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FORMULATION AND EVALUATION OF FLOATING PULSATILE DRUG DELIVERY SYSTEM FOR RANOLAZINE

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ABSTRACT :

Formulation and evaluation of floating pulsatile drug delivery systems for ranolazine, a medication used to treat chronic angina, involves developing a formulation that ensures controlled release of the drug in a pulsatile manner while maintaining buoyancy to prolong gastric residence time. The objective of this work was to develop and evaluate a floating- pulsatile drug delivery of ranolazine. The floating-pulsatile concept was applied to increase the gastric residence of the dosage form by having lag phase followed by a burst release. The system was generated which consisted of three different parts: a core tablet, containing the active ingredient; an erodible outer shell; and a top cover buoyant layer. A multiple unit oral floating drug delivery system of ranolazine was developed to prolong gastric residence time, target stomach mucosa and increase drug bioavailability. The rapid release core tablet (RRCT) was prepared by using super disintegrants along with active ingredient. A chrono delivery system, based on biological rhythms, is a state-of-the-art technology for drug delivery to increase safety, efficacy and also improves overall drug performance.

Keywords: Preformulation study, Materials and Methods, Preparation of floating pulsatile tablet, Coating of Core Tablet, Evaluation of floating pulsatile tablet.

INTRODUCTION :

Research on floating pulsatile drug delivery systems aims to develop a novel approach to drug delivery. Combining floating and pulsatile properties enables site-specific and time-specific delivery. Traditional controlled release systems rely on single-or multiple-unit reservoirs or matrices, providing constant drug levels over an extended period [1]. However, biological factors in the upper gastrointestinal tract affect drug transit time, posing challenges for drugs with local stomach activity, high pH instability, or poor solubility in the lower gastrointestinal tract [2-4]. To overcome these limitations, strategies are needed to increase drug residence time in the stomach for optimal therapeutic outcomes. Mucoadhesive and floating systems have been explored to achieve this goal [5,6]. Floating systems, also known as hydrodynamically controlled systems, are designed to remain buoyant in the stomach without affecting gastric emptying rates, thereby prolonging residence time [7].

1.2. Floating Pulsatile Drug Delivery System

The concept of floating drug delivery systems involves a design that maintains a lower bulk density than gastric fluids, enabling them to float in the stomach without affecting the gastric emptying rate for an extended duration. These systems release the drug gradually at a controlled pace while floating on the gastric contents.[8] On the other hand, pulsatile drug delivery systems feature a distinct release mechanism characterized by the rapid and transient release of a specific dosage of drug molecules post a predetermined delay, termed the lag time. This mechanism guarantees a quick and complete drug delivery after the lag period, creating a pattern known as pulsatile release.[9]

1.3. Angina pectoris

Angina pectoris refers to substernal chest pain, pressure, or discomfort that tends to worsen with physical activity and/or stress, lasting for more than 30 to 60 seconds but subsiding with rest.[10] Stable angina is described as symptoms that manifest solely with exertion. In contrast, unstable angina or symptoms that occur at rest necessitate prompt evaluation and treatment. Symptoms of stable angina pectoris typically present as chest pain triggered by exertion or emotional stress, with possible radiation to the jaw, left shoulder, and arm.[11] Patients experiencing exertional stable angina pectoris may have underlying conditions such as severe anemia, hyperthyroidism, or other issues affecting the balance between myocardial oxygen supply and demand.

