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IN FORMULATION, CHARACTERIZATION AND EVALUATION OF TICAGRELOR ORODISPERSIBLE TABLET

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ABSTRACT

The present study involves the formulation, characterization, and evaluation of Oro dispersible tablets (ODTs) of Ticagrelor to enhance patient compliance and ensure rapid onset of action, particularly in emergency cardiovascular conditions. Ticagrelor, an antiplatelet agent with poor solubility and bioavailability issues was formulated into ODTs using direct compression technique with various superdisintegrants. Among the different formulations developed, Formulation F2 was identified as the optimized batch based on comprehensive evaluation parameters. F2 exhibited excellent pre-compression and post-compression characteristics, including rapid disintegration, uniformity in weight, acceptable hardness and friability, and satisfactory drug content. In-vitro dissolution studies demonstrated a maximum drug release of 99.98% within 30 minutes, indicating fast and efficient drug delivery. FTIR analyses confirmed the compatibility of Ticagrelor with the excipients used. The study concludes that the optimized F2 formulation of Ticagrelor ODT holds significant potential for providing a patient-friendly dosage form with rapid therapeutic action and improved bioavailability.

INTRODUCTION:

The oral route of administration is considered as the most widely accepted route because of its convenience of self administration, compactness and easy manufacturing. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patients incompliance particularly in case of pediatric and geriatric patients [1]. but it also applies to people who are ill in bed and to those active working patients who are busy or traveling, especially those who have no access to water. Over a decade, the demand for development of orally disintegrating tablets (ODTs) has enormously increased as it has significant impact on the patient compliance. Orally disintegrating tablets [2] are appreciated by a significant segment of populations particularly who have difficulty in swallowing. It has been reported that Dysphagia [**3**] (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients ,psychiatricpatients and patients with nausea, vomiting, andmotion sickness complications. ODTs with good taste and flavor increase the acceptability of bitter drugs by various groups of population. This dosage form combines the advantages of dry and liquid formulation. Some novel ODT technology allow high drug loading, have an acceptable taste, offer a pleasant mouth felling, leaving minimal residue in the mouth after oral

administration.ODT have been investigated for their potential in improving bioavaibility [4] of poorly soluble drug through enhancing the dissolution profile of the drug and hepatic metabolism drugs. Orally disintegrating tablets are also called as orodispersible tablets, quickdisintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets,porous tablets, and rapimelts. However, of all the above terms, United States Pharmacopoeia (USP) approved these dosage forms as ODTs. Recently, European Pharmacopoeia has used the term orodispersible tablet for tablets that disperses readily and within 3 min in mouth before swallowing.**[5]** United States Food and Drug Administration (FDA) defined ODT as "A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." The disintegration time for ODTs generally ranges from several seconds to about a minute [**6].** In the present study orodispersible tablets of Ticagrelor were designed using direct compression method using various excipients and super disintegrants with prime objective arriving of a cost effective product.

MATERIALS AND METHODS

MATERIALS: Ticagrelor Procured From Mylan Laboratories Ltd., India. We purchased Primojel, Ac-di-Sol, Polyplasdone XL10, Aspartame, Talc, Magnesium Stearate, and Microcrystalline cellulose 102 from Shreya Life Sciences, Aurangabad, India. The rest of the chemicals and solvents were all of analytical quality.

METHODS

Pre-formulation studies [7,8]

Analytical method used in the determination of Ticagrelor

Preparation of standard graph in phosphate buffer pH 6.8: 100 mg of Ticagrelor was dissolved in 100 mL of pH 6.8 phosphate buffer to give a concentration in 1mg/mL (1000µg/mL) 1 ml was taken and diluted to 100 ml with pH 6.8 phosphate buffer to give a concentration of 0.01 mg/ml (10µg/ml). From this stock solution aliquots of 0.5 ml, 1 ml, 1.5 ml, 2.0 ml, 2.5 ml, were pipette out in 10 ml volumetric flask and volume was made up to the mark with pH 6.8 phosphate buffer to produce concentration of 5,10,15,20 and 25µg/ml respectively. The absorbance of each concentration was measured at respective (λmax) i.e., 300 nm.

