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Formulation and Evaluation of Bioadhesive Pulsatile Drug Delivery of Ranolazine

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ABSTRACT :

This study presents the formulation and evaluation of bioadhesive pulsatile tablets of ranolazine, a drug primarily used in the management of chronic angina. The approach of combination of bio-adhesive pulsatile formulation is suitable for gastro retention and time specific drug delivery. The study was carried by preparation of fast disintegrating core tablet followed by incorporation of core tablet to design bio-adhesive pulsatile tablet by press coating. The tablets were designed to exhibit a pulsatile drug release profile, mimicking the circadian rhythm of angina attacks, thereby optimizing therapeutic efficacy and patient compliance. The tablets were prepared using a combination of bioadhesive polymers or binder, polyvinyl pyrolidone (pvp), and carbapol along with a pulsatile drug release agent, ethyl cellulose, employing combination of direct compression and compression coating techniques. Various formulation parameters such as polymer concentration, compression force, and drugto-polymer ratio were optimized to achieve desired drug release kinetics. The prepared tablets were evaluated for physicochemical properties, swelling behavior, mucoadhesive strength, and in vitro drug release studies under simulated physiological conditions. Pharmacokinetic studies in animal models confirmed the suitability of the formulation for achieving desired plasma drug concentrations over a 24-hour period. Overall, the developed bioadhesive pulsatile tablet of ranolazine offers a novel approach for chronotherapeutic drug delivery, addressing the circadian variation of angina symptoms. By modulating drug release according to physiological rhythms, this formulation has the potential to improve patient compliance and therapeutic outcomes in the management of cardiovascular diseases.

Keyword: Bioadhesive, Pulsatile, Release, Ranolazine, Chronotherapy

Introduction:

Noval Drug Delivery System

A new technique that integrates creative formulations, modern equipment, and novel procedures to securely distribute pharmaceutical chemicals in the body where they are needed to produce the desired pharmacological effects is known as a novel drug delivery system, or NDDS. By creating an easy-to-administer dosage form, innovative drug delivery systems (NDDS) attempt to improve patient compliance while also improving the safety and effectiveness of currently used pharmacological molecules.

One of the key instruments in the pharmaceutical industry for growing drug markets is NDDS. By improving product shelf life, patient compliance, safety, and efficacy, NDDS can reduce issues[1,2]. In the innovative drug delivery systems (NDDS), there are many carriers with advantages over those based on type. The conventional dosage forms exhibit instability, first pass effect, high dose and limited availability, fluctuating plasma drug levels, and rapid release of pharmaceuticals[3].

Bioadhesive Drug Delivery System (BDDS)

The creation of an interaction between two biological surfaces or between a biological and a synthetic surface is referred to as bioadhesion. The word "bioadhesion" is usually used to refer to the adherence between synthetic or natural polymers and soft tissues in the context of bioadhesive medication delivery systems. Bioadhesion is the adherence of artificial or naturally occurring macromolecules to mucous membranes or epithelial surfaces. The term mucoadhesion refers to the bioadhesive interactions that mostly take place with the mucus layer when applied to the mucosal epithelium[4].

Bo-adhesion Mechanisms :

There are two phases to a bioadhesion mechanism: the contact stage and the consolidation step. The beginning of the bio adhesive's deep engagement with the mucous layer is marked by both the initial contact with the mucous membrane and the following swelling and spreading of the formulation. The bio-adhesion materials become active during the consolidation step when moisture is present. When the system gets moist, it becomes plastic, which permits the molecules involved in bioadhesion to split apart and create weak hydrogen and van der Waals linkages[5].

Pulsatile Drug Delivery System

The most intriguing and time-specific drug delivery method according to the pathophysiological requirements of the diseases is the pulsatile drug delivery system. A pulsatile drug delivery system is distinguished by a brief interval of non-release (lag time) succeeded by a swift and comprehensive release of the drug. The kind of pulsatile delivery mechanism (rupturable polymeric coating, osmotic system, or capsule system) used in the formulation affected the drug release. Replacing the dissolving and swelling chemicals shortened the lag time. The medication release was completed ahead of schedule by shortening the lag period[6].

Combination of Bioadhesive Pulsatile Drug Delivery System:

The combination of pulsatile formulation and bioadhesive technology is an appropriate technique for time-sensitive medication delivery and gastro retention. Since it attaches to the stomach mucous membrane and causes gastro-retention for longer periods of time to improve bioavailability, the bioadhesive drug delivery system (BDDS) is more interested in designing the dosage form[7,8]. A planned off-release session that lags time depending on the disease and is always longer than the gastrointestinal emptying time is represented by PDDS as the rapid release of a specific dosage in a shorter amount of time. It emerged as a result of the body's circadian rhythm[9,10]. The anti-anginal medication ranolazine, which has a 6-hour lag time and can be administered before bedtime (9.00 pm), was produced for this study's BPDDS.