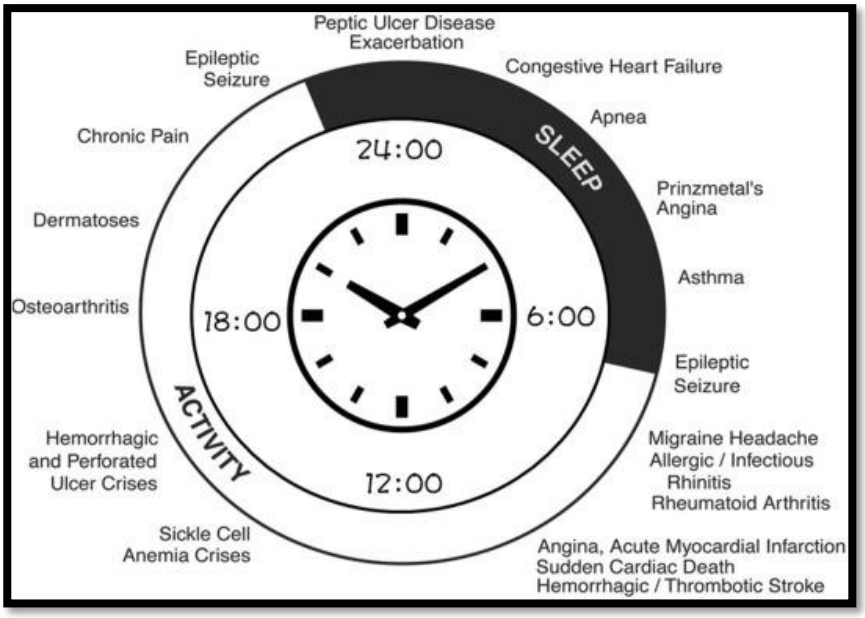


Fig No 1: Biological Clock

1.4. Chronotherapy in Angina pectoris

Ranolazine for Night-time Use as a Controlled Onset Extended Release 24-Hour Dosage-Administering ranolazine in a unique controlled onset-extended release form before bedtime can enhance the management of patients with ischemic heart disease and essential hypertension. The period between 6 am and 12 noon presents a heightened risk for myocardial infarction (heart attacks), angina (chest pain), sudden cardiac death, and transient ischemic attacks (mini-strokes). During the morning hours, blood pressure typically rises due to increased vascular tone, elevated platelet aggregation, and reduced natural thrombolytic activity, which collectively contribute to the potential formation of harmful blood clots.[13]

2. EXPERIMENTAL WORK

2.1. Preformulation studies

a) Organoleptic properties

A small amount of the drug sample was put in a watch glass, and its physical attributes such as color and odor were visually assessed.

b) Determination of melting point

Using the capillary tube method, the melting point the temperature at which a solid turns into a liquid was determined for ranolazine. This required inserting a little medicine sample into a capillary tube, closing one end of the tube, and using a thermometer in a melting device to measure the melting temperature.

c) Solubility studies

Studies on the drug solubility of ranolazine were carried out using a range of solvents. In each of these studies, a test tube containing a little amount of the drug sample was filled with 1 milliliter of various solvents. Using a vortex mixer, the drug and solvent were mixed until the drug was fully dissolved in the particular solvent.

d) Construction of calibration curve

A 100 ml volumetric flask was filled with methanol and precisely weighed 100 mg of ranolazine, which was then dissolved to produce a solution that had a 1000µg/ml concentration. Then, by pipetting 50 ml and 20 ml, respectively, from the stock solution and diluting in 100 ml volumetric flasks, working stock solutions of 500µg/ml and 100µg/ml were obtained. The 100µg/ml solution's highest absorbance was found at 273 nm after UV scanning. Working solutions with concentrations ranging from 20 to 140µg/ml were made from the stock solution and their absorbance at 273 nm was measured in order to create the calibration curve. Next, a graph was created that plotted concentration against absorbance.

e) UV Visible Spectroscopy

The drug's standard solution's absorption maxima were found by scanning in the 200–400 nm range.

f) Drug excipient incompatibility studies using Fourier transform infrared (FTIR) analysis

In order to determine the physiochemical compatibility of ranolazine with the polymers employed in the study, IR spectrum investigations were conducted using a Bruker Fourier transform infrared spectrophotometer. The medication was combined with all of the excipients to create the sample.

MATERIAL AND METHODS

Ranolazine was purchased from Swapnroop Drug and Pharmaceuticals, Aurangabad, India.Sodium starch glycolate, Microcrystalline cellulose, Polyvinylpyrrolidone and Ethyl cellulose were issued from AMCP, PethVadgaon, Kolhapur. Magnesium stearate and carbapol issued from our college (AMIP, Ambap, Kolhapur). All chemicals used were of analytical grade

3.1 Direct Compression Method

Ranolazine tablets were produced using the direct compression process. For fifteen minutes, all components were thoroughly mixed and precisely weighed. PVP was utilized as a binder, microcrystalline cellulose was used as diluent, magnesium stearate was used as lubricant, and sodium starch glycolate was used as a disintegrating agent. After that, a single rotating tablet compression machine was used to compress the resulting powder combination into tablets.

Table 1: Formulation of Core Tablet of Ranolazine

Ingredients (mg)	**C1**	**C2**	**C3**	**C4**	**C5**
Ranolazine	500	500	500	500	500
Sodium Starch Glycolate	6	8	10	12	14
Magnesium Stearate	2	2	2	2	2
Microcrystalline Cellulose	182	180	178	176	174
Polyvinyl Pyrrolidone	10	10	10	10	10
Total	700	700	700	700	700

3.2 Formulation of the Floating Pulsatile Release Tablet by Direct Compression (FPRT)

Coated dry By putting the excipient layer on a 13 mm die and the core tablet on top of it, a floating pulsatile tablet was created. After covering the core tablet with the remaining floating pulsatile release layer in the die, the 500 mg tablet was compacted using a KBR tablet machine. (13.5 mm in die diameter).