Compatibility studies

Fourier Transform Infrared Spectroscopy (FTIR): A Fourier Transform – Infra Red spectrophotometer was used to study the non-thermal analysis of drug-excipient (binary mixture of drug: excipient 1:1 ratio) compatibility. The spectrum of each sample was recorded over the 400-4000 cm^{-1}.Pure drug with physical mixture (excipients) compatibility studies were performed [9].

Methods of preparation of tablets: Drug and different concentrations of super disintegrants (Primojel, Ac-di-Sol and PolyplasdoneXL10) and required ingredients were accurately weighed and passed through a 40-mesh screen to get uniform size particles and mixed in a glass motor for 15 min. The obtained blend was lubricated with magnesium Stearate and Glidant (Aspartame) was added and mixing was continued for further 5 min. The resultant mixture was directly compressed into tablets by using punch of rotary tablet compression machine. Compression force was kept constant for all formulations (Table 1).

Evaluation of pre-compression blend [10,11]

Pre compression parameters: The angle of repose, tapped and bulk density andCarr's index (C.I) parameters were measured by specific procedures for prepared granules. The fixed funnel technique was used for the measurement of the granular repose angle. Bulk density apparatus (Sisco, India) was used for the measurement of tapped and bulk density respectively.

For the determination of C.I. the following formula was used.

$$\% \text{ C.I.} = \frac{e_{tap} - e_{bulk}}{e_{tap}} \times 100$$

Where e_{tap} is the tapped density of granules and e_{bulk} is the bulk density of granules.

Post-compression parameters [12, 13]

Hardness: Buccal tablets hardness was measured by a Monsanto hardness tester (0-20 Kg)(Sisco, India).

Friability test: The friability test of tablets is carried out using the Roche friabilator(Sisco, India). 20 tablets of initial weight ($W_{initial}$) were noted. Subsequently tablets were kept in a Roche friabilator. 100 Revolutions were made. Afterwards the tablets weight is noted (W_{final}). The friability percentage was determined.

Weight variation test (WVT): Individual 20 tablets weight was taken of each batch by weighing machine. The average weight of tablets was measured. Subsequently, it was compared to the individual weight of tablets. The % WVT for tablet was determined followed by a comparison along USP specifications.

Uniformity of drug content test: The content of drug carried out by 5 randomly selected tablets of each formulation. The 5 tablets were grinded to get powder; this powder was dissolved in pH 6.8 phosphate buffer by sonication for 30 min and filtered through filter paper. The drug content was analyzed spectrophotometrically at 300 nm using UV spectrophotometer. Each measurement was carried out in triplicate and the average drug content was calculated

Disintegration test: Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets. Apparatus was run for 10 min. and the basket was lift from the fluid, observe whether all of the tablets have disintegrated

In vitro* dispersion time*: This test is performed to ensure disintegration of tablets in the salivary fluid, if it is to be used as an orodispersible tablet. *In vitro* dispersion time was measured by dropping a tablet in a measuring cylinder containing 6 mL of simulated salivary fluid of pH 6.8. Three tablets from each formulation were randomly selected and *in vitro* dispersion time was measured.

***In vitro* dissolution study (IVDS):** Drug release from Ticagrelor tablets was determined by using dissolution test USP 24 type II (paddle). The parameters used for performing the dissolution were pH 6.8 medium as the dissolution medium of quantity 900 ml. The whole study is being carried out at room temperature of 37˚ C and at a speed of 50 rpm. 5 ml aliquots of dissolution media were withdrawn each time intervals (5, 10, 15, 20, 30, min) and appropriate dilution by UV spectrophotometer. The concentration was calculated using standard calibration curve.

Accelerated stability studies (ASS): As specified by ICH (The International Council of Harmonization) guidelines the developed batches were undergone ASS, stability chamber (Thermo Lab Scientific Equipment Pvt. Ltd., Mumbai, India) was used to keep packed tablets in a suitable container at 75 ± 5% RH and40 ± 2 ºC for three months[14,15]. The tablets were intermittently withdrawn along with the estimation of different parameters.

RESULTS AND DISCUSSION

Pre-formulation studies

Analytical methods for the estimation of drug: For *in vitro* estimation of drug during drug content study and dissolution studies, calibration curve of pure drug was obtained in phosphate buffer pH 6.8. The scanning graph for λmax of drug in phosphate buffer pH 6.8 was found 300. nm. Calibration curve of Ticagrelor in phosphate buffer pH 6.8 was shown in Figure 1. The Regression Coefficient was found to be 0.999 which indicates a linearity with an equation of $y = 0.0331x - 0.0035$.