Drug : Ranolazine
Chemical Name:
N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]piperazin- 1-y}acetamide

Material and Experimental Methods

1. Materials:
The supplier of ranolazine was Yarrow Chem Products in Mumbai, India. The AMCP, PethVadgaon, Kolhpur supplied sodium starch glycolate, microcrystalline cellulose, polyvinyl pyrrolidone (PVP), and ethyl cellulose. Our college (AMIP, Ambap, Kolhapur) supplied magnesium stearate and carbapol. Analytical grade compounds were all that were utilized.

2. Experimental Methods

Preformulation Studies:

A. Organoleptic Properties
Among the organoleptic properties are color, taste, and odor; the recording of color is crucial in order to identify appropriate batches.

B. Determination of Melting Point
The amount of ranolazine is measured using the capillary technique. First, take a capillary tube and seal one end of it. Next, the capillary tube is filled with finely ground ranolazine powder. Using the rubber band, secure the capillary to the thermometer. The sample is heated to its melting point using a thermometer and a capillary tube that are inserted into the equipment' sample holder. It was noted what temperature the powder melted at.

C. Spectroscopic Studies

a) UV-Visible Spectroscopy:
By scanning between 200 and 400 nm, the absorption maxima of the reference drug solution in methanol were found.

b) Determination of λ max in Methanol:
Make a ranolazine stock solution. A 50 ml volumetric flask containing 50 mg of ranolazine was filled with methanol (1000 µg/ml) to make the volume reach 50 ml (stock 1). Subsequently, 5 ml of the stock solution was extracted from stock 1 and placed into a second 50 ml volumetric flask. The volume was increased to 50 ml, or 100 µg/ml, of the solution (stock 2). Additionally, methanol was used to make ranolazine dilutions (1, 2, 3, 4, and 5 µg/ml), and a UV Visible spectrophotometer was used to measure absorbance at 273 nm. After undergoing UV spectrophotomeric examination, the final solution's λ max was ascertained.

D. Thermal analysis: Differential Scanning Calorimetric (DSC) Study:
The most widely used method for calculating the heat absorbed or released during different temperature-related transitions in the sample is differential scanning calorimetry. Purity, polymorphism, deterioration, and excipient compatibility are all evaluated using it. A Mettle DSC 1 was used for DSC

investigations (Mettle Toledo, Germany). An indium standard was used to calibrate the device. Precisely weighed specimens (5–10 mg) were inserted into closed, perforated aluminum pans with a flat bottom. From 30 to 350°C, differential scanning calorimetry (DSC) scans were acquired at a steady heating rate of 10°C/min. Pumped nitrogen gas flowed at 80 milliliters per minute. Notables included melting points, peak maxima, the emergence of any new peaks, and variations in peak morphology.

E. Compatibility Study: FTIR of Drugs & Excipients:

Drug excipient interactions have been identified with the help of FT-IR. Fourier transform infrared spectroscopy (FTIR) [Agilent Cary 630] was utilized to record the ranolazine spectra and demonstrate structural change. After a small sample of approximately 100 mg was obtained, it was placed on an FTIR platform, and its spectra were recorded. The 4000 and 400 cm-1 areas were used to analyze the sample[11].

Preparation Methods:

a) Preparation Method of Core Tablet(CT):

By using the direct compression method, 500 mg of ranolazine per day were manufactured as core tablets. A 500 mg tablet's weight can be adjusted by adding or subtracting 10 mg of polyvinylpyrolidone, 1 mg of magnesium stearate, 6/8/10/12/14 mg of sodium starch glycolate, and 182,180,178,176,174 mg of microcrystalline cellulose. After that, every component was precisely weighed and thoroughly combined for fifteen minutes. The final powder mixture was then compressed using a single direct compression machine and a 9.5 mm die to create tablets. In the formulation Sodium starch glycolate used as disintegrating agent, Polyvinyl pyrrolidone used as binder, Magnesium stearate were used as a lubricant and Microcrystalline cellulose were used as diluents[12-14].

Ingredients (mg)	C1	C2	C3	C4	C5
Ranolazine	500	500	500	500	500
Sodium starch glycolate	6	8	10	12	14
Magnessium stearate	2	2	2	2	2
Microcrystalline cellulose	182	180	178	176	174
Polyvinyl pyrolidone	10	10	10	10	10
Total (mg)	700	700	700	700	700

Table No 1: Formulation chart for Ranolazine core Tablet

b) Preparation of Bioadhesive Pulsatile Release Tablet (BPRT) by using direct compression process:

Different concentrations of ethyl cellulose and carbopol were utilized to finish the dry coating process. PVP, magnesium stearate, and microcrystalline cellulose were also used to coat the core tablet (Table 2). To make a fine mixture, all ingredients were weighed and painstakingly blended. The 13 mm die and punch set was used to prepare the BPRT. First, a core tablet was placed on the die after 40% of the final blend had been added. After adding the final 60% blend, a KBr tablet press machine was used to compress the tablet.(Diameter of die: 13 mm)[15,16].