Table 2: Composition of FPRT of Ranolazine

Ingredients (mg)	**C1**	**C2**	**C3**	**C4**	**C5**
Core Tablet	700	700	700	700	700
PVP	50	100	150	-	-
Eudragit	25	507	75	100	125
Sodium Bicarbonate	45	45	45	45	45
MCC	172.5	97.5	22.5	147.5	122.5
Magnesium Stearate	7.5	7.5	7.5	7.5	7.5
Total	1000	1000	1000	1000	1000

Determination of flow properties

a) Bulk density

A 10-milliliter measuring cylinder was filled with one gram of precisely weighed valsartan. The drug's volume was measured by tapping the cylinder three times on a hard surface. The following formula was used to determine the bulk density. The figures are given in gm/cc3.

$$\text{Bulk density} = \frac{\text{Weight of Powder}}{\text{Volume of Powder}} * 100$$

b) Tapped density

A precisely weighed 1g dose of medication was added to a 10ml measuring cylinder. One inch above the ground, the cylinder was dropped 100 times onto a hard surface. The final volume was noted, and the following formula was used to determine the tapped density. In gm/cc3, the values are expressed.

$$\text{Tapped density} = \frac{\text{Weight of Sample}}{\text{Tapped Volume of Sample}} * 100$$

c) Carr's compressibility index

A common tool for determining a powder's flowability is the Carr's index. The blend's flow characteristics is determined by its compressibility index. Excellent flow is indicated by a number of less than 15. The formula is used to calculate it.

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} * 100$$

Table 3:Flow Properties of powders according to Carr's index are as follows:

Sr .no	Carr's index (%)	Flow
1	5-15	Excellent
2	12-16	Good
3	18-21	Fair to passable
4	23-35	Poor
5	33-38	Very poor
6	>40	Extremely poor

d) Hausner's ratio

An indicator of a powder's compressibility is Hausner's ratio. A powder's flowability can often be determined using the Hausner's ratio. Excellent flow is indicated by a number less than 1. The formula is used to calculate it.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Sr.no	Hausner's ratio	Flow
1	1.05-1.18	Excellent
2	1.14-1.20	Good
3	1.22-1.26	Fair to pass
4	1.30-1.54	Poor
5	1.50-1.61	Very poor
6	1.67	Very very poor

Table 4: Flow Properties of powders according to Hausner's ratio are as follows:

e) Angle of repose (θ)

The funnel's tip was barely touched by the pile's height because the sample powder was allowed to spill out of it. The funnel was altered so that the horizontal surface is 2.5 cm above the funnel's stem. By tracing a boundary around the pile's circumference and averaging its three diameters, the diameter of the pile was calculated. Excellent flow is indicated by a number of less than 20. The following formula can be used to determine the angle of repose:

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

Were,

θ is angle of repose,

h is the height of the pile,

r is the radius of the pile.

Table 5: Flow Properties of powders according to Angle of repose (θ) are as follows:

Sr .no	Flow Property	Angle of Repose (Degrees)
1	Excellent	25-30
2	Good	31-35
3	Fair-aid not needed	36-40
4	Passable may hang up	41-45
5	Poor must agilate, vibrate	46-55

6	Very poor	56-65
7	Very very poor	>66

4. EVALUATION PARAMETERS OF FLOATING PULSATILE TABLET

a) Thickness:

Using vernier callipers, the thickness of each of the five tablets across all batches was measured. Vernier callipers were also used to measure the diameter. Data on thickness and diameter were shown.

b) Hardness test:

A Monsanto hardness tester was used to measure the hardness of five tablets from each batch. A compressible spring is housed inside a barrel that is sandwiched between two plungers to form the tester. A zero reading is obtained by touching the tablet with the lower plunger. The tablet is then cracked by rotating a thread bolt, which forces the upper plunger against a spring. A pointer that travels along a gauge inside the barrel to show the force—a measurement of hardness—is activated when the spring is compressed.

c) Friability test:

For this test, the Roche Friabilator was utilized. With each revolution of the plastic chamber, which rotates at 25 RPM for 4 minutes and drops the tablets from a distance of 6 inches, the device subjects a number of tablets to the combined effects of shock and abrasion. Ten tablets that have been preweighed are typically put in the friabilator and spun 100 times. After that, the tablets are reweighed and dedusted. For the majority of pills, a weight loss of no more than 1% is considered acceptable.

%Friability = (Initial weight –Final weight) / Initial weight ×100

d) Weight variation test:

20 randomly chosen tablets were weighed, and the average weight was determined. After that, the percentage departure from the mean was computed. IP requirements state that no individual weight deviates from the average weight by more than twice the percentage indicated below, and that no individual weight deviates from the average weight by more than two.

