 6.7 0.27 kg/cm2 (approx.) Tablet thickness was also used to determine tablet quality. Floating tablets ranged in thickness from 1.99 to 2.58 mm. All formulations passed the friability test, demonstrating adequate resistance to mechanical shock and abrasion of less than 1%. The active component content in all formulations was calculated, and it ranged from 98 to 99 percent.

3.4 Evaluation of buoyancy of the tablets

In vitro buoyancy tests in 0.1 N HCl (pH 1.2) indicated variances in buoyancy for all formulations. In the presence of hydrochloric acid in the dissolution medium, sodium bicarbonate was utilized as the effervescent base, which produces carbon dioxide gas. The gas produced is retained and protected within the gel, lowering the tablet's density. The tablet becomes buoyant when its density falls below 1 (the density of water). Preliminary research was conducted to determine the appropriate amount of effervescent base required to achieve a fast floating lag time while maintaining long-term buoyancy. In formulations, sodium bicarbonate in the amount of 20-30 mg created tablets with a lag time of less than a minute.

3.5 Swelling index of Pitavastatin sodium Floating Tablets:

The hydration ability of the formula is significant because it affects tablet buoyancy and (ii) hydrogel polymer adhesion ability. The test medium absorption of the produced tablets appears to be dependent on the type of polymer. Table 4 shows that after 8 hours, the maximum swelling index of this formula, 243.69, was obtained.

Table 4 Swelling index and Floating Duration of Pitavastatin sodium Tablets

Formulation Code	Swelling index Time(Hrs)					Floating Duration
	1	2	4	6	8	(In Hrs)
F1	56.46	87.38	141.65	179.52	199.86	>12
F2	67.75	95.47	163.41	201.76	201.39	>12
F3	79.43	118.59	178.66	229.53	243.69	>12
F4	31.74	70.87	131.94	174.88	185.57	>12
F5	55.63	85.36	143.88	183.36	193.49	>12
F6	68.71	99.47	156.59	210.58	216.38	>12

3.6 In vitro drug release:

The findings of in vitro dissolving tests in 0.1 N HCl (1.2 pH) are shown in Fig. 3.7. Formulations F3, F4, and F5 had up to 99.53, 97.33, and 96.73 percent release for 12 hours, respectively. F1, F2, and F6 had a release time of less than 12 hours.

It's possible that the longer-lasting effect was due to the combination of hydrophilic polymer and hydrophobic retardant, which had a positive effect even at low concentrations. A hydrophilic polymer was used as a filler, as well as a sustaining agent and a gas (carbon-di-oxide) entrapping agent. It was discovered that the amount of hydrophobic retardant used is inversely related to the rate of release. Formulation-3 (F3) is the optimal formulation based on the above evaluation parameters.

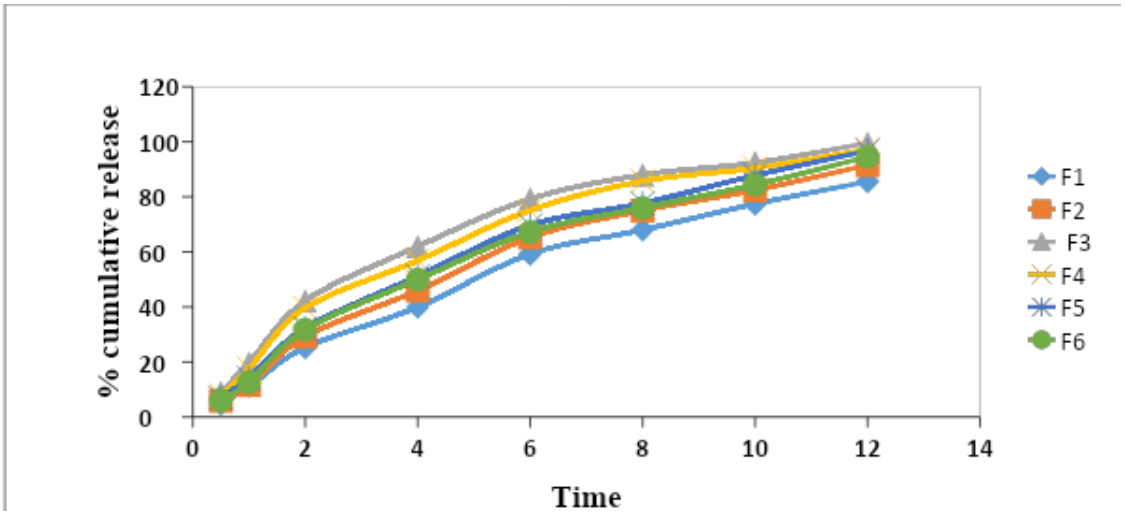
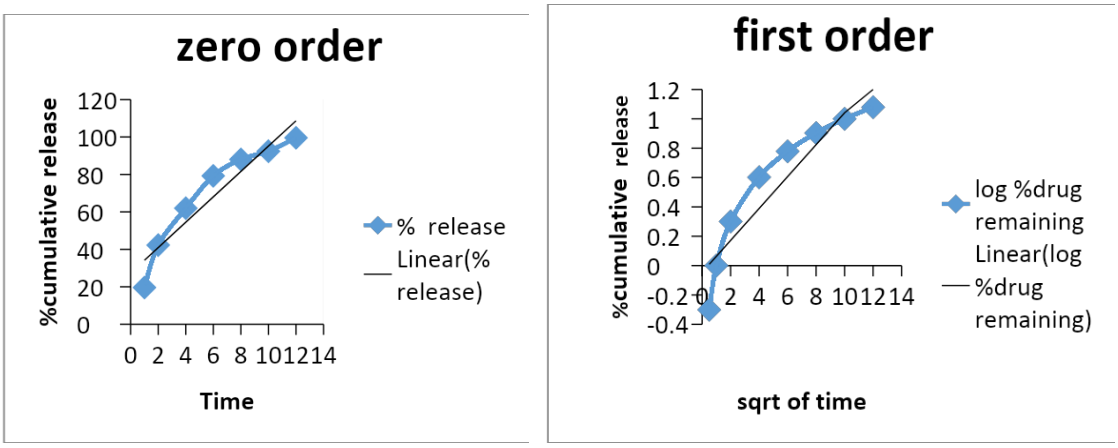


