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FORMULATION AND EVALUATION OF FAST DISINTEGRATING CLOPIDOGREL TABLET BY DIRECT COMPRESSION METHOD

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ABSTRACT
The primary goal of this research project is to develop Clopidogrel Fast Disintegrating tablets by direct compression method. Clopidogrel, a BCS Class-II antiplatelet medication, is used to prevent heart attacks and hypertension by reducing platelet activation and aggregation. Clopidogrel Fast Disintegrating Tablets were made utilizing the Direct Compression technique, clopidogrel, Sodium Starch glycolate, croscarmellose sodium, polyvinylpyrrolidone (PVP), Mannitol, Magnesium stearate, Talc, Lactose were used for preparation of tablet with varying concentrations of Sodium Starch glycolate and Croscarmellose sodium in different combinations as a Superdisintegrant. Sodium Starch glycolate and Croscarmellose sodium concentrations were chosen as independent variables (X and X, respectively),Formulation F3 can be Considered as an optimized, Nine formulations were created and tested in terms of hardness, Thickness, Friability, wetting time, disintegration time, and in-vitro drug release. Can be successfully formulated while also increasing bioavailability.

KEYWORDS: Clopidogrel, Direct compression Method, Superdisintegrants, Bioavailability, Antiplatelet, etc.

INTRODUCTION
Orally given formulations account for 50–60% of all pharmacological dosage forms available on the market. Because of its simplicity, ease of administration, lack of pain, and patient compliance, oral administration is regarded as the most frequently recognized route.[1] Many pediatric and geriatric patients, however, refuse to take solid preparations because they are afraid of choking or have difficulties swallowing (dysphagia). Furthermore, ingesting oral dosage forms necessitates the consumption of water, which is not always available.[2,3] For these reasons, tablets that dissolve or disintegrate quickly in the mouth have gotten a lot of attention.[4,5] These tablets are also known as Fast dissolving tablets, orally disintegrating tablets (ODTs) or mouth-dissolving pills. When placed on the tongue, fast dissolving tablets instantly disintegrate, releasing the medication, which dissolves or disperses in the saliva.[6] According to FDA guidelines, orally disintegrating tablets are solid oral preparations that disintegrate rapidly in the oral cavity with an in vitro disintegration time of less than 30 seconds [7]. In the production of orally disintegrating pills, superdisintegrants are required. Cross-linked carboxymethyl cellulose (croscarmellose®), sodium starch glycolate (primogel®, explode®), and crospovidone (polyplasdone®) are examples of these materials. When the tablet is placed on the tongue, these superdisintegrants cause it to disintegrate instantly. Some medications' bioavailability may be enhanced by oral absorption of some of the drug, as well as pregastric absorption of saliva containing dispersed drug that goes down into the stomach. Furthermore, when compared to traditional tablets, the amount of medication susceptible to first pass metabolism is reduced.[8] Sanofi found clopidogrel hydrogen sulfate (hereinafter clopidogrel). Sanofi–Synthelabo presently sells it under the PLAVIX® brand name all over the world. Clopidogrel is an antiplatelet drug that reduces platelet aggregation by preventing the binding of adenosine diphosphate (ADP) to its platelet receptor and blocking the following GPIIb/IIIa complex. [9]

Clopidogrel has been shown to have clinical advantages and is used worldwide to prevent atherothrombotic events such as myocardial infarction, stroke, peripheral arterial disease, and acute coronary syndrome.[9] The goal of this study was to use direct compression to make fast disintegrating clopidogrel tablets and to see how the type and concentration of superdisintegrant used affected the physical qualities of the tablets as well as drug dissolution and disintegration. The direct compression method was chosen over wet granulation because the porous nature of direct compression tablets allows for faster disintegration.[17] The direct compression approach was used to make ODT tablets in this study since it is relatively easy and does not require any sophisticated

equipment. Direct compression is the simplest and most cost-effective method of tablet production. ODT is a basic method to drug delivery systems that has proven to be sensible in the pharmaceutical arena due to its convenience, compliance, speedier production, and avoidance of hydrolytic or oxidative reactions during dosage form processing.[18]

As a result, in this study, an attempt is made to synthesize Clopidogrel Fast Dissolving Tablets utilizing Sodium starch glycolate and Croscarmellose sodium. To investigate the effect of formulation factors on release qualities, a conventional statistical tool called design of experiments is used instead of the normal and trial methods. Large-scale production necessitates a simpler formulation with the most cost-effective dose form. In large-scale production, the direct compression method of formulating Fast Dissolving Tablets is the most appropriate.[18]

DRUG PROFILE

Clopidogrel [Methyl (S)— (2chlorophenyl)6,7-dihydro thieno[3,2-c]pyridine-5(4H)acetate sulfate (1:1)] is a weak base. It is essentially insoluble in water at neutral pH, readily soluble in aqueous buffer at pH 1, and soluble in methanol, methylene chloride, and ethyl ether [10]. Clopidogrel active metabolite binds irreversibly to the P2Y12 class of ADP receptors on platelets, inhibiting platelet activation and aggregation. Platelet aggregation is inhibited by preventing the activation of the glycoprotein IIb/IIIa pathway. After a single dose of oral Clopidogrel, platelet inhibition can be seen 2 hours later, however the initiation of action is gradual (so that a loading-dose of 300-mg is followed by 20 mg once daily). The active metabolite operates by creating a disulfide bond with the platelet ADP receptor and has a half-life of roughly six hours.[11,12] Clopidogrel is classified as a class II agent (poorly water soluble and extremely permeable) by the biopharmaceutics classification system (BCS), with very low solubility (0.0099 mg/ml) and bioavailability.[10] Clopidogrel has a limited oral bioavailability (less than 50%) due to its poor water solubility. As a result, the medication is chosen for the Direct Compression method of producing Fast Dissolving Tablets.[18]

MATERIAL AND METHODS

Materials used in this research were obtained from different sources. Clopidogrel was obtained from Aarti Drug Limited, Thane. Polyvinylpyrrolidone K30 was purchased from Balaji drug. Croscarmellose sodium, Sodium starch glycolate, magnesium stearate, Mannitol, Talc and Lactose was kindly supplied by Research-Lab fine chemical industries, Mumbai.

METHODOLOGY

Differential Scanning Calorimetry (DSC)

DSC was used to investigate the thermal behavior of Clopidogrel alone and in physical combinations with tablet excipients. Samples (3-5 mg) were weighed and hermetically sealed in aluminum pans, then heated at a continuous rate of 10 °C/min between 25 and 250°C. Differential scanning calorimetry was used to produce sample thermograms (DSC-60, Shimadzu, Japan). A TA 50I PC system with Shimadzu software packages was used to record thermal analysis data. The DSC temperature and enthalpy scales were calibrated using an indium standard. The purging gas was N2 at a rate of 30 mL/min.[17]

Fourier transform infrared spectroscopy (FTIR)

A Perkin Elmer FTIR spectrophotometer was used to record the FTIR spectra of TNX, KL, and their binary complexes (Spectrum BX). Before scanning from 4000 to 600 cm-1, samples were combined with spectroscopic grade potassium bromide and crushed into discs using a hydraulic press. Perkin Elmer software was used to analyze the data (Spectrum V5.3.1).

UV Visible Spectroscopy

Determination of λ max in methanol.

The UV spectrum of clopidogrel was obtained by using UV – visible spectrometer (UV 3000). Accurately weighing 10 mg of the drug was added to 100 ml of volumetric flask. Volume was make up to 100 ml with methanol (100microgram/ml) .This solution was used to stock solution. From the stock solution 1 ml of aliquots was withdrawn and volume was made up to 10 ml using water to obtain the concentration of 10 microgram/ml. The resultant was scanned from 200 to 400 nm and the spectrum was recorded to obtain the value of maximum wavelength in respective solvent.

Preparation of calibration curve of clopidogrel in methanol.

Stock solution of drug 100ug/ml was used to prepare in different dilutions in the range of 5 to 30ug/ml. The absorbance of the resulting solution was measured at 240 nm using respective solvent by UV- Visible spectroscopy.

Preparation of Clopidogrel Fast Disintegrating Tablets By Direct Compression

Direct compression was used to make Clopidogrel Tablets. Table 2 lists the ingredients for each tablet. Sieve #40 was used to sieving the drug, diluents, and superdisintegrants. All of the above materials were thoroughly combined (in a poly-bag), weight of mannitol was mixed with initial mixture. In a poly-bag, talc and magnesium stearate were passed through mesh #80 and combined and blended with the initial mixture. After mixing, the powder blend was compressed into tablets weighing 300 mg using 8 mm circular punches on an 8 station rotary punch tableting machine (Cemach Machineries, Station, D tooling), with the same hardness used for the needed number of tablets. Official and unauthorized testing were used to assess compressed tablets. The tablets were stored in light-resistant and moisture-proof containers.

Table 1: Formulation for the preparation of Fast disintegrating clopidogrel tablet.

Sr. No.	Excipient (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Clopidogrel	20	20	20	20	20	20	20	20	20
2	Croscarmellose Sodium	22	22	22	21	21	21	20	20	20
3	Sodium starch glycolate	20	21	22	20	21	22	20	21	22
4	Polyvinylpyrrolidone k30	30	30	30	30	30	30	30	30	30
5	Mannitol	36	36	36	36	36	36	36	36	36
6	Magnesium stearate	5	5	5	5	5	5	5	5	5
7	Talc	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5
8	Lactose	161.5	160.5	159.5	162.5	161.5	160.5	163.5	162.5	161.5

Pre-compression evaluation

The Bulk density, Tapped density, Angle of repose, Carr's index, and Hausner's ratio were used to analyze the flow properties of powder mixtures of various compositions.

EVALUATION OF CLOPIDOGREL FAST DISINTEGRATING TABLETS

Weight variation

Twenty tablets from each batch were weighed separately (analytical balance, wensar, PEG-300), and the average weight ±SD was calculated.

Hardness

A Monsanto hardness tester was used to assess the tablet crushing strength (hardness) for samples of 10 compressed tablets for each tablet formula. A hardness of about 3-5 kg/cm² is considered adequate for mechanical stability. The average values of weight ±SD were recorded [13].

Friability

The tablet's friability was determined using a Roche friabilator (veego, VMP-D). 20 tablets were taken and weighed, as well as the original weight (W0), and allowed to rotate 25 rpm for 4 min (100 revolutions in a Roche Friabilator), and weighed (W) again. The drop in weight was used to calculate percentage friability, as shown in the equation below. There should be no more than 1% weight loss [13].

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

Clopidogrel content

A 300 mg orally disintegrating clopidogrel tablet, equivalent to 20 mg clopidogrel, was weighed properly, finely powdered, and put into a volumetric flask. After adding 60 mL of 0.1 N HCl, the flask was sonicated for 10 minutes, mechanically shaken for 30 minutes, and the volume increased to 100 mL with the same solvent(0.1 N HCl), followed by sonication and filtering. At 240 nm, the drug concentration was measured spectrophotometrically.[15] The test was performed ten times for each tablet, and the average drug content SD was displayed.

The tablets contained not less than 85% or not more than 115 %(100±15%) [13].

Thickness

Vernier calipers were used to measure the thickness of all tablet formulations by putting the tablet between two arms of the calipers.[13]

Wetting Time

A piece of tissue paper folded twice was placed in a tiny petri dish (internal diameter= 6.5 cm) holding 5 ml of distilled water to evaluate tablet wetting time. A tablet was placed on the paper, and the time it took for the tablet to completely wet was recorded in seconds.[15-16]

In vitro Disintegration test

The disintegration periods of produced tablets were tested in vitro using a USP disintegration device at 37 °C±2 °C and phosphate buffer (pH 6.8) as the disintegration medium. In each of the basket's six tubes, one tablet was placed (Electro lab, India, USP-TDT-081). The mean ±SD of six tablets was recorded using the time required for complete tablet breakdown.[10]

In vitro Dissolution study

The Clopidogrel Fast Disintegrating tablets in-vitro dissolution study was performed in a USP type-II dissolution test apparatus Paddle type (Electro lab India, USP-TDT-081). With 900 ml of Phosphate buffer pH 6.8 as the dissolution medium at 50 rpm and 37±0.5°C. 5 ml of the samples were withdrawn at specified time intervals using a syringe fitted with a pre-filter, and the volume withdrawn at each interval was replaced with the same amount of fresh dissolving medium. After appropriate dilutions, the samples were evaluated for the presence of the drug release by measuring the absorbance at 240 nm with a UV Visible spectrophotometer (Equiptronics, UV-3000*). The measurements were made in triplicate (n=3) [10].

Table 2: In vitro drug release studies detail.

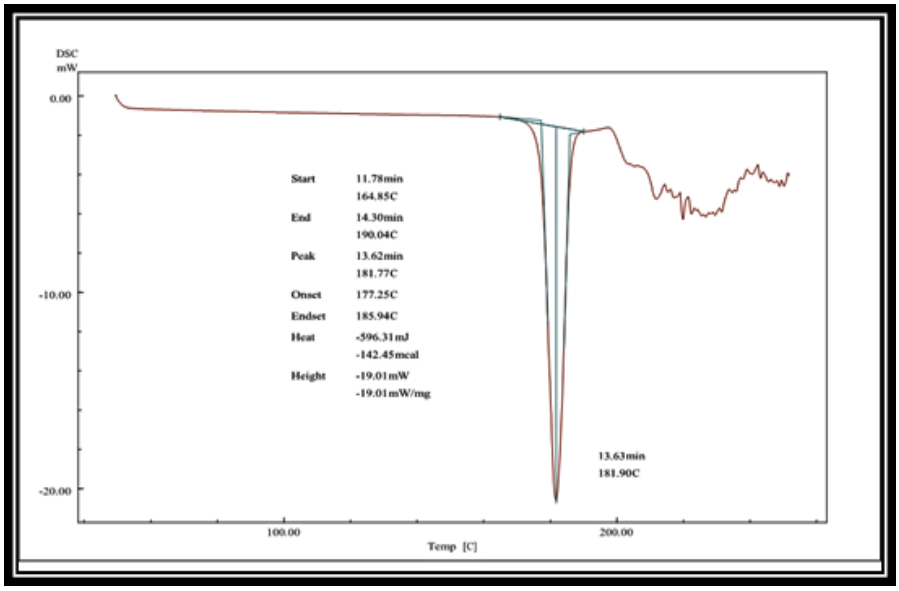
Apparatus used	USP Type 2 dissolution test apparatus
Dissolution medium	Phosphate buffer pH 6.8
Dissolution medium volume	900 ml
Temperature	37±0.5°c
Speed of basket	50 rpm

Sampling interval	5 min
Sample withdraw	5 ml
Absorbance measured	240 nm

RESULTS AND DISCUSSION

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) was used to evaluate the melting point, crystallinity, decomposition and drug-excipient interaction by studying the thermal behavior of the preparation. The drug clopidogrel was confirmed by DSC by keeping the heating rate of 1°C/min. The thermogram of clopidogrel exhibited a sharp endothermic peak with onset temp 177.25°C and peak temp 181.90°C which corresponds to its melting point as shown in Figure 1.

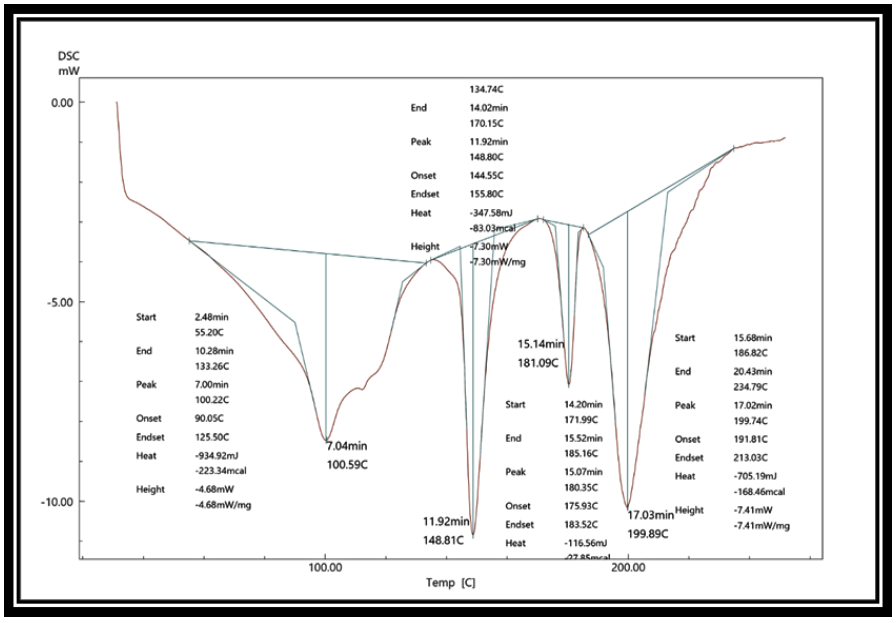


"Fig 1": DSC curve of clopidogrel.

Drug-Excipient interaction study

Differential Scanning Calorimetry (DSC)

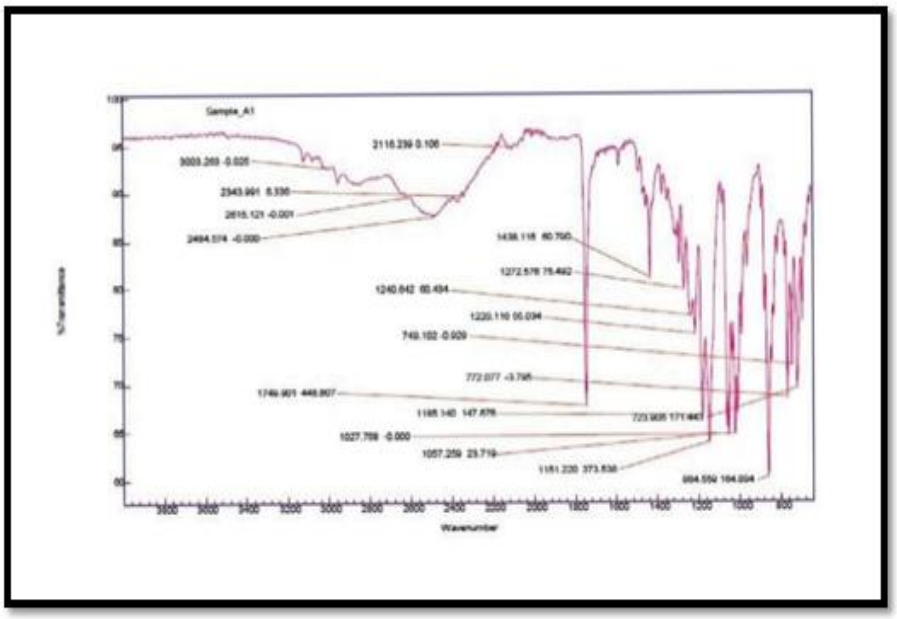
Diffract gram of drug was already shown in figure 1 and drug – excipient were reported in figure 2 respectively. DSC thermogram of drug shown the typical clopidogrel melting endothermic peak, at 181.90°C figure 1 And DSC thermogram of drug excipient mixture indicate broadening of base peak and sight shifting of melting point to 181.09°C figure 2. Thus, it indicates the absence of chemical interaction between the drug and excipient mixture in the ratio 1:1.



"Fig" 2: DSC curve of Clopidogrel + Excipient physical mixture.

Fourier transform infrared spectroscopy (FTIR)

An infrared spectrum of clopidogrel was taken. The scanning range was 400-4000 cm^{-1} and the resolution was obtained $1cm^{-1}$.



"Fig 3": FTIR of pure clopidogrel.

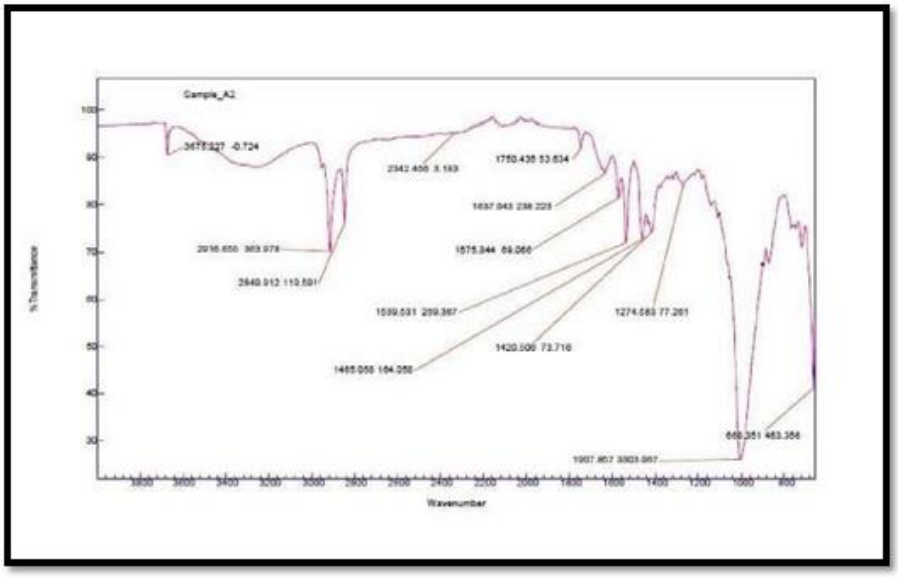
Table 3: Range of functional group present in FTIR spectrum clopidogrel.

Sr. No.	Frequency cm^{-1}	Functional group
1	3003.26	(C-H) Aromatic
2	1749.9	C=O Stretching
3	1185.14	C-O Stretching

Drug- Excipient Interaction Study

FTIR

An IR spectrum of clopidogrel was already shown in Figure 3 and an IR spectra of drug-excipient physical mixture was reported in Figure 4. The FT-IR studies were conducted to ensure interactions among the clopidogrel and excipients used in the formulation. The same peaks were also observed in the formulation indicating the stable nature of the drug. All the physical mixtures of clopidogrel and individual excipients show insignificant changes in actual peaks. The same peaks with little difference were observed in the formulation indicating the stable nature of the drug No change in the peak of the drug indicates that there was no drug-excipient interaction between drug and excipients which were used in formulation of Fast disintegrating tablet.



"Fig 4": FTIR spectrum of clopidogrel + Excipient physical mixture

Ultra violet spectroscopy

a) Determination of λ max in methanol

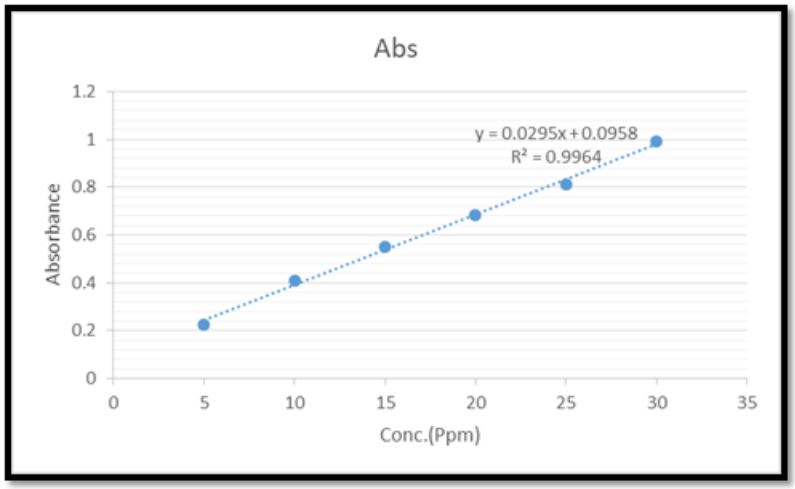
The UV spectrum of Clopidogrel solution 10µg/ml scanned between 400-200 nm using a UV spectrophotometer. Clopidogrel showed maximum absorption wavelength at 240 nm in Methanol.

b) Calibration curve of clopidogrel in methanol

The calibration curve of clopidogrel was performed in methanol. The calibration curve was found to be linear in the concentration range of 5-30 µg/ml having coefficient of regression value R^2= 0.9964 slope y= 0.0295+ 0.0958. The calibration curve of clopidogrel in methanol is shown in figure 5.

Table 4: Concentration and absorbance values for Clopidogrel in methanol

Sr.No.	Concentration (µg /ml)	Absorbance (λ max240nm)
1	5	0.227
2	10	0.407
3	15	0.552
4	20	0.685
5	25	0.81
6	30	0.991



"Fig 5": calibration curve of Clopidogrel in methanol

PRE-COMPRESSION EVALUATION

The micromeritic properties of several medication and tablet excipient blends were examined, as indicated in Table 5. For all powder mixes examined, the computed bulk density was between 0.38-0.43 g/cc, while the tapped density was between 0.42±0.005-0.49±0.006 gm/cc. The angles of repose and Carr's indices were found to be 30±0.40-33.5±0.66 percent and 9.56-12.26 percent, respectively. The Hausner's ratio was discovered to be lower than 1.15. Because all of the formulations had the needed mix qualities for direct compression, tablets were made using this method.

Table 5: pre-compression parameters for the formulations.

Formulation code	Angle of repose	Bulk density(g/cc)	Tapped density(g/cc)	Carr's index (%)	Hausner's ratio
F1	31.4±0.48	0.43±0.005	0.49±0.006	12.26	1.13
F2	32.3±0.58	0.41±0.004	0.45±0.004	10	1.1
F3	33±0.68	0.40±0.005	0.45±0.005	11.46	1.12
F4	33.5±0.66	0.40±0.004	0.44±0.004	11.30	1.12
F5	32±0.61	0.4±0.003	0.44±0.004	11.30	1.12
F6	32.5±0.60	0.38±0.003	0.42±0.005	9.56	1.03
F7	32.6±0.58	0.38±0.004	0.44±0.006	12.4	1.13
F8	30.4±0.35	0.41±0.003	0.45±0.003	10	1.12
F9	30±0.40	0.40±0.004	0.45±0.004	11.47	1.12

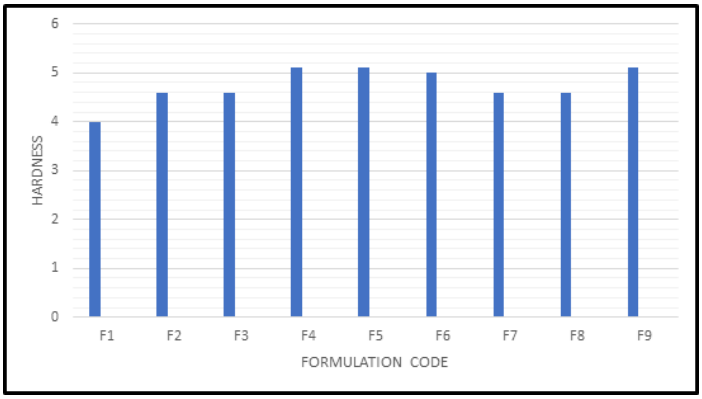
TABLET EVALUATION

According to official methods, all of the produced tablets were analyzed for different post compression parameters, including drug content, mean hardness, friability, mean thickness, and weight variation, and the results are shown in Table 5. The hardness of the tablets ranged from 3.1±0.21 to 3.9±0.47 Kg/cm2. In the friability test, the weight loss was less than 0.86 percent. The drug content of the manufactured tablets was merely within acceptable limits. Wetting time of the tablet ranged between 20.21±1.2 to 24.33±1.9 seconds. The disintegration time of tablets was between 10±0.58 to 15±1.53 seconds. All post-compression parameters' results were tabulated or displayed in table 6. Phosphate

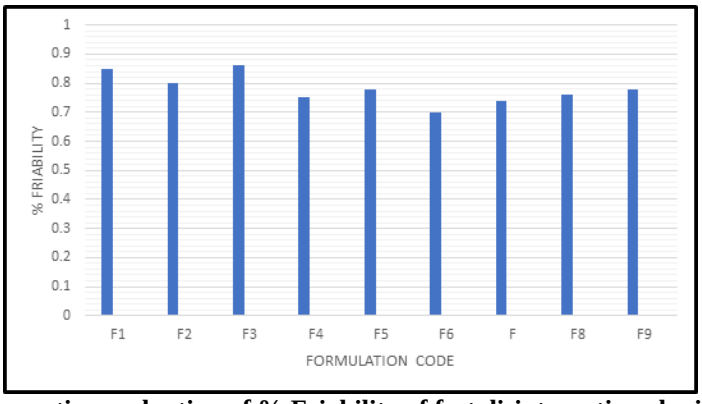
buffer pH 6.8 was used as a dissolution media in in-vitro dissolution testing for manufactured tablets at 50 rpm at 37±0.5°C. Figures 9 depict wetting time charts and disintegration charts comparatively.

Table 6: post compression parameter for fast disintegrating clopidogrel tablet.

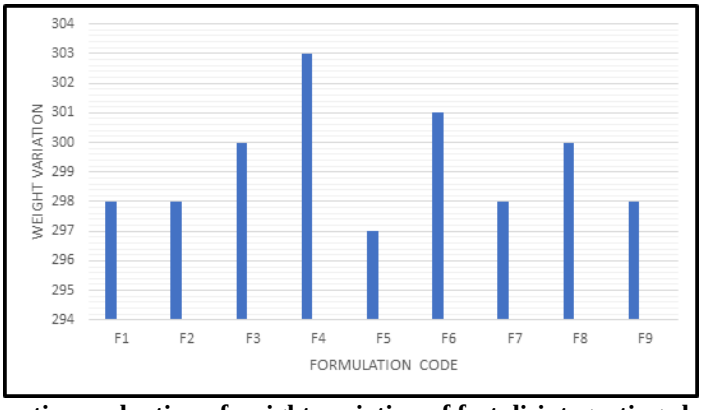
Formulation code	Weight (mg)	Thickness (mm)	Hardness (Kg/cm²)	Disintegration time (sec.)	CL content (%)+/-SD	Wetting time (sec)	Friability (%)
F1	298±0.38	6.2±0.2	4.0±0.50	10±5.0	101.30±0.51	20.59±1.4	0.85±.0.10
F2	298±0.54	6.1±0.2	4.6±0.26	11±0.87	98.50±0.42	22.91±1.5	0.80±0.14
F3	300±0.72	6.2±0.2	4.6±0.34	10±0.58	100.09±0.50	20.21±1.2	0.86±0.14
F4	303±0.63	6.3±0.1	5.1±0.22	12±0.60	100.10±0.66	24.12±1.3	0.75±0.24
F5	297±0.61	6.2±0.2	5.1±0.19	14±1.0	101.00±0.72	22.12±1.2	0.78±0.15
F6	301±0.37	6.1±0.3	5.1±0.21	13±1.0	99.77±0.53	21.23±1.5	0.70±0.31
F7	298±0.49	6.2±0.1	4.6±0.23	14±1.0	101.30±0.60	20.32±1.2	0.74±0.21
F8	300±0.73	6.3±0.1	4.6±0.32	15±1.53	101.10±0.90	24.33±1.9	0.76±0.20
F9	298±0.68	6.2±0.2	5.1±0.47	12±0.58	101.20±0.64	22.12±1.4	0.78±0.21



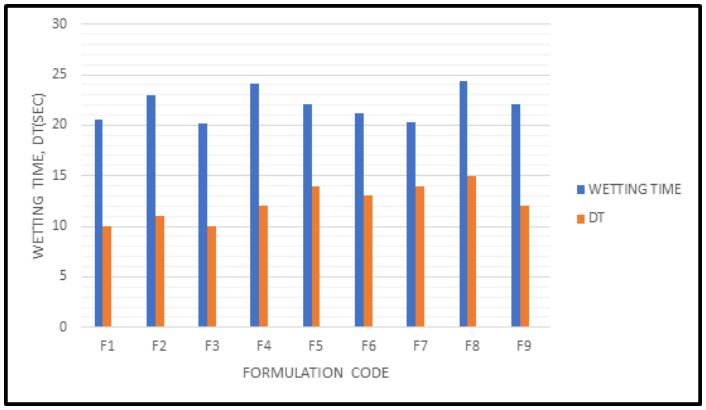
"Fig 6": Comparative evaluation of hardness of fast disintegrating clopidogrel tablet.



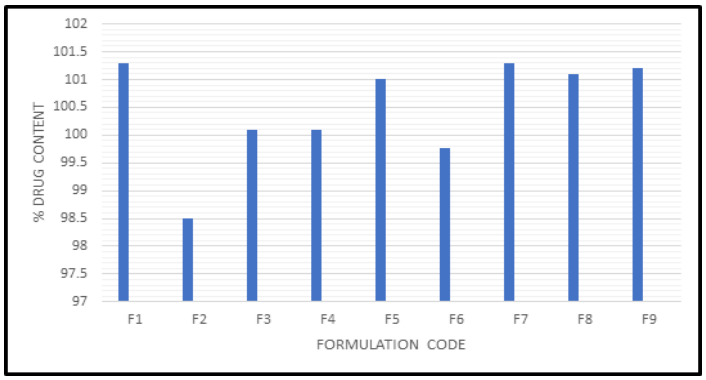
"Fig 7": Comparative evaluation of % Friability of fast disintegrating clopidogrel tablet.



"Fig 8": Comparative evaluation of weight variation of fast disintegrating clopidogrel tablet.



"Fig 9": Comparative evaluation of wetting time and disintegration time of fast disintegrating Clopidogrel tablets.



"Fig 10": Comparative evaluation of % drug content of fast disintegrating Clopidogrel tablet.

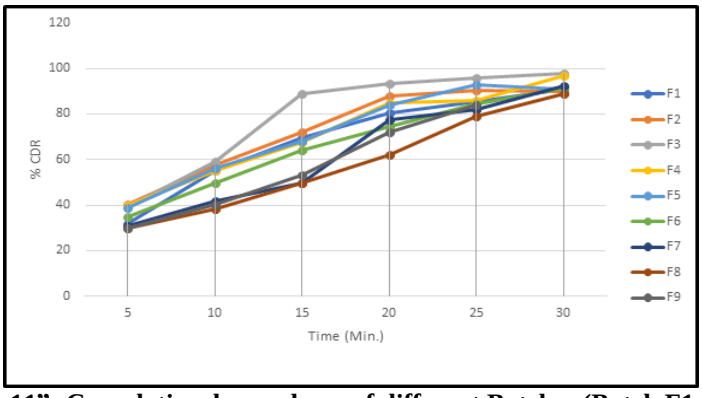
IN-VITRO DISSOLUTION STUDY

In-vitro drug release study of FDT of Clopidogrel

Percent drug release data expressed in Table 7 and Figure 11 Indicate In-Vitro release study was shown 97.64% release of Clopidogrel through F3 formulation. Formulation F3 showed less disintegration time and percent cumulative drug release 97.64% so it was declared as an optimized formulation and was subjected for further evaluation and stability studies.

Table 7: Dissolution data of FDT of Clopidogrel % CDR for Formulation Batches.

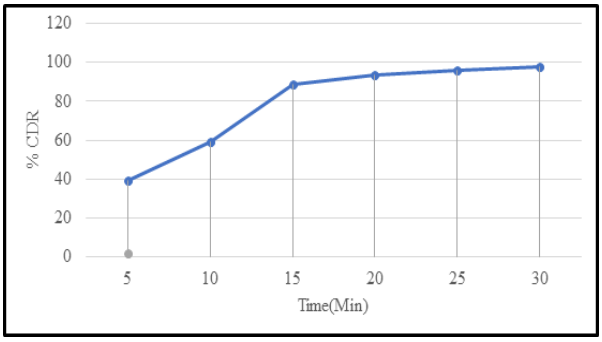
Time Min	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	31.75±1.16	40.46±0.9	39.36±1.63	39.95±1.63	38.95±0.65	34.84±0.83	30.96±0.25	29.71±0.32	29.99±1.03
10	55±0.94	57.87±1.24	59.06±0.85	55.05±0.49	55.91±0.49	49.76±0.76	41.70±0.34	38.54±0.93	40.51±1.19
15	69.66±0.45	71.80±2.1	88.82±0.41	67.64±0.65	68.26±1.89	64.10±0.67	49.58±1.02	49.58±0.07	53.23±0.10
20	80.68±1.58	87.89±0.13	93.44±0.21	85.06±0.29	84.09±1.00	74.58±0.12	77.27±0.97	62.21±0.54	71.85±1.98
25	85.41±0.61	90.39±0.79	95.92±0.51	85.64±0.75	92.66±0.33	84.36±0.51	81.84±0.14	78.76±0.02	83.75±0.27
30	90.95±0.95	90.06±1.4	97.64±1.02	96.84±1.31	90.80±0.03	91.34±1.01	92.16±0.92	88.63±1.66	89.62±0.07



"Fig 11": Cumulative drug release of different Batches (Batch F1-F9).

Table 8: Results of in vitro dissolution study of optimized Batch (F3)

Sr.No.	Time (min)	% CDR
1	5	39.36±1.63
2	10	59.06±0.41
3	15	88.82±0.41
4	20	93.44±0.21
5	25	95.92±0.51
6	30	97.64±1.02



"Fig 12": Graphical representation of Dissolution profile of optimized batch (F3).

CONCLUSION

In conclusion, Clopidogrel fast disintegrating tablet mechanical integrity, content uniformity, and acceptable palatability were created to allow convenient administration to patients of various ages. Direct compression was used to make the Fast disintegrating tablets. All of the tablets had a hardness of 4.0-5.1 kg/cm² and a friability of less than 1%. All formulations were within official limits in terms of weight variation and drug content. Fast disintegrating tablets disintegrated quickly in vitro and released more than 97% of the medication. It was clear from the results that as the concentration of Superdisintegrant increased, the drug's release rate became RAPID (Improved Solubility), and that both of these Superdisintegrants can be used in combination because they do not interact with the drug, making them more useful in achieving the desired fast disintegrating of the dosage form for rapid action and improved bioavailability.

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