% Deviation = (Individual weight - Average weight / Average weight) x 100

e) In vitro Disintegration test:

This test is run to make sure the core tablets have broken down. In two tubes of the IP disintegration apparatus, one tablet is inserted. The device, which is suspended in a beaker with distilled water within, is run until the tablet dissolves. The amount of time needed for the tablet to completely dissolve is indicated.

f) In Vitro Dissolution Study

The tablet was placed inside the dissolution test device (paddle), which was then rotated at 75 rpm. After an hour, 5 ml of the sample was removed and diluted with 0.01N HCL in a 25 ml volumetric flask. Two dilutions, or 0.1 ml each in a 10 ml volumetric flask, were then taken. The removed sample was examined using a UV spectrophotometer set to 296 nm in wavelength.[14]

5. RESULT AND DISCUSSION :

5.1.Peformulation

Sr.no	EXPERIMENT	RESULT
1	**Physical properties** a) Colour b) Odour	 a) A White to off-white crystalline powder b) Odourless
2	**Solubility** a) Sparingly Soluble b) Slightly Soluble c) Practically insoluble	 a) Dichloromethane b) Methanol c) Water
3	**Melting point**	The reported melting point of Ranolazine is in the range of 150ºC-160ºC the observed melting point is158ºC

The first logical step in creating a new drug's pharmaceutical dosage form is called formulation. The development of an efficient dosage form and the physiochemical properties of a novel medicinal component are the main topics of formulation research. Ranolazine, a pure medication, has an observed melting point of 158°C and a claimed melting point in the range of 150°C to 160°C. It was verified that the powdered medication had just pure ingredients and that the active ingredient was ranolazine.