Figure 3.7. Dissolution profile of formulation F1-F6

Kinetic analysis of release data:

Dissolution data was fitted into multiple release kinetic models Fig.3.8 to understand the rate and mechanism of drug release from optimized tablet formulation. Based on the correlation coefficient value (r2) obtained from various kinetic models, the model that best fit the release data was chosen (3.4). Korsmeyer Peppas equation and Higuchi equations could best express the in vitro drug release profile from all of these formulations, as plots demonstrated the maximum linearity with r2 value. The linear plot in the Korsmeyer Peppas equation was for the optimized formulation, which has a high correlation coefficient (r2) of 0.983 and a Higuchi value of 0.974. It was determined that the improved formulation used a mixed diffusion and erosion mechanism for drug release, also known as an anomalous/non-Fickian diffusion mechanism.

A) Zero-Order Kinetics Plot **B) First-Order Kinetics Plot**



C) Higuchi Plot **D) Korsemeyer – Peppas model Kinetics Plot**

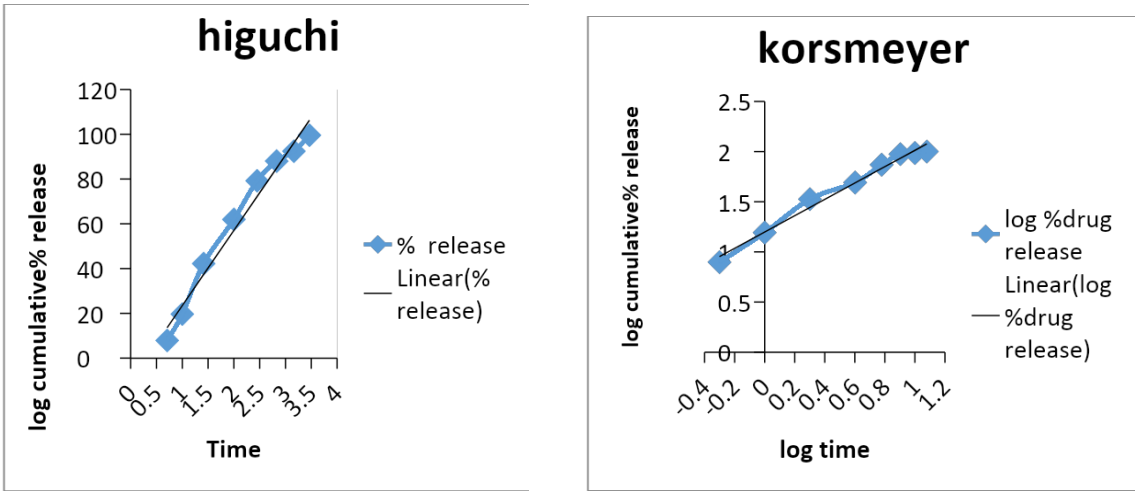


Figure 3.8 Kinetics Plots for optimized formulation F3

Table 5 Kinetic modeling parameters for F3

Kinetics	**R^2**	**N**
Zero order release kinetics	0.897	-
First order release kinetics	0.867	-
Higuchi release kinetics	0.974	-
Korsmeyer – Peppas model release kinetics	0.983	n = 0.814

4. Conclusion:

The most promising approach was an effervescent-based floating medicine delivery system. The combination of a hydrophobic retardant and a hydrophilic polymer offered its own advantages in terms of maintaining tablet integrity and buoyancy. In addition, the first burst effect was reduced. It can be inferred that the hydrophobic retardant and hydrophilic polymer must be employed in the right ratio for proper floating time and in vitro release. Formulation F3 was deemed an optimal formulation because it released 99.53 percent of the medication in 12 hours. The release kinetics of F3 were based on zero order, Higuchi, and Korsmeyer Peppas. The goal of making Pitavastatin sodium gastroretentive pills was accomplished.

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