Compatibility study: The major peaks which are present in pure drug **Ticagrelor** are also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug. There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions (Figure 2 and Figure 3).

Evaluation of pre-compression blend: The pre-compression blend of ODTs was characterized with respect to angle of repose, bulk density, tapped density, car's index and Hausner's ratio**.** All the batches were showing good flow properties depicted in Table 2.

Table 1: Formulation tablets of different batches

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ticagrelor	60	60	60	60	60	60	60	60	60
Primojel	60	120	180	-	-	-	-	-	-
Ac-di-Sol	-	-	-	60	120	180	-	-	-
PolyplasdoneXL10	-	-	-	-	-	-	60	120	180
Aspartame	15	15	15	15	15	15	15	15	15
Talc	8	8	8	8	8	8	8	8	8
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Microcrystalline cellulose 102	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total weight	300	300	300	300	300	300	300	300	300

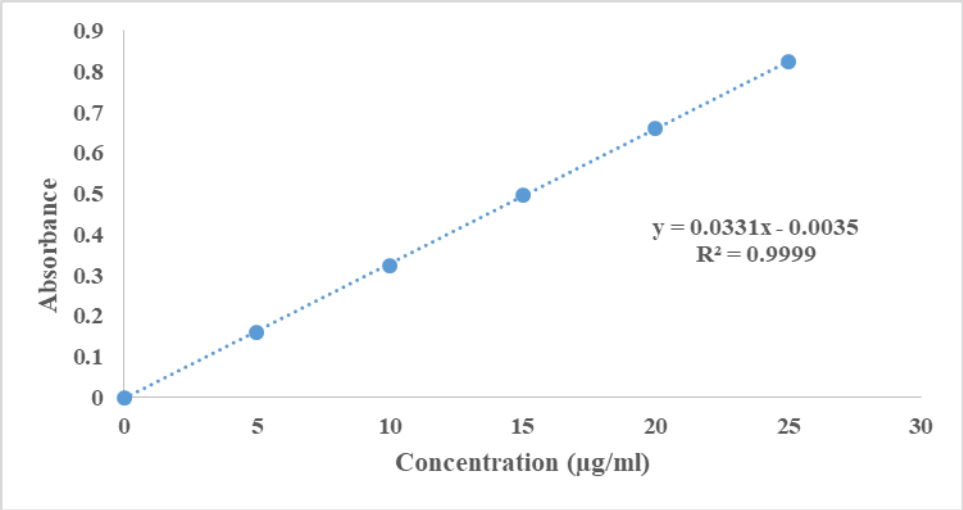