Thermal Analysis

5.2.1 Differential Scanning Calorimetric (DSC) Study

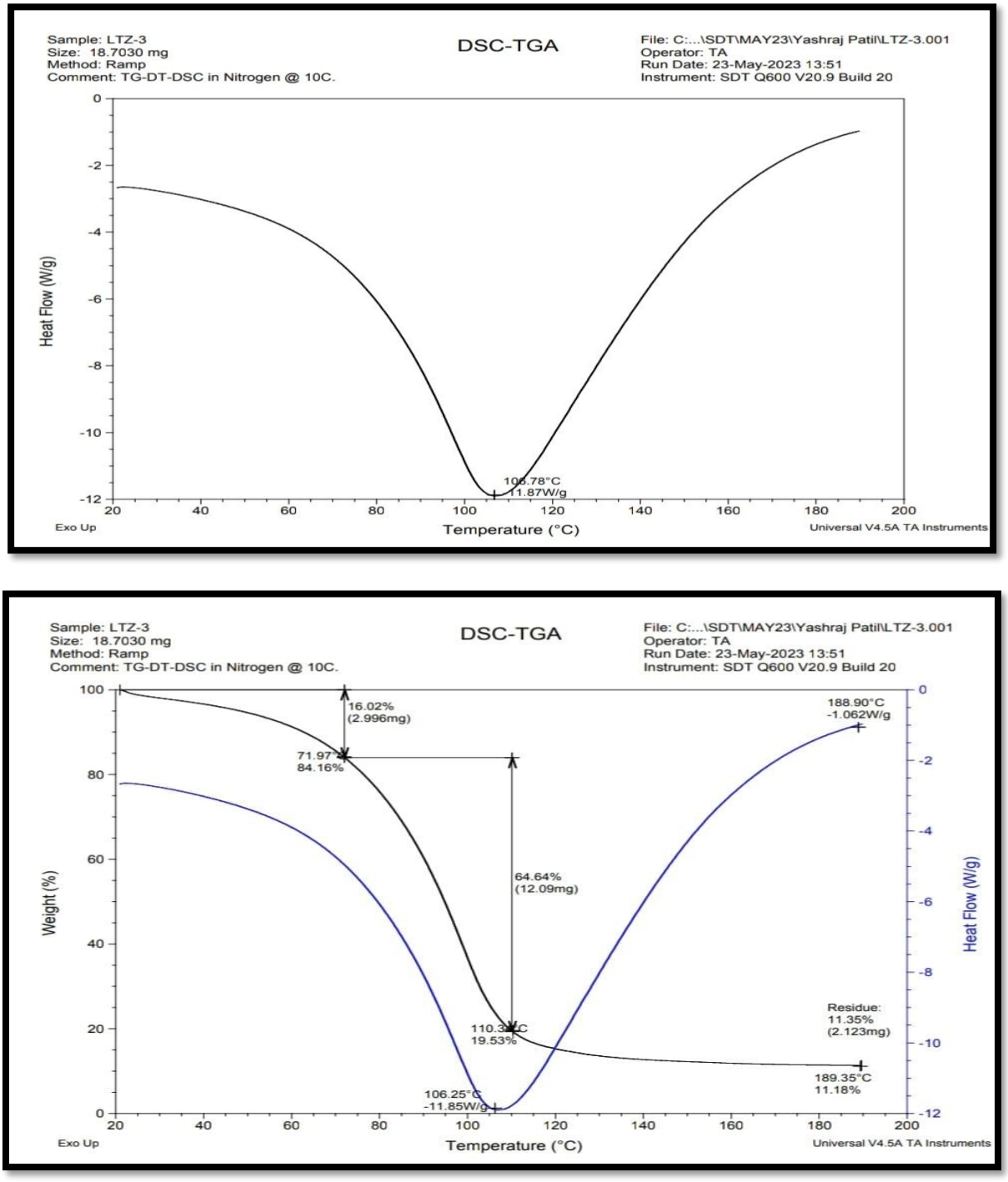


Fig no 2: Differential Scanning Calorimetric Graph

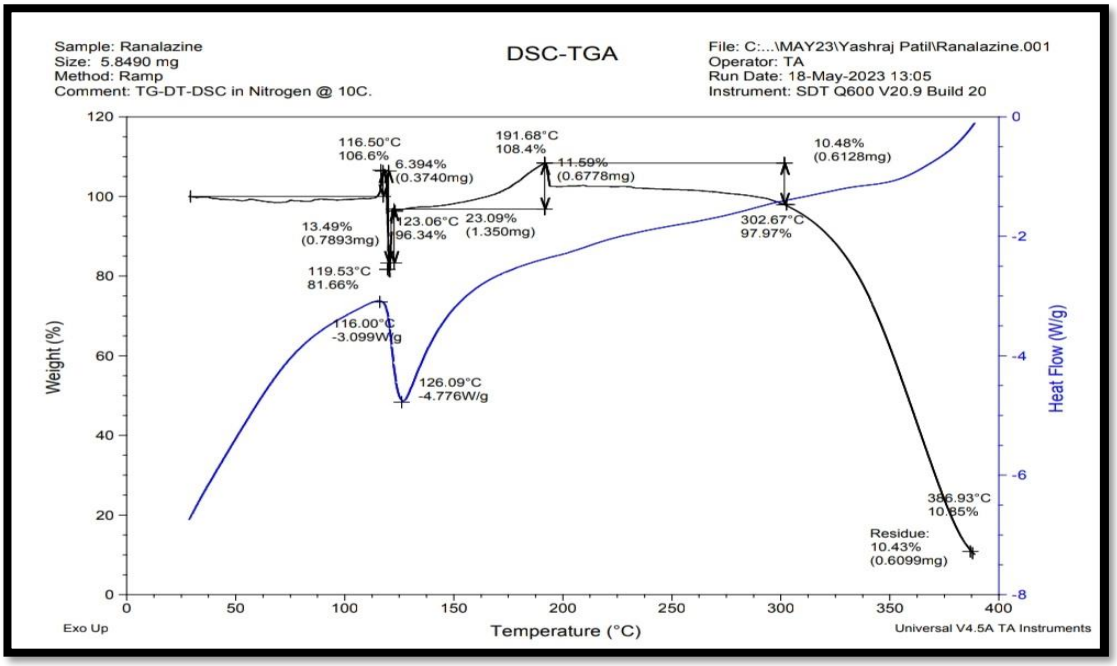


Fig no 3: Differential Scanning Calorimetric Graph of Ranolazine

Mettle DSC 1 (Mone Toledo, Germany) was used for DSC investigations. An indium standard was used for instrument calibration. A precise weight of 5–10 mg of sample was added to closed, perforated aluminum pans with a flat bottom. From 30 to 350oC, the DSC scan was recorded at a steady heating rate of 