Ingredients (mg)	C1	C2	C3	C4	C5
Core tablet	700	700	700	700	700
Magnesium Stearate	3	3	3	3	3
Polyvinyl pyrolidone	15	15	15	15	15
Ethyl cellulose	141	98.5	141	70.5	70.5
Carbapol	98.5	141	141	98.5	98.5
Microcrystaline cellulose	42.5	42.5	-	113	113
Total (mg)	1000	1000	1000	1000	1000

Table No 2: Formulation chart BPRT

Characterization:

A. Pre compression parameters of blends (powders):

a) Bulk density: Measuring the volume of a known mass of powdered sample in a graduated cylinder (100 ml) yields the bulk density of the powder.

Bulk density= Weight of powder / Bulk volume

b) Tapped density: To find the tapped density, mechanically tap a graduated 100 ml cylinder containing the powdered sample 100 times.

Tapeed desity = Weight of powder / Tapped volume

c) Carr's index: Based on bulk and tapped densities, the Carr's Index of any given powder is computed to determine its compressibility.

Car's index = Tapped desity – Bulk desity /Tapped desity ×100

d) Hausner ratio: Hausner ratio is the ratio of a powder's tapped density to its poured (loose) bulk density.

Hausner ratio = Tapped density / Bulk density

e) Angle of repose:. The fixed funnel method, which fills the containers with a sample and gradually raises them so the sample accumulates and forms a conical heap on the surface, is used to calculate the angle of repose.

$\tan\theta = h/r$

B. Evaluation of core tablets: In vitro disintegration time

Using a digital tablet disintegration instrument (LABINDIA), the in vitro disintegration time of six tablets from each formulation was determined. The USP device in vitro disintegration test apparatus, which has 10 mesh screens at the bottom end and 6 glass tubes open at the top, was used to conduct the disintegration test. Tablets were inserted into each of the six basket tubes to measure the disintegration time. This test used 900 ml of 0.1N HCL and a temperature of 37 °C±2 °C. Then, at a rate of 28 to 30 cycles per minute, move the tablet-filled basket up and down a distance of 5 to 6 cm. The amount of time it took for the tablet to completely dissolve and leave no trace on the wire screen was noted.

C. Post-compression evaluation of tablets

a) Weight variation test: Using a digital weighing balance, weigh each batch of 20 pills separately for the study weight variation, and then conduct the test in accordance with the prescribed protocol.

b) Hardness: The force required across the tablet's diameter to shatter it is known as the tablet's hardness. Using a Pfizer tablet hardness tester, the average hardness of the ten tablets in each batch was computed. For mechanical stability, a tablet hardness of roughly 2-4 kg/cm2 is thought to be sufficient.

c) Friability: To find out if the tablets are stable against abrasion, a friability test should be performed. The Roche friabilator is used to test friability. Twenty pills are weighed and put into the machine's plastic drum, which is rotated at 25 rpm for four minutes, or 100 spins. Next, tablets are weighed one more. This is how percentage friability is determined:

$$\% \text{ Friability} = (W_1 - W_2)/ W_1 \times 100$$

Where, W_1 = Initial weight of 20 tablet, W_2 = Weight after 100 revolutions

The weight loss should not be more than 1% w/w.

d) Thickness: Using a vernier caliper, the thickness of each of the ten tablets was measured in millimeters (mm). They noted the average thickness.

e) In-Vitro dissolution study: The dissolution experiments of core tablets and BPT were conducted in 900 ml of 1.2 pH 0.1 N HCl using a USP type II dissolution test instrument (LABINDIA, DS8000). For every dissolving investigation, a constant temperature of 37±2◦C was maintained together with 75 rpm stirring. The sample was withdrawn and diluted with 1.2 pH 0.1 N HCl in a 25 ml volumetric flask after an hour. The next dilution was made with 0.1 ml in a 10 ml volumetric flask. Using a UV spectrophotometer set at 296 nm, the drug's concentration was determined (UV-Visible spectrophotometer).

f) In-vitro bioadhesion test: Two pan balances were used in the preparation of the model for the mucoadhesion test. A physical balance's two pans were removed and swapped out for beakers weighing the same amount. The whole setup was elevated to accommodate a glass petri dish underneath the left beaker, maintaining a 0.5 cm gap between the two. Before the mucoadhesion evaluation study, the chicken ileum was removed, washed, and equilibrated at 37ºC for 30 minutes in 0.1 N HCl medium. The ileum was securely fastened using thread to the mucus on the glass slide, which was subsequently filled with 0.1N hydrochloric acid and maintained at 37ºC to the point where the 0.1N acid barely touched the ileum membrane to maintain moisture. Using this glass slide underneath the left beaker and lowering it to the left beaker's petri plate, the tablet was placed on the base of the beaker using two-way adhesive tape and the balance beam. The left beaker was then covered with a constant weight of 10 gm for five minutes, allowing the tablet to make complete contact with the ileum membrane. The weight (in gm) required to remove the tablet from the membrane was then measured by adding weights to the right beaker, and the amount of time needed to separate the tablet from mucus membrane

was recorded as the adhesion time[17].