Figure 1: Standard graph of Ticagrelor in pH 6.8 phosphate buffer

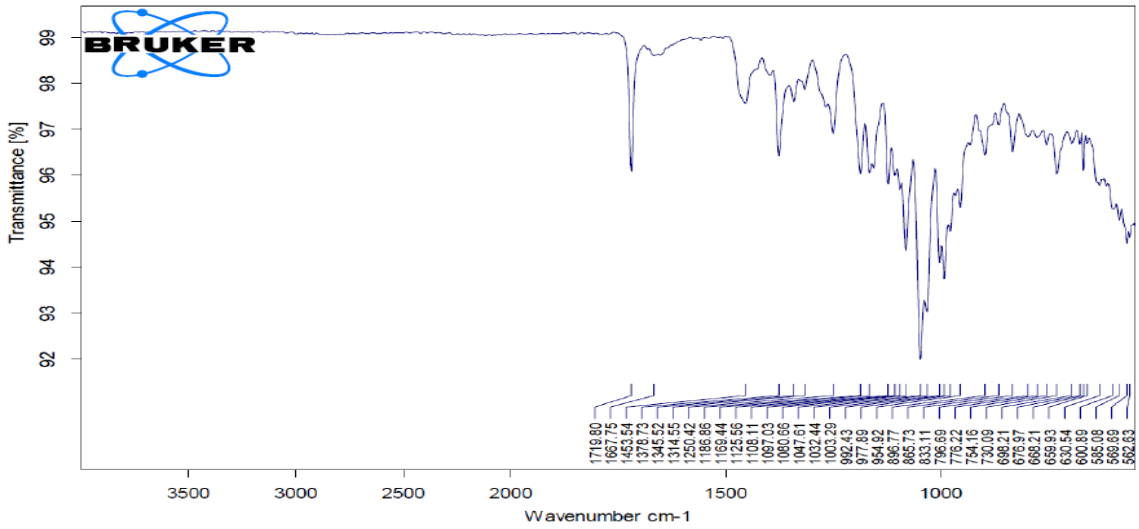

Figure 2: FTIR Peak of pure drug Ticagrelor

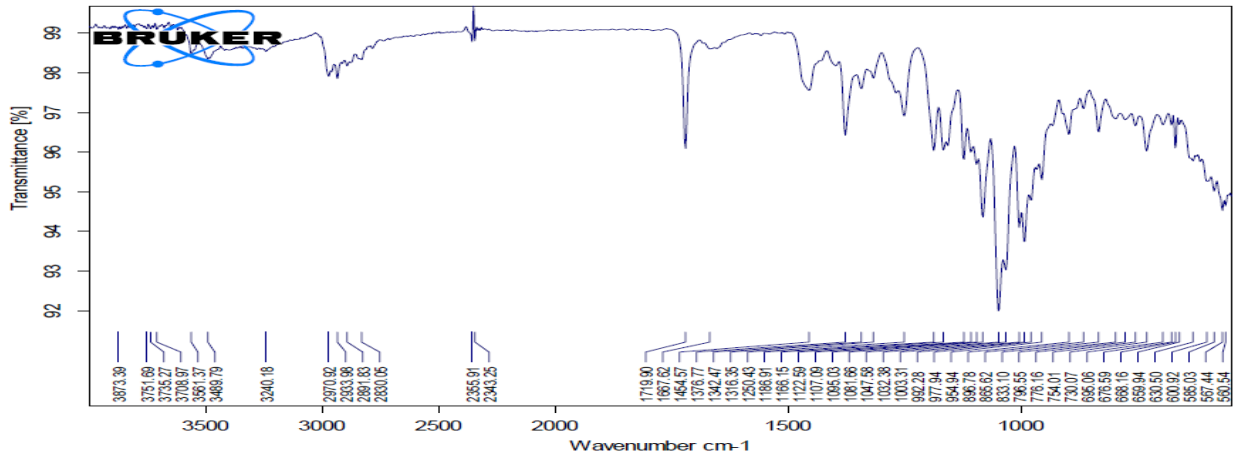

Figure 3: FTIR Peak of Optimized formulation

Table 2: Physical properties of pre-compression blend

Formulation Code	Angle of Repose (Θ) ± S.D	Bulk density (gm/mL) ± S.D	Tapped density (gm/mL) ± S.D	Carr's index (%)± S.D	Hausner's Ratio ± S.D
F1	19.68 ± 0.22	0.632 ± 0.82	0.787 ± 0.92	20± 0.9	1.28± 0.31
F2	24.08 ± 0.38	0.621 ± 0.54	0.775 ± 0.67	20± 0.42	1.26± 0.38
F3	21.42 ± 0.31	0.612 ± 0.25	0.765 ± 0.88	16.83± 0.9	1.18± 0.42
F4	25.29 ± 0.25	0.598 ± 0.42	0.747 ± 0.36	19.89± 0.37	1.25± 0.31
F5	26.44 ± 0.9	0.618 ± 0.85	0.772 ± 0.67	20± 0.31	1.25± 0.38
F6	27.33 ± 0.77	0.602 ± 0.31	0.762 ± 0.81	21.04± 0.67	1.26± 0.37
F7	21.01 ± 0.2	0.619±0.22	0.725 ± 0.75	14.62± 0.42	1.17± 0.37
F8	29.89 ± 0.18	0.638 ± 0.37	0.785 ± 0.83	18.20± 0.38	1.22± 0.67
F9	24.08 ± 0.26	0.618 ± 0.85	0.772 ± 0.67	20± 0.83	1.25± 0.9