10oC/min. An 80 ml/min flow rate of nitrogen gas was pumped. Notable aspects included the meting point, peak maxima, emergence of any additional peaks, and variations in peak morphology. DSC was utilized to evaluate the medication ranolazine's thermal behavior in the fig. Just one DSC The melting point of ranolazine is shown as a single, distinct endothermic peak (T peak, 106.78o C) on the thermogram of the substance. Additionally, the presence of only one peak suggests that the medicine sample is pure.

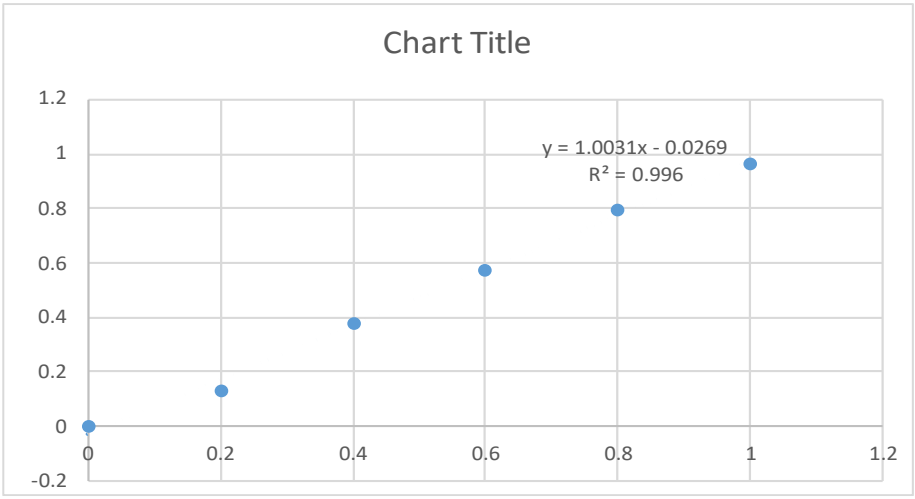
Calibration Curve of Ranolazine:

The calibration curve for ranolazine was determined to be linear, with a coefficient of 0.968, within the range of 0 to 1µg/ml.

Table no 6: Reading of Calibrations Curve of Ranolazine.

Sr.no	Concentration µg/ml	Absorbance
1	0	0
2	0.2	0.134
3	0.4	0.378
4	0.6	0.571
5	0.8	0.797
6	1	0.968

Fig no 4: Calibrations Curve of Ranolazine



The pure substance ranolazine was discovered to have a λ max of 273 nm. It shows that the powder is pure and validates that the substance is ranolazine. According to Beer's Law, the calibration curve for ranolazine has a slope of 0.0269 and an R2 of 0.996. Therefore, it is evident from the calibration curve and λ max that the powder medication sample provided is pure ranolazine.

COMPATIBILITY STUDY:

Fourier transform infrared spectroscopy was utilized to record the infrared spectra of both pure ranolazine and a physical combination. This indicates that the medicine, along with the polymer and other excipients, maintained its usual value throughout the formulation. This observation makes it abundantly evident that the medication, polymer, and excipient employed in this investigation do not interact.

5.4.1 FTIR Spectra of Pure Drug Ranolazine and excipient

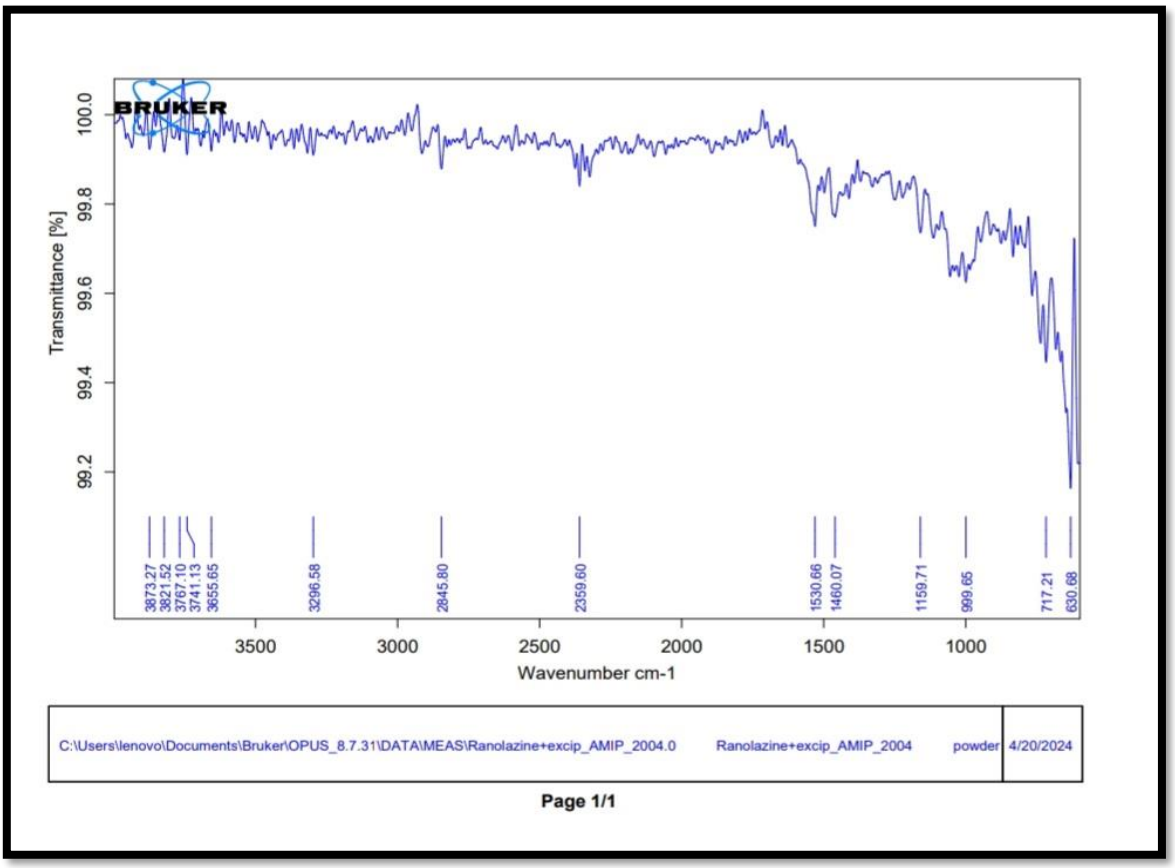


Fig No 5: FTIR Spectra of Drug and excipients

PreCompression and Post Compression Parameter

5.5.1 Pre Compression parameter

Batch Code	Hausner's Ratio	CARR'S INDEX (%)	ANGLE OF REPOSE (θ)
C1	1.150	14.15	25º.76'
C2	1.125	14.11	22º.50'
C3	1.152	15.48	23º.49'
C4	1.163	15.90	26º.39'
C5	1.150	14.30	21º.77'

Table No 7: Pre parameters of CT

Several evaluation tests were conducted on the tablet formulations, including thickness, uniformity of weight, hardness, friability, and drug content. The results are displayed in a table.

a) **Hanser's Ratio:** Table No. 7 displays the Hauser's ratio results for the different batches. It was discovered that every batch exhibited superb flow characteristics. Every batch fell between Lits and 1.150 and 1.163.

b) **Carr's Index:** After applying Carr's index, the outcome is displayed in Table No. 7. It was discovered that every batch had outstanding and good flow characteristics. Every batch fell between 14.11 and 15.90.

c) **Angle of Repose:** The core tablet's angle of repose was measured, and the results are displayed in Table No. 7. It was demonstrated that batches C2, C3, and C4 had good flow qualities and batches CI and C5 had excellent flow properties. It was discovered that the angle of repose ranged from 21°.77 to 26°.39.

Evaluation of Disintegration Time and Drug Content of Core Tablet

Table No 8: Evaluation of Disintegration Time and Drug Content of Core Tablet

Batch Code	Disintegration time (sec)
C1	185
C2	160
C3	145
C4	90
C5	88

In order for the tablet to dissolve completely and release the medication into the bodily fluid for disintegration, it must first disintegrate. Batch C1 through C5 core pill disintegration times were found to be 185, 160, 145, 90, and 88 minutes, respectively. The disintegration time decreases as sodium starch glycolate concentration increases as the disintegrating agent. The medication content is within the recommended range.

Post Compression Parameter of FPRT

Table No 9: Post Compression Parameter of FPRT

Batch Code	Weight variation(mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (% loss of weight)
C1	840± 1.79	4.0	7.5	0.43
C2	846 ±1.50	4.3	7.65	0.37
C3	840± 1.65	4.1	7.89	0.30
C4	850 ±2.30	4.6	7.50	0.26
C5	848 ±1.84	4.3	7.24	0.38

a) Weight Variation Test

The percentage weight variation of all formulation was shown in table no 9,as Abatch possess weight variation test within pharmacopeia limit and it was found between840± 1.65 to 848 ±1.84

b) Thickness

The thickness of FPRT tablet is shown in table. The thicknesses of FPRT table no 9, were measured by vernier calliper. In that all of formulation shown uniform thickness. The thickness of all formulation ranged between 4.0 to 4.6mm. The thickness should be controlledwithina±4% variation of standard.

c) Hardness Test-

The hardness of batches of FPRT tablet no 9, was found to be range between 7.5 to 7.89kg/m^3

d) Friability Test

The batches of all formulation of friability test were shown in table no 9, all tables insuring as the tablet were mechanically stable. According to B.P specification, the total loss should not excide than 1%

Dissolution Study of Core Tablet:

Table no 10: Post Compression Parameter of FPRT

Time (min)	C1	C2	C3	C4	C5
5	22.20	22.28	22.3	25.8	44.2
10	28.70	30.81	30.4	38.3	60.8
15	30.08	42.35	34.7	42.4	72.0
20	42.43	42.98	49.1	70.6	95.8
25	50.05	53.35	62.8	92.8	_
30	55.25	76.10	86.7	_	_