N = bioadhesive strength/100 X 9.81

g) Effect of independent variables on bioadhesion time (Y2): The most crucial factor in the bioadhesive drug delivery system is the mucoadhesion time. If the tablet demonstrates the necessary adhesion time, the medication can be released into the stomach without difficulty following the 8-hour lag period needed for angina pectoris. Furthermore, mucoadhesion time influences medication release and absorption rates. The influence of independent factors on mucoadhesion time can be explained by the following equation.

Bioadhesion time $Y2 = +8.43+0.6583\ X_1+0.3917\ X_2$

7. RESULT AND DISCUSSION :

7.1 Preformulation Studies

7.1.1 Organoleptic Properties & Melting Point:

SR. NO.	EXPERIMENTS	RESULT
1.	**Physical properties** **a)** Colour **b)** Odour **c)** Taste	**a)** White to off white solid powder **b)** Odourless **c)** Bitter
2.	**Solubility** **a)** Sparingly soluble **b)** Soluble **c)** slightly soluble **d)** very slightly soluble	**a)** Ethanol **b)** Methanol **c)** Toluene **d)** Water
3.	**Melting point**	158°C -160°C

Table no 3: Preformulation

The initial stage in the methodical development of a new drug's pharmaceutical dosage form is called preformulation. The observed melting point of pure ranolazine is between 158 and 160°C, while the reported melting point of the medication is between 164 and 166°C. It was verified that the powdered medication had just pure ingredients and that the active ingredient was ranolazine.

7.1.2 Spectroscopic Studies: Clibration Curve of Ranolazine

It was discovered that the ranolazine calibration curve in methanol was linear within the range of 2 to 10 µg/ml.

Sr. no.	Concentration (µg/ml)	Absorbance
1	2	0.109
2	4	0.194
3	6	0.298
4	8	0.376
5	10	0.469

Table no 4: Reading of Clibration curve of Ranolazine

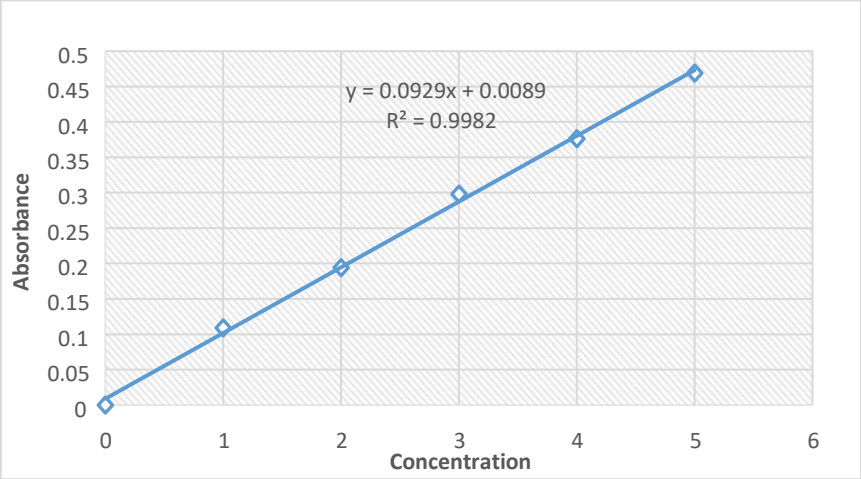
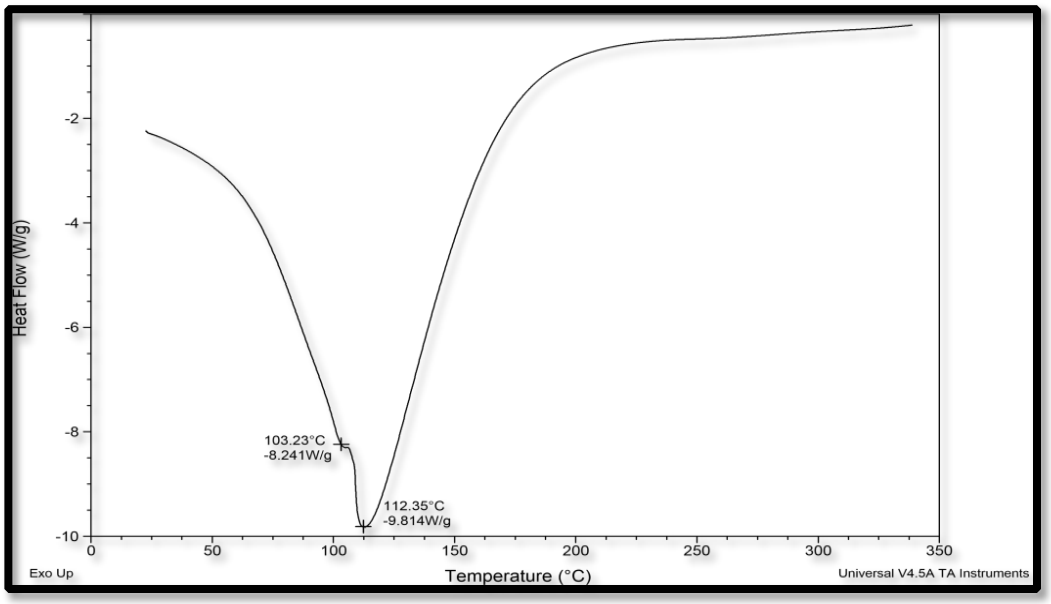


Fig no 1: Clibration curve of Ranolazine in Methanol

It was discovered that the pure substance ranolazine had a λ max of 273 nm. It confirms that the powder provided is ranolazine and shows that the medicine sample is pure in nature. According to Beers law, the ranolazine calibration curve has a slope of 0.0089, an intercept of 0.092, and a R of 0.9982. Therefore, based on the calibration curve and λ max, it is evident that the green powder drug sample is pure ranolazine.

7.1.3 Thermal Analysis: Differential Scanning Calorimetric (DSC) Study:

Mettle DSC 1 (Mettle Toledo, Germany) was used for differential scanning calorimetry (DSC) investigations. An indium standard was used to calibrate the device. Precisely weighed specimens (5–10 mg) were inserted into closed, perforated aluminum pans with a flat bottom. From 30 to 350°C, DSC scans were collected at a steady heating rate of 10°C/min. Pumped nitrogen gas flowed at 80 milliliters per minute. Notables included melting points, peak maxima, the emergence of any new peaks, and variations in peak morphology. Ranolazine's thermal behavior was evaluated using DSC.
A single, distinct endothermic peak (T peak = 112.35°C), which represents the melting point of ranolazine, can be seen in the DSC thermogram of the compound in Figure 3. Additionally, the presence of only one peak suggests that the medicine sample is pure.



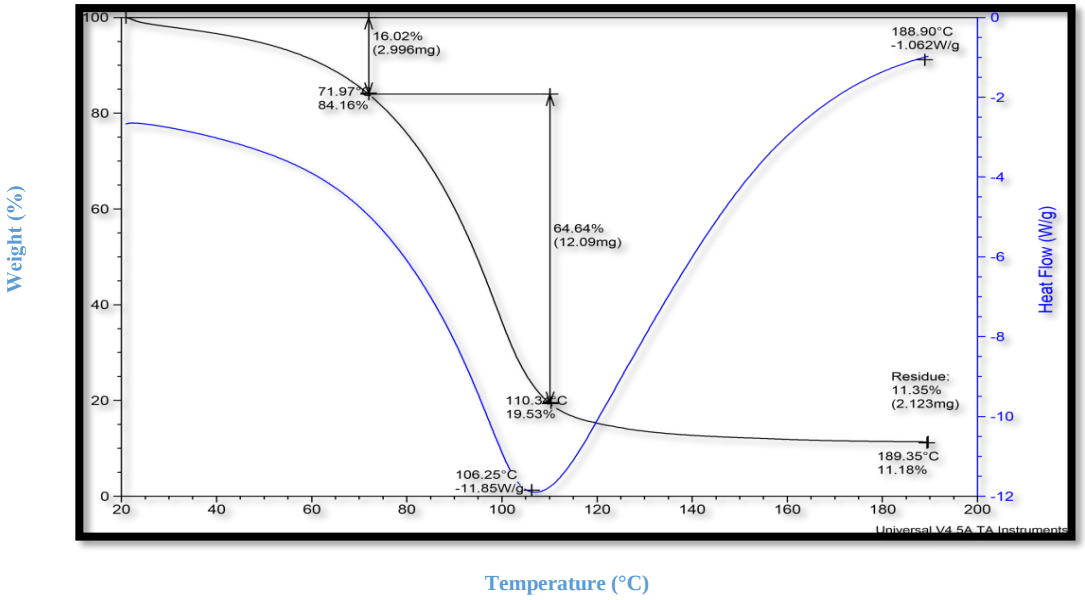


Fig no 2: Differential Scanning Calorimetric Graph

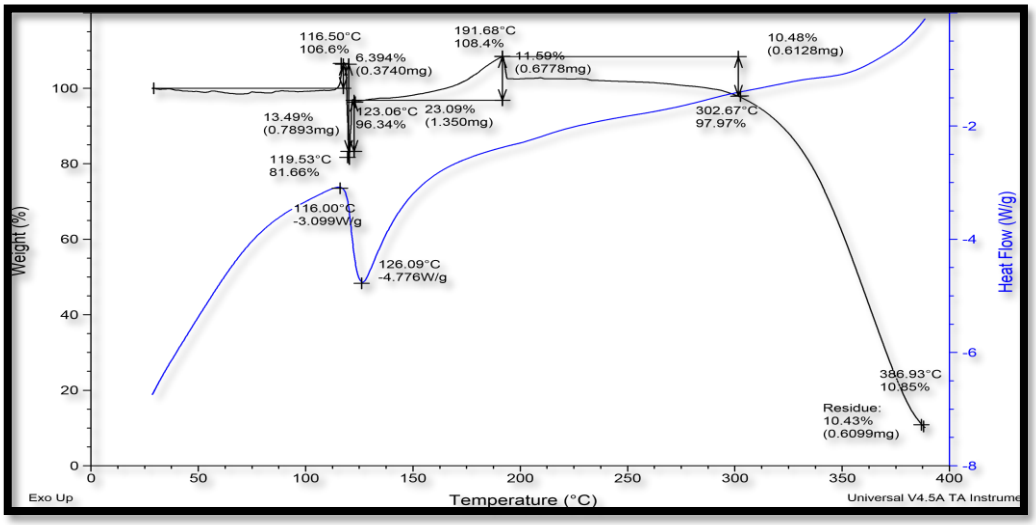
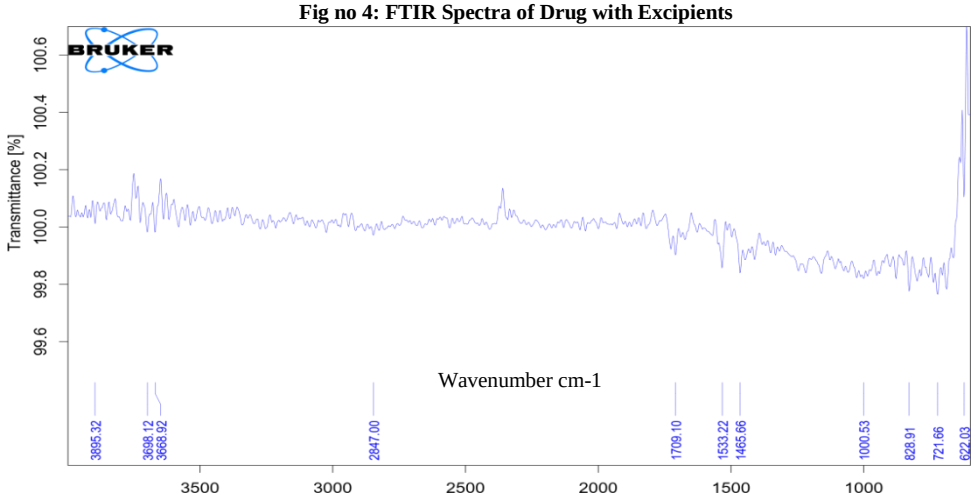


Fig no 3: Differential Scanning Calorimetric Graphof Ranolazine

7.1.4 Compatibility Study: FTIR Spectra of Pure Drug with Excipient

Using Fourier transform afrared spectroscopy, the infrared spectra of pure ranolazine and a physical combination were recorded (Agilent carry 630). This indicates that the medicine, along with the polymer and other excipients, maintained its usual value throughout the formulation. This observation unequivocally shows that the medication, polymer, and excipient employed in this investigation did not interact.

Fig no 4: FTIR Spectra of Drug with Excipients



7.2 Characterization

7.2.1 Pre compression parameters of blend

Batch code	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Cars index (%)	Angle of repose
C1	0.398±0.04	0.471±0.04	1.373±0.08	15.49±1.07	18.20±0.41
C2	0.384±0.04	0.456±0.06	1.187±0.07	15.78±1.09	20.01±1.09
C3	0.456±0.07	0.452±0.06	0.99±0.02	15.05±1.12	24.15±0.28
C4	0.471±0.08	0.476±0.04	1.010±0.06	10.50±0.68	25.13±0.38
C5	0.471±0.08	0.476±0.04	1.010±0.06	10.50±0.68	30.01±0.25

Table no 5: - Pre compression parameters of blend

The combination of tablets with varied formulations were put through a battery of evaluation tests, including bulk and tapped density.The car's index thickness, homogeneity of weight, friability, hardness, and disinetgression time, among other factors. The outcome appeared in the table:

a) **Bulk density:** Table No. 5 displays the bulk density results for the different batches, all of which have good qualities. Every batch fell between 0.384±0.04 to 0.471±0.08.
b) **Tapped density:** Table No. 5 displays the bulk density results for the different batches, all of which have good qualities. Every batch fell between 0.452±0.06 and 0.476±0.04.
c) **Hauser's Ratio:** Table No. 5's Hauser's ratio results for the different batches indicate that each batch has exceptional flow characteristics. The range of all the batches was between 0.99±0.02 and 1.373±0.08.
d) **Carr's Index:**After applying Carr's index, the outcome is displayed in Table No. 5. It was discovered that every batch had exceptional and good flow characteristics. The range of all hatches was 10.50±0.68 to 15.78±1.09.
e) **Angle of Repose:** The core tablet's angle of repose was measured, and the results are displayed in Table No. 5. It was demonstrated that batches C1, C2, and C3 had good flow qualities and batches C4and C5 had exceptional flow properties. The range of the angle of repose was determined to be 18.20±0.41 to 30.01±0.25.

7.2.2 Evaluation of disintegration time of core tablet:

Batch code	Disintegression time (sec)
C1	200±10
C2	180±18
C3	155±24
C4	120±40
C5	75±67

Table no 6:- Evaluation of disintegration time of core tablet

The tablet needs to dissolve the drug in the bodily fluid in order for it to be completely available for absorption. Batch C1 through C5 core tablet disintegration times were 200±10, 180±18, 155±24, 120±40, and 75±67, in that order. The disintegration time decreases as the concentration of the sodium starch glycolate disintegrating agent increases.

7.2.3 Post Compression Parameters of Tablet

Batch code	Weight variation (mg)	Thickness (mm)	Hardness ($kg/cm^{3)}$	Friability (% loss of wt)	Bioadhesive strength	Bioadhesive Time (Hrs)
C1	865±1.1	7.2±0.02	7.1±0.16	0.53±0.01	28.25±1.7	9:10±0.2
C2	900±3.2	7.0±0.11	8.3± 0.24	0.63±0.02	35.45±1.9	8:35±0.4
C3	855±2.4	7.2±0.01	8.1±0.11	0.54±0.01	36.15±2.6	8:40±0.2
C4	890±1.1	7.3±0.10	7.4±0.14	0.67±0.01	32.15±3.1	9:05±0.5
C5	870±2.8	7.1±0.02	7.6±0.11	0.65±0.02	27.15±2.7	8:10±0.3

Table no 7:- Post compression parameters of Tablet

a) **Weight Variation Test:** Table No. 7 displayed the percentage weight variation for each formulation. Every batch has a weight variation test that falls within the pharmacopeia limit, ranging from 865±1.1 to 900±3.2.

b) **Thickness:** Table No. 7 displays the BPRT tablet's thickness. Using a verniarcaliper, the thicknesses of the BPRT pills were measured. Because every formulation exhibited the same thickness. All formulations had thicknesses ranging from 7.0±0.11 to 7.3±0.10 mm. The thickness ought to be regulated to within a standard deviation of ± 5%.

c) **Hardness Test:** It was discovered that the hardness of the BPRT tablet batches ranged from 7.1±0.16 to 8.3±0.24 kg/cm3.

d) **Friability Test:** Table No. 7 displayed the batches for every formulation of the friability test, ensuring the mechanical stability of each tablet. The overall loss should not exceed 1%, according B.P. specifications.

e) **Bioadhesion strength:** The table displayed the batches of each bioadhesive strength formulation. Between 27.15±2.7 to 36.15±2.6 was the range of tablet strengths.

f) **Bioadhesivon time:** A table was created that displayed the batches of each bioadhesive formulation. Eighty-ten to ninety-two was the range of tablet strengths. The C5 formulation showed the lowest mucoadhesion time whereas the C1 formulation showed the longest mucoadhesion time.

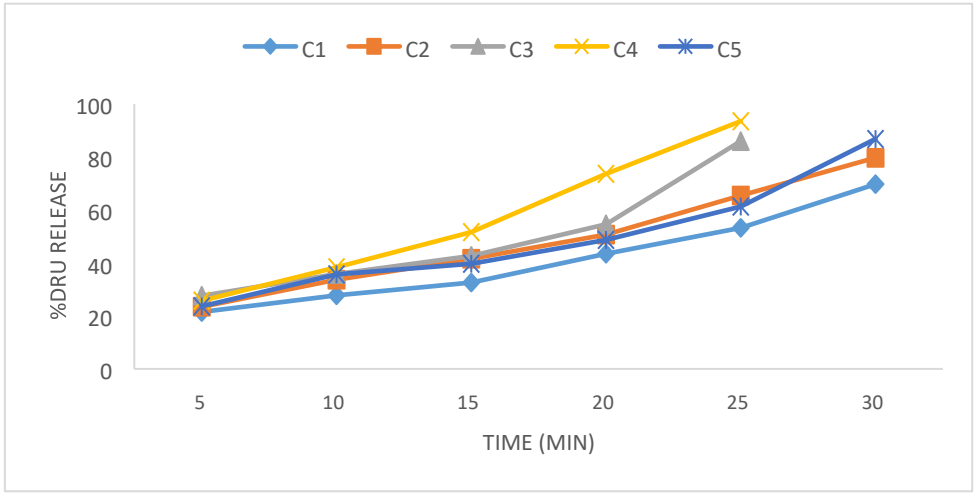


Fig no 5: Drug release of Core Tablet

Dissolution study of Core Tablet:

Time (min)	C1	C2	C3	C4	C5
5	21.5	23.45	27.6	25.71	23.61

10	27.73	33.71	35.8	38.3	35.72
15	32.61	41.56	42.6	51.64	39.65
20	43.51	50.69	54.52	73.65	48.71
25	53.25	65.5	85.96	93.5	61.25
30	69.71	79.71	-	-	86.8

Table no 8:- Dissolution study of Core Tablet

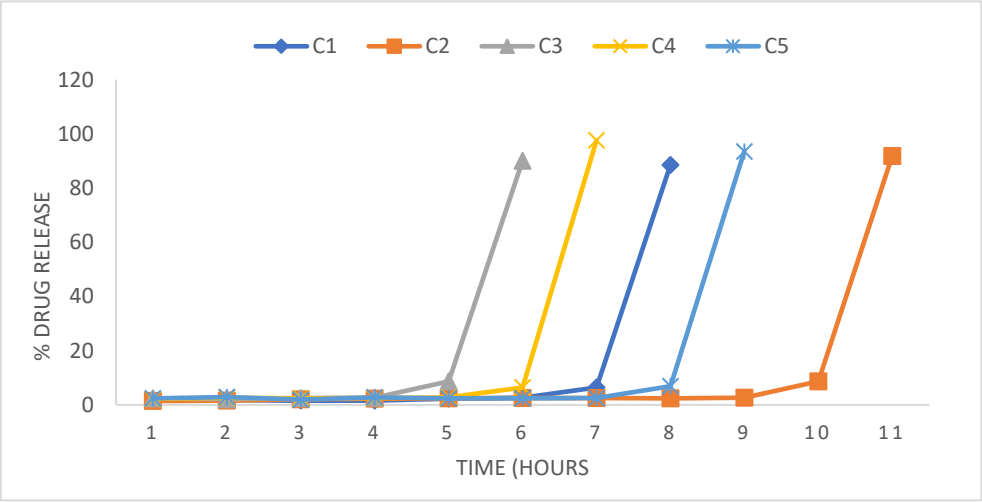


Fig no 6: Drug release of BPRT

Time (Hrs)	C1	C2	C3	C4	C5
1	1.58	1.44	2.43	2.21	2.41
2	1.79	1.63	2.09	2.66	2.89
3	1.54	2.09	2.53	2.45	1.98
4	1.64	2.35	2.61	2.53	2.76
5	2.35	2.46	8.64	2.74	2.45
6	2.69	2.53	90.1	6.44	2.39
7	6.45	2.59	-	93.56	2.53
8	88.53	2.44	-	-	6.85
9	-	2.61	-	-	97.53
10	-	8.05	-	-	-
11	-	93.8	-	-	-

Table no 9 :- Dissolution study of BPRT Tablet

The bioadhesive pulsatile release tablet disintegration investigation revealed that the percentage of medication released from batch Cl to batch C5 is displayed in the table. Compared to previous batches, batch no. C5 exhibits a greater drug release. It is vital to release the tablet in the morning (AM surge) in order to treat Angina pectoris; therefore, the medicine must be released after a lag time of eight hours. According to the drug release graph, there was no C5 drug release in the batch after eight hours.

Due to the release of more pharmaceuticals from batch no. C5, which is 23.45 to 97.53, and the drug's release after 8 hours. which, since it addresses the angina pectoris disease's circadian rhythm, batch no. C5 is the optimal batch.

CONCLUSION :

By offering tailored, time-specific drug release, the creation of a bioadhesive pulsatile drug delivery system can greatly enhance medication therapy. Finally, a viable strategy for enhancing medication administration and patient outcomes is provided by the bioadhesive pulsatile drug delivery system. Because of its capacity to deliver exact timing and localization of therapeutic activity, it is especially helpful for conditions needing regulated, site-specific drug release. Future developments in this area are probably going to produce even more adaptable and efficient medication delivery solutions. This method can increase patient adherence to the prescribed course of action, lessen adverse effects, and increase therapeutic efficacy. But in order to guarantee the end product's stability, safety, and effectiveness, careful material selection and evaluation are necessary during the formulation process.

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