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FORMULATION AND EVALUATION OF CLOPIDOGREL ORODISPERSIBLE TABLETS

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ABSTRACT

In the present quality assurance research work pharmaceutical manufacturing has largely grown in recent years. This and many other factors have led to the ability of manipulating pharmaceutical dosage forms and routes of administration. One example of such unique dosage forms is Orodispersible tablets ODTs, which are solid dosage forms intended to be dissolved in mouth in a relatively short time, ranging from a few seconds to up to 3minutes. In this research, Clopidogrel bisulfate was chosen to be the active pharmaceutical ingredient (API) in Orodispersible tablets ODTs formulations. Clopidogrel bisulfate is thieno pyridine class antiplatelet agent used to inhibit blood clots in coronary artery disease, peripheral vascular disease and cerebrovascular disease, its solubility is very low and has very low bioavailability. A total of nine formulations of Orodispersible tablets ODTs of Clopidogrel bisulfate with Superdisintegrants like; croscarmellose sodium, and/or crospovidone in different ratios were prepared with a view to increase its effect by decreasing the time required for the drug to be released. The ingredients of the formulation were tested for compatibility study; all ingredients were compatible. Clopidogrel bisulfate and the excipients were mixed together in different ratio in nine formulation and submitted to pre-formulation tests. The powders were then compressed into tablets by direct compression method. The prepared batches of tablets were evaluated for

thickness, wight variation, hardness, friability, disintegration time, wetting time, in-vitro dispersion time and in vitro dissolution studies which tested in comparing with innovator product (PLAVIX®). Clopidogrel bisulfate ODTs showed better results than PLAVIX® depending on dissolution test. Among the nine formulations the drug release of F2 and F3 formulations were found to be 92.34% and 91.8% at 5 minutes in 0.1NHCl medium while the drug release of F9 formulation were found to be 69.7% at 5minutes in phosphate buffer. The formulations F2 and F9 were the best formulations as it showed a drug release percentage 92.34% and 69.7% at 5minutes and the assay of Clopidogrel was within the acceptable limit.

KEYWORDS: Clopidogrel bisulfate, Orodispersible tablets, Superdisintegrants, Antiplatelet therapy.

INTRODUCTION

Researchers throughout the world are focusing intensively on the methods for the development of new drug delivery systems to enhance patient's compliance. Orodispersible tablets become an emerging trend in the pharmaceutical industry. Fast dissolving tablets are ideal for all types of people, including for people who have swallowing difficulties, pediatric, geriatric, and bedridden patients. It is also for active patients who are busy, travelling and may not have access to water. Fast dissolving tablets are also known as Orodispersible tablets, mouth-dissolving tablets, orally disintegrating tablets, melt-in mouth tablets, rapid melts, porous tablets, quick dissolving, etc. Many drugs have the potentials to be made into Orodispersible tablets. They vary from analgesics to neuroleptics and antipsychotic drugs. However, only a small percentage of them are researched on and some have been manufactured and marketed. Fast-dissolving drug-delivery systems were initially developed in the late 1970s as an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experiences difficulties in swallowing traditional oral solid-dosage forms.[1-3]

The speed of solubility of drug affects the rate of absorption of the drug. The faster the drug dissolve into solution, quicker the absorption and onset of clinical effect. They should readily dissolve or disintegrate in the saliva generally within less than 60 seconds. Some drugs are absorbed from the mouth, pharynx, and esophagus as the saliva passes down into the stomach The significance of Orodispersible dosage forms is progressively being recognized in both, industry, and academics in the oral cavity. The medication can then be absorbed partially or entirely into the systemic circulation from blood vessels in the sublingual mucosa, or it can be swallowed as a solution to be absorbed from the gastrointestinal tract The sublingual route

usually produces a faster onset of action than orally ingested tablets and the portion absorbed through the sublingual blood vessels by passes the hepatic first-pass metabolic processes. [4-6] Various processes employed in formulating ODTs include freeze-drying or lyophilization, cotton candy process, molding, spray drying, mass extrusion, and compaction (wet granulation, dry granulation, direct compression).[5-10]

Advantages of ODTs

Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability. Administration to the patients who cannot swallow, such as the elderly, stroke victims, bedridden patients, patients affected by renal failure & patients who refuse to swallow such as pediatric, geriatric and psychiatric patients, rapid drug therapy intervention, convenient for administration and patient compliant for disabled, bedridden patients and for travelers and busy people, who do not always have access to water, good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patients, the risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety, rapid dissolution of drug and absorption which may produce rapid, onset of action, some drugs are absorbed from the month pharynx and esophagus as the saliva passes down into the stomach, which achieve increased bioavailability/rapid absorption, ability to provide advantages of liquid medication in the form of solid preparation and pre gastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects.[1-20]

Ideal Properties of ODTs

The performance of ODTs depends on the technology used during their manufacture. The necessary property of such tablets is the ability to disintegrate rapidly and disperse or dissolve in saliva, thereby obviating the need for water. various technologies have been developed that enable ODTs to perform this unique function. An ideal ODTs should meet the following criteria : Does not require water for oral administration yet disintegrates and dissolves in oral cavity within a few seconds, has sufficient strength to withstand the rigors of the manufacturing process and post-manufacturing handling, allow high drug loading, has a pleasant mouth feel, is insensitive to environmental conditions such as humidity and temperature, is adaptable and amenable to existing processing and packaging machineries, is

cost-effective, fast absorption or wetting of water into the tablets and disintegration of associated particles into individual components for fast dissolution, the drug properties should not significantly affect the tablet property.[10-25]

Challenges to Develop Orodispersible Tablets

Mechanical strength and disintegration time: ODTs are formulated to obtain disintegration time usually less than a minute. While doing so, maintaining a good mechanical strength is a prime challenge. Many ODTs are fragile and there are many chances that such fragile tablet will break during packaging, transport or handling by the patients. Tablets based on technologies like Zydis need special type of packaging. It is very natural that increasing the mechanical strength will delay the disintegration time. So, a good compromise between these two parameters is always essential. Taste masking: Many drugs are bitter in taste. A tablet of bitter drug dissolving/ disintegration in mouth will seriously affect patient compliance and acceptance for the dosage form. So effective taste masking of the bitter drugs must be done so that the taste of the drug is not felt in the oral cavity. Mouth feel: The ODTs should not disintegrate into larger particles in the oral cavity. The particles generated after disintegration of the ODTs should be as small as possible. ODTs should leave minimal or no residue in mouth after oral administration. Moreover, addition of flavors and cooling agents like menthol improve the mouth feel.[5-16]

Sensitivity to environmental conditions: ODTs generally should exhibit low sensitivity to environment conditions such as humidity and temperature as most of the materials used in an ODTs are meant to dissolve in minimum quantity of water. Amount of drug: For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. Size of tablet: It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve. Cost: The technology used for an ODTs should be acceptable in terms of cost of the final product. Methods like Zydis and Orasolv that require special technologies and specific packaging increase the cost to a remarkable extent.[10-27]

The need for development of ODTs for non-invasive delivery systems persists due to patients, poor acceptance of, and compliance with existing delivery regimes, limited market size for drug and drug uses, coupled with high cost of disease management.

Clopidogrel[6-9]

Clopidogrel, a weak base known chemically as Methyl (S)- α- (2chlorophenyl)- 6,7-dihydrothieno[3,2-c] pyridine-5(4H)- acetate sulfate (1:1)]. It is practically insoluble in water at neutral pH, freely soluble in aqueous buffer at pH 1, and in methanol, sparingly soluble in methylene chloride, and practically insoluble in ethyl ether.

Pharmacokinetic data: Bioavailability >50% Protein binding; 94–98% Metabolism: Hepatic Biological half-life: 7–8 hours (inactive metabolite) Excretion: 50% renal and 46% biliary. Absorption and distribution Clopidogrel is rapidly absorbed after oral administration of repeated doses of 75-milligram Clopidogrel (base), with peak plasma levels (about 3 mg/l) of the main circulating metabolite occurring around one hour after dosing. The pharmacokinetics of the main circulating metabolite are linear (plasma concentrations increased in proportion to dose) in the dose range of 50 to 150 mg of Clopidogrel. Absorption is at least 50% based on urinary excretion of Clopidogrel related metabolites. Clopidogrel and the main circulating metabolite bind reversibly in vitro to human plasma proteins (98% and 94%, respectively). The binding is not saturable in vitro up to a concentration of 110 μg/ml. Metabolism and elimination: In vitro and in vivo, Clopidogrel undergoes rapid hydrolysis into its carboxylic acid derivative. In plasma and urine, the glucuronide of the carboxylic acid derivative is also observed. The active metabolite has an elimination half-life of about 0.5 to 1.0 h, and acts by forming a disulfide bridge with the platelet ADP receptor. Patients with a variant allele of CYP2C19 are 1.5 to 3.5 times more likely to die or have complications than patients with the high-functioning allele. Following an oral dose of 14C-labeled Clopidogrel in humans, about 50% was excreted in the urine and 46% in the feces in the five days after dosing.

Clopidogrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y12 class of ADP receptors on platelets. The blockade of inhibits platelet aggregation by blocking activation of the glycoprotein IIb/IIIa pathway. Platelet inhibition can be demonstrated 2 h after a single dose of oral Clopidogrel, but the onset of action is slow (so that a loading-dose of 300mg is followed by 75mg once daily). According to the biopharmaceutics classification system (BCS), Clopidogrel is categorized as a class II agent (poorly water soluble and highly permeable) its solubility is very low and has very low bioavailability. Oral bioavailability of clopidogrel is very low, due to poor water solubility.

In the present study, it was proposed to formulate Orodispersible tablets of Clopidogrel by using direct compression technique method, with the aim of reaching high serum concentration of the drug in a short time period. In this study, effort has been made to formulations the Orodispersible tablets using superdisintegrants like sodium starch glycolate and croscarmellose sodium and crospovidone.

MATERIAL AND METHODS

As shown in Tables 1 and 2.

Table 1: List of Materials Used.

NO	Materials
1	Clopidogrel Bisulfate
2	Avicel PH101
3	Crospovidone
4	Croscarmellose Sodium
5	Magnesium Stearate
6	Talc
7	Sodium Starch Glycolate
8	Lactose
9	Saccharin Sodium
10	Mannitol
11	HCL
12	Methanol
13	Monobasic Potassium Phosphate (KH2PO4)
14	Sodium Hydroxide (NaOH)
15	Distilled water
16	Poly Ethylene Glycol
17	CaCO3
18	Poly Vinyl Pyrrolidone (PVP K30)
19	All materials were gift from (Shaphaco Pharmaceutical Industry Company-Yemen).
20	PLAVIX®75mg tablets (Yemeni Pharmacies Market)

Table 2: List of Equipment's Used.

NO.	Equipment's
1	Balance (Sartorius).
2	Oven (Incubator) by STUART scientific.
3	PH Meter (HANNA)
4	Hardness Tester. (Rimek - India)
5	Disintegration Tester. (Rimek – India)
6	Fourier Transform Infrared Spectrometer (FT/IR-4200) made by JASCO
7	UV/VIS –Spectrophotometer(V-530). made by JASCO

8	Melting Point Tester. (automatic melting point) SMP40
9	Tablet Machine (CIP machineries PVT.LTD). Table machine (Rimek)
10	Friability Tester (FRIABILATOR USP) made by Rimek India
11	Digital Dissolution Tester. (JASCO DT-810)
12	Digital Over Head Stirrer

UV Scanning of Clopidogrel in 0.1 N HCl and Phosphate Buffer at pH 6.8

UV scanning of Clopidogrel in 0.1 N HCl and phosphate buffer at (pH 6.8): The absorption spectra of Clopidogrel in 0.1 N HCl and phosphate buffer at pH 6.8 were studied. A preliminary scanning of Clopidogrel in 0.1N HCl to determine the ʎ max by screening a 2.5µg/ml solution of Clopidogrel in 0.1N HCl and phosphate buffer screening 5µg/ml these between 400-200nm.

Preparation of Standard Solutions

Preparation of solvent in calibration curve; in 0.1N HCl - 8.8ml of 35%HCl and diluted by distill water to 1000ml. In phosphate buffer (pH 6.8) - take 50ml of 0.2M of KH2PO4 and add 22.4 ml of 0.2 M NaOH and dilute with water to 200ml to prepare it in pH 6.8.

Calibration: in 0.1N HCl 1mg of Clopidogrel bisulfate was weighed accurately and dissolved in small amount of 0.1N HCl and volume was made up to 100 ml (500 µg/ml) using the same, which is called as stock-I solution, further dilution was carried out in 0.1N HCl. From this stock-I solution serial dilutions were made to obtain solutions of the drug concentration ranging from 2.5, 5, 10, 15 and 20 µg/ml. The absorbance of these solutions was measured at 217nm against a blank 0.1N HCl. The calibration curve was plotted between concentration and absorbance. In phosphate buffer pH 6.8; 1mg of Clopidogrel bisulfate was weighed accurately and dissolved in small amount of phosphate buffer pH 6.8 and volume was made up to 100 ml (500 µg/ml) using the same, which is called as stock-I solution, further dilution was carried out in phosphate buffer pH 6.8. From this stock-I solution serial dilutions were made to obtain solutions of the drug concentration ranging from 5, 10, 15, 20, 25 and 30 µg/ml. The absorbance of these solutions was measured at 220nm against a blank phosphate buffer pH 6.8. The calibration curve was plotted between concentration and absorbance.

Solubility Studies

The solubility of the drug sample was carried out in different solvents (Methanol, Purified water, 0.1N HCl and Phosphate buffer pH6.8) according to the United States Pharmacopoeia. Solubility can be determined by saturating the drug with different solvents used in Solubility

studies in a vial. Then vial was tightly closed and agitated at constant temperature for 24hrs in Rotary Mechanical Shaker. The amount of drug in solution is determined periodically by filtering samples through filter paper and assayed by using U.V – Visible Spectrophotometer at 220 nm. The results are then compared with those given in the United States Pharmacopoeia.

Formulation of Orodispersible Tablets ODTs[6-9, 25-56]

Orodispersible tablets containing selected solid dispersion were prepared by direct compression method using single punch tablet machine to produce convex faced tablets weighing 230mg. 100 tablets were prepared for each batch. The formulations were developed by using Superdisintegrants. The superdisintegrants were used to develop the tablets. All the ingredients were shown in Table 3 were passed through sieve no. 70 and were co-grounded in a glass pestle motor. These blends were evaluated for mass-volume relationship (bulk density, tapped density, hausner ratio, and Compressibility Index) and flow properties (angle of repose). The mixed blend of excipients was compressed using a single punch tablet machine (Rimek) to produce convex faced tablets. Mixing and Compression Processes: Mixing was done by using geometric mixing, in where all excipients accurately weighted and blended with Clopidogrel. This method of ordering mixing of excipients with Clopidogrel for all formulae. Then each mixture has compressed directly after testing powder properties that will be shown in preformulation tests.

Table 3: Formulation of Clopidogrel ODTs.

Ingredients	Quantity Per Tablet (mg)								
	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Clopidogrel Bisulfate	75	75	75	75	75	75	75	75	75
Avicel PH101	93,5	80	102.6	113.5	113.8	125.2	125.2	125.2	30.4
Crospovidone	25	25	25	-----	-----	13.5	------	-----	15.34
Croscarmellose Na	25	20	-----	25	------	-----	13.5	-----	12.27
Mg Stearate	2.25	2.25	2.2	2	2	2	2	2	1.35
Talc	2.2	2.2	-----	-----	-----	-----	-----	-----	-----
Na Starch Glycolate	----	5	-----	-----	25	-----	-----	13.5	-----
Lactose	----	13.5	7.2	7.2	7.2	7.2	7.2	7.2	------
Saccharin Sodium	5.2	5.2	5.2	5.2	5.2	5.2	5.2	5.2	12.27
PEG	----	----	----	----	----	----	----	----	30
Calcium	----	----	----	----	----	----	----	----	39.35

Carbonate									
PVP K30	----	----	----	----	----	----	----	----	6.13
Mannitol	----	----	----	----	----	----	----	----	6.13
Flavor (Peppermint)	2	2	2	2	2	2	2	2	2

Evaluation of Clopidogrel Powder [25-56]

Pre-Compression Evaluation of The Powder

Micrometric Properties

Angle of Repose (θ)

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane. The frictional force in a loose powder or granules can be measured by angle of repose as shown in Table 4.

$\tan \theta = h / r$

$\theta = \tan^{-1} (h/r)$ Where, θ is the angle of repose, h is the height of pile, r is the radius of the base of pile.

Table 4: Relationship Between Angle of Repose and Flow Properties.

Flow Property	Angle of Repose
Excellent	<25
Good	25-30
Passable	40-30
Very Poor	>40

Bulk Density

Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another.

$$LBD = \frac{\text{Weight of the powder (m)}}{\text{Volume of the packing (vo)}}$$

Tapped Density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (ρ_t) was calculated using the following formula:

$\rho_t = M / V_t$

Compressibility Index

The compressibility index of the granules was determined by Carr's compressibility index as shown in Table 5.

(%) Carr's Index can be calculated by using the following formula:

Carr's Index (%) = TBD -LBD /TBD x100

Hausner Ratio

Hausner ratio is an indirect index of ease of power flow. It is calculated by the following formula:

Hausner ratio = ρ_t / ρ_d

Where ρt is tapped density and ρ_d is bulk density. Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Table 5: Grading of the Powders for Their Flow Properties According to Carr's Index.

Compressibility Index	Flow Properties
5-15	Excellent
12-16	Good
18-21	Fair to Passable
23-35	Poor
33-38	Very Poor
>40	Very Very Poor

Taste Masking of Clopidogrel

After compression of the formulae and formed tablets, their taste was slightly bitter, so we tried to mask this bitterness in formulae F9 as possible as in where taste masking is an essential requirement for mouth dissolving tablets for commercial success. Taste masking of the active ingredient can be achieved by various techniques like solvent evaporation on solvent extraction. In present study, Clopidogrel has unacceptable bitter taste that can be ratified by using different effervescing agents like Stearic acid, calcium carbonate and isopropyl alcohol in different ratios. Calcium carbonate was used, which was added to Clopidogrel in 1:1.5 ratio by using PVPK 30 as a binding agent and purified water as a solvent. This complex was put in oven at 45 C° till forming paste, then this paste was triturated in mortar then passed through 70# sieve. After that it was added to all excipient were blended with specified quantity of Clopidogrel for 15 minutes, whereas the other excipients were blended for 5 minutes and added to the former excipients. Then all formulae were passed through sieve #70 for particle size uniformity. Then compressed directly by using single batch tablet machine (Rimek).

Evaluation of Clopidogrel ODTs [25-56]

Post Compression Parameters

General Appearance

The general appearance of tablet is its visual identity and all over elegance, shape, color, surface textures. These all parameters are essential for consumer acceptance.

Hardness Test

Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under the condition of storage transformation and handling before usage depends on its hardness. The hardness of ODTs is generally kept lower than conventional tablets as increased hardness delays the disintegration of the tab. Hardness of tablets (randomly) from whole tablet batch was determined by Rimek hardness tester. Hardness measured in kg/cm^2.

Thickness Test

The thickness of the tablets was determined by using vernier calipers. Randomly 10 tablets selected were used for determination of thickness that expressed in Mean SD and unit is mm.

Weight Variation Test

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets randomly from whole batch was determined and the average was calculated. The individual weights of the tablets were also determined accurately and allowed deviation rang was calculated from average weight. The tablets pass the USP test if no more than 2 tablets deviate from (average weight +- allowed deviation) and if no tablet differs by more than 2 times the allowed deviation as shown in Table 6.

Table 6: Limits According to U.S.P.

Average Weight of Tablet	%Deviation
80mg or less	±10
More than 80 mg but less than 250 mg	±7.5
250 mg or more	±5

Friability Test

Friability test is the loss of weight of tablet in the container due to removal of fine particles from the surface during transportation or handling. Rimek friabilator was employed for finding the friability of the tablets. For tablets with an average weight of 0.75g or less take a

sample of whole tablets corresponding to about 4.5g and for tablets with an average weight of more than 0.75 g take a sample of 6 whole tablets. Rimek friabilator is rotated at 25rpm for 4 minutes for 100rounds. The tablets were dedusted and weighed again. The percentage of weight loss was calculated using the formula:

%f= W0-W1/W0*100

%f = Percentage friability

W0 = Initial weight (before test)

W1 = Final weight (after test)

% Friability of tablets less than 1% are considered acceptable.

Wetting Time Test

The ODTs wetting time is another significant parameter that needs to be measured in order to gain insight into the tablet's disintegration. The wetting time of the tablets were measured using a simple procedure. A piece of tissue paper (diameter 10 cm) folded twice was placed in a small Petri dish (internal diameter 10 cm) containing 10ml of water with a yellow water-soluble dye (sunset dye). The ODTs tablet was cautiously placed on top of it. The time taken for the water to reach the upper surface of the tablet and to completely wet it was noted as wetting time.

***In-Vitro* Dispersion Time Test**

This test is performed to ensure disintegration of tablets. In vitro dispersion time was measured by dropping a tablet in a measuring cylinder containing 10 ml of phosphate buffer pH 6.8 (simulated saliva fluid). The time required for complete dispersion was determined. Three tablets from each formulation were randomly selected and In vitro dispersion time was performed. In vitro dispersion time is expressed in seconds.

Disintegration Time Test

Disintegration time test is the process of breakdown of a tablet into smaller particles is called as disintegration. The USP device to rest disintegration was six glass tubes that are “3 long, open at the top, and held against 10” screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is poisoned in 900ml beaker of distilled water at 37± 2°C, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker.

Assay of Clopidogrel

In both HCl and phosphate buffer to determine the percentage of active ingredient in the tablet according to range of pharmacopeia this done by grinding ten tablet and weight amount of powder then divided to 10 the result is amount of powder that well be taken to dissolve in 100ml of 0.1N HCl or in phosphate buffer and sonication for one hour then filtration by filter paper, take 2ml from filtrate and diluted to 100ml by D.W then measure the absorbance. So measure practical and use this equation %(amount dissolve)=(practical /theoretical) × 100 Where:- practical =conc. × dilution factor × volume Theoretical =75mg the range of Clopidogrel bisulfate is (90 – 110).

***In-Vitro* Dissolution Studies of Clopidogrel ODTs**

The dissolution of Clopidogrel from different tablet formulations was tested by using BP dissolution tester (JASCO DT-810). The paddle was made to rotate at 50 rpm, the dissolution in two medium was first is 1000 ml phosphate buffer pH 6.8, maintained and the second is 900 ml of 0.1N HCl at 37±0.5 C°. At predetermined time intervals (5,10,15 & 20 minutes in phosphate buffer), while in 0.1N HCl was at (2,4,6 and 8 minute) the aliquots of the dissolution medium were withdrawn and properly diluted and analyzed for Clopidogrel content by measuring the absorbance at λmax 217nm, using 0.1N HCl and measuring the absorbance at λmax 220nm using phosphate buffer pH 6.8. The withdrawn samples were replaced by an equal volume of phosphate buffer pH 6.8 or 0.1N HCl. This test done in comparing with conventional tablets PLAVIX® which tested under similar condition that used in testing the different formulae. To prove our purpose of studying and formulation. Different formulae must have lower dissolution time with high amount of released drug.

RESULTS AND DISCUSSION

UV Scanning of Clopidogrel

The calibration curve of Clopidogrel bisulfate was prepared in two solutions, the first in 0.1N HCl the absorbance at λmax 217nm and the second in phosphate buffer at pH 6.8, the absorbance of these solutions was measured at 220nm.

Evaluation of Clopidogrel Orodispersible Tablets ODTs

Micromeritic Properties

The powder of Clopidogrel was evaluated for the following parameters such as angle of repose, bulk density, tapped density, compressibility index and Hausner ratio. The results are given in Table 7.

Table 7: Characterization Angle of Repose of Blend of Formulations ODTs.

Formulation Code	Bulk D	Tapped D	Bulkiness	Angle of Repose	Evaluation of Angle of Repose	Carr's Index	Hausner's Ratio	Flowability	Powder Taste
F1	0.472	0.715	2.118	41.18	Passable	33.98	1.514	Poor	Bitter
F2	0.531	0.726	1.883	42.61	Passable	26.85	1.367	Passable	Bitter
F3	0.436	0.661	2.293	41.34	Passable	34.03	1.516	Very Poor	Bitter
F4	0.407	0.736	2.457	43.47	Passable	44.70	1.808	Very Poor	Bitter
F5	0.337	0.672	2.967	43.31	Passable	49.85	1.994	Very Poor	Bitter
F6	0.379	0.571	2.638	47.19	Poor	33.62	1.506	Very Poor	Bitter
F7	0.430	0.658	2.325	44.34	Passable	34.65	1.530	Very Poor	Bitter
F8	0.449	0.615	2.227	46.88	Poor	26.99	1.369	Passable	Bitter
F9	0.571	0.728	1.75	37.4	Good	21.56	1.27	Good	Sweet

Table 8: Thickness results of Formulation of Clopidogrel ODTs.

NO.	Formulation Code								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	3.04	3.03	3	2.86	2.86	2.99	3.04	2.87	3.1
2	3.07	3.02	2.98	2.77	2.88	2.91	3.05	3	3.17
3	3.02	2.97	2.91	2.82	2.88	2.82	3.04	2.89	3.15
4	3.01	3.08	2.99	2.85	2.93	2.99	2.90	3.05	3.14
5	3.03	3.00	2.98	2.87	2.87	2.85	2.83	2.95	3.16
6	3.04	2.99	3.02	2.77	2.87	2.86	2.92	**3**	3.1
7	3.04	2.97	**3**	2.79	2.79	2.96	2.95	2.89	3.17
8	3.05	3.07	3.04	2.75	2.90	2.86	2.98	2.88	3.15
9	3.06	3.00	2.98	2.77	2.88	**3**	3.1	3.01	3.14
10	3.06	3.01	3.02	2.82	2.89	2.9	2.94	2.94	3.16

The hardness of the tablets was measured and the values were found in the range of 2.3 to 5.3Kg. The prepared tablets possessed good mechanical strength with sufficient hardness. The thickness of the tablets was measured and were found in the range of 2.81mm to 3.14mm, all the formulations possessed uniform Thickness. The percentage of friability values of the prepared Clopidogrel Orodispersible tablets showed less than 1%.

Table 9: Friability Results of Formulation of Clopidogrel ODTs.

NO.	Formulation Code								
Weight(g)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
W(b)	2.3264	2.2966	2.3028	2.323	2.2872	2.2862	2.4722	2.3154	2.4646
W(a)	2.3192	2.2848	2.2994	2.3174	2.2708	2.2800	2.4672	2.3112	2.4622
Friability (%)	0.309	0.513	0.147	0.241	0.717	0.271	0.202	0.181	0.097

Table 10: Hardness Results of Formulation of Clopidogrel ODTs.

NO.	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	3.8	2.5	4.3	4.3	2.2	4.3	5.4	4.1	2.04
2	4.1	2.5	4.6	4.3	2.2	4.4	5.1	4.1	2.55
3	3.5	2.3	4.3	4.4	2.3	4.5	5.3	4	2.55
4	4	2.4	4.4	4.5	2.3	4.6	5.1	4.1	2.04
5	3.9	2.4	4.5	4.5	2.2	4.4	5.3	4	2.75
Mean Hardness (Kg/cm^2)	3.9	2.5	4.5	4.4	2.3	4.5	5.3	4.1	2.38

Table 11: Disintegration Time Results of Formulation of Clopidogrel ODTs.

Formulation Code	Time (sec)
F1	18
F2	30
F3	35
F4	152
F5	122
F6	165
F7	182
F8	328
F9	175
PLAVIX®	498

Table 12: Evaluation Parameters of Formulation of Clopidogrel ODTs.

Formulation Code	Average Weight(mg) S.D ±	Thickness (mm) S.D ±	Friability (%)	Mean Hardness (Kg/cm^2)	Wetting Time(sec)	Dispersion Time(sec)	In-Vitro Disintegration Time (sec)
F1	234.8 ±16.4	3.05 ±0.176	0.309	3.9	50	41	18
F2	232.16 ±16.6	3.01 ±0.15	0.513	2.5	72	35	30
F3	233 ±16.7	3 ±0.15	0.147	4.5	55	60	35
F4	230.18 ±16.5	2.81 ±0.14	0.241	4.4	240	300	152
F5	230.18 ±16.5	2.88 ±0.143	0.717	2.3	270	250	122
F6	232 ±16.6	2.91 ±0.145	0.271	4.5	240	300	165
F7	233.5 ±17.8	2.98 ±0.149	0.202	5.3	225	230	182
F8	230.7 ±17.3	2.95 ±0.148	0.181	4.1	379	420	328
F9	230.5 ±18.41	3.14 ±0.157	0.097	2.38	105	360	175

All formulations of Clopidogrel Orodispersible tablets passed the weight variation test since the values are within the acceptable variation limit of the tablet as shown in Table 12. As shown in Table 12, the wetting time of Clopidogrel Orodispersible tablets were found to be in the range between 50 to 379 seconds.

In-Vitro dispersion time of the Clopidogrel Orodispersible tablets were found between 41 to 360 seconds. Formulation F1 showed rapid dispersion (41 sec) compared with all other formulations. The disintegration time of Clopidogrel Orodispersible tablets ranges between 18 to 328 seconds. From the results, it was concluded that the formulation F1 showed better tableting properties compared to the other formulations as shown in Tables 11 and 12.

Solubility Test

It was determined as per procedure. The Solubility studies of drug revealed that Clopidogrel is soluble in organic solvent like methanol and also freely soluble in 0.1N HCl pH1.2, and is practically insoluble in water and aqueous media as shown in Table 13.

Table 13: Solubility Study of Clopidogrel Bisulfate.

Solvent	Mg/ml	Solubility of Clopidogrel Bisulfate
0.1N HCL pH1.2	694.5	Freely soluble
Methanol	89.