a) % Drug Release Batches C1 to C5

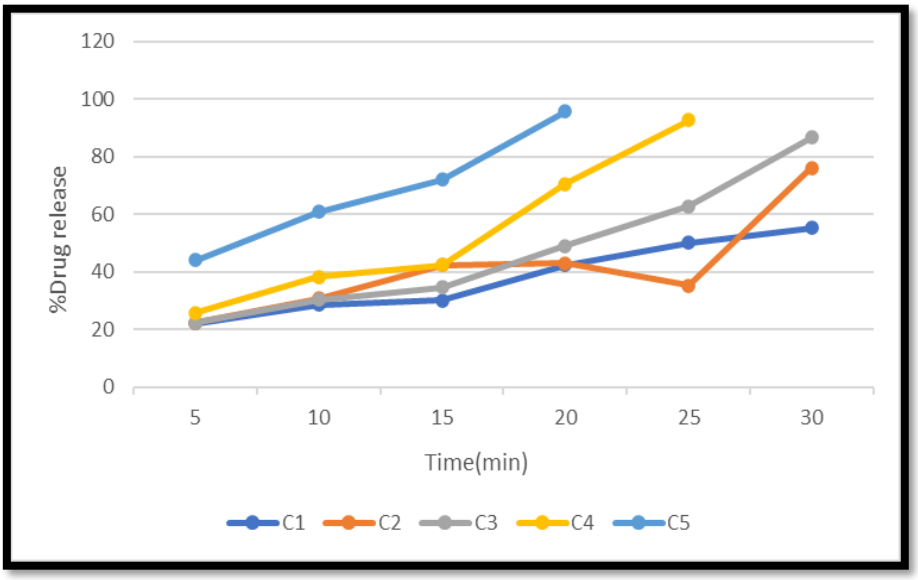


Fig No 4: % Drug Release Batches C1 to C5

5.5.4 Dissolution Study of FPRT Tablet

Table no 11: Dissolution Study of FPRT

Time (Hrs)	C1	C2	C3	C4	C5
1	1.50	1.18	2.27	2.35	2.21
2	1.72	1.65	2.08	2.90	2.79
3	1.46	2.10	2.65	1.99	2.55
4	1.69	2.38	2.51	2.66	2.56
5	2.30	2.40	2.11	2.48	5.48
6	2.52	8.51	2.34	2.87	97.60
7	6.30	90.9	2.49	2.40	-
8	86.50	-	2.55	6.87	-
9	-	-	2.63	93.58	-
10	-	-	8.74	-	-
11	-	-	91.80	-	-

Graph of Drug Release

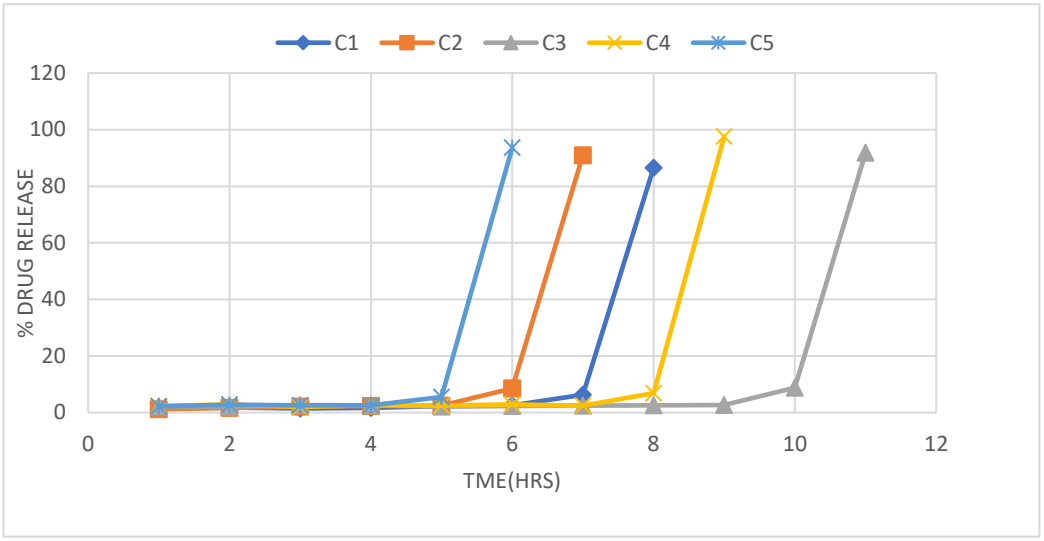


Fig No 5: % Drug Release Batches C1 to C5

In the dissolution study of Floating pulsatile release tablet, the percent drug release from batch C1 to C5 was found to be 86.50, 90.9, 91.80, 93.58, 97.60,respectively. In that batch no. C5 show more drug release compared to other batches. For the treatment of Angina pectories, it is necessary to release of tablet in morning (AM surge) hence there are required release of drug after lag time that is 8 hrs. Graph of drug release show that in the batch no C5 release of drug after 8 hrs.

Because of more drugs release of batch, no C5 that is 97.60 and release of drug after 8 hrs. Which is concerned with circadian rhythm of disease of Angina pectories, hence batch to C5is optimized batch**.**

Table No 12: Data for Total Floating Time

Formulation Code	Tablet Floating Time (hrs)
C1	>8
C2	>8
C3	>8
C4	>8
C5	>8

Fig No 7: Dissolution apparatus

Fig No 8: Disintegration

Fig No 9: Floating Tablet

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