Table 3: Physical evaluation of ODTs

Formulation codes	Average Weight (mg) ± S.D	Hardness (kg/cm^2) ± S.D	Friability (%loss) ± S.D	Thickness (mm) ± S.D	Drug content (%)± S.D	*In vitro* Disintegration Time (min) ± S.D
F1	299.36±0.61	4.15±0.14	0.59±0.14	2.12±0.32	98.89±0.14	5.65±0.49
F2	300.72±0.44	4.29±0.28	0.21±0.14	2.35±0.65	99.16±0.28	3.51±0.88
F3	292.65±0.14	4.33±0.64	0.28±0.14	2.23±0.44	97.52±0.33	5.83±0.28
F4	297.26±0.76	4.18±0.33	0.35±0.49	2.30±0.76	99.37±0.88	4.21±0.49
F5	299.39±0.14	4.23±0.49	0.39±0.54	2.28±0.23	98.65±0.33	3.63±0.61
F6	298.53±0.14	4.25±0.54	0.41±0.88	2.33±0.82	98.75±0.14	4.82±0.28
F7	297.86±0.61	4.26±0.88	0.56±0.54	2.18±0.21	97.92±0.61	4.92±0.14
F8	298.73±0.14	4.28±0.61	0.33±0.61	2.22±0.48	99.43±0.88	5.02±0.61
F9	296.96±0.14	4.17±0.46	0.45±0.33	2.26±.38	98.71±0.33	5.23±0.61

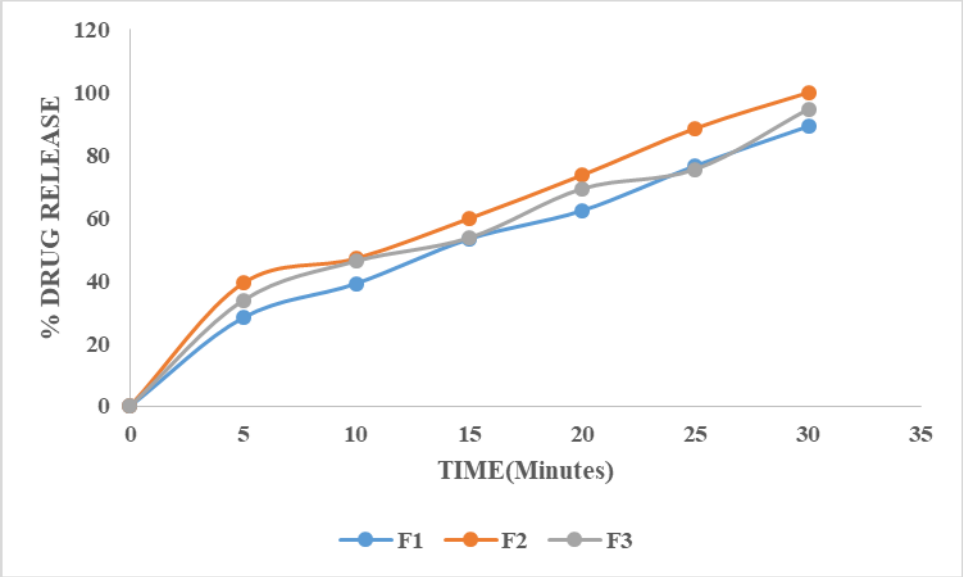

Figure 5: *In vitro* dissolution data for formulations F1 – F3

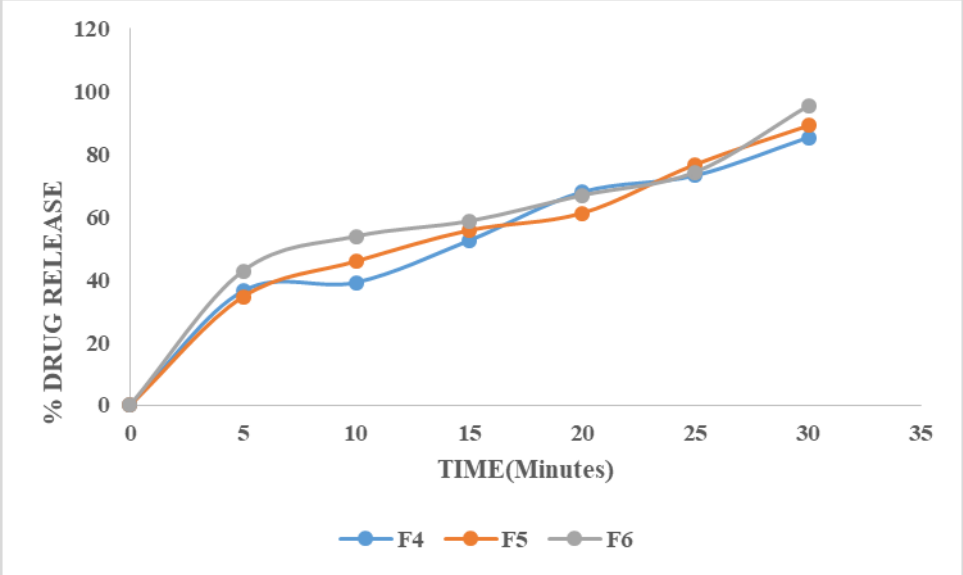

Figure 6: *In vitro* dissolution data for formulations F4–F6

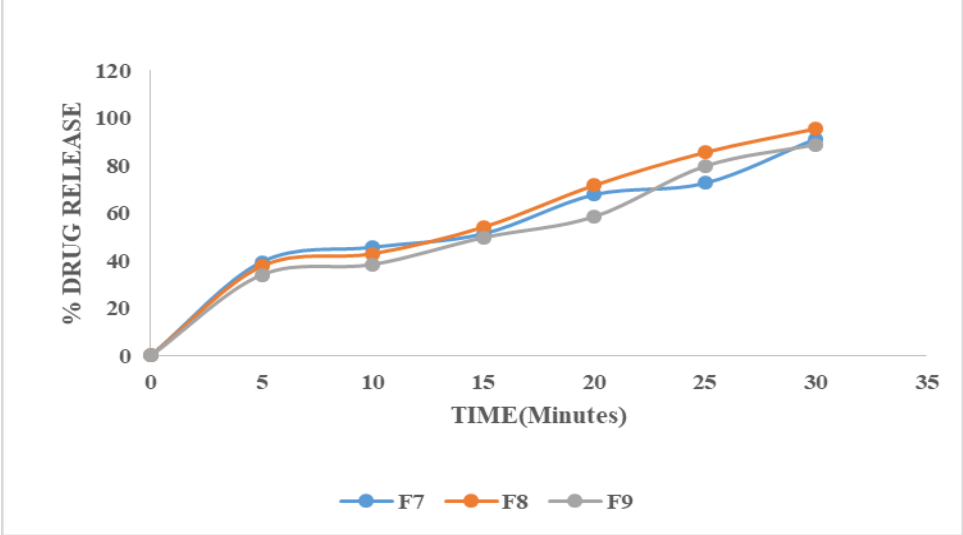

Figure 7: *In vitro* dissolution data for formulations F7- F9

Evaluation of tablets:

Physical evaluation of tablets: The results of the weight variation, hardness, thickness, friability and drug content of the tablets are given in Table 3. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limits. Thus all the physical attributes of the prepared tablets were found to be practically within control limits.

***In vitro* dissolution studies:** *In vitro* drug release studies were conducted in phosphate buffer pH 6.8 and the studies revealed that the release of Ticagrelor from different formulations varies with characteristics and composition of matrix forming polymers as shown in graphs 5 to 7. From various batches finally concluded that F2 formulation was optimized better formulation. It shows good drug release with 99.98% than the other polymers. F2 formulation was considered as optimized formulation.

ASS: The optimized formulation F2 short-term stability were carried out for physical characteristics, friability, hardness, drug content, and *in vitro* drug release. It was found no significant changes.

CONCLUSION

The present study successfully focused on the formulation, characterization, and evaluation of Ticagrelor Oro dispersible tablets (ODTs) aimed at improving patient compliance and ensuring rapid onset of action. Various formulations were prepared using different super disintegrants, and among them, the optimized batch exhibited excellent pre-compression and post-compression parameters, including uniform weight, hardness, friability, disintegration time, and drug content. The *in-vitro* dissolution studies revealed that the optimized formulation showed rapid and complete drug release within a few minutes, meeting the desired criteria for Oro dispersible tablets. FTIR studies confirmed the compatibility of Ticagrelor with the selected excipients, and no significant interaction was observed. Thus, it can be concluded that Ticagrelor ODTs are a promising alternative to conventional dosage forms, particularly for patients with swallowing difficulties or requiring a faster therapeutic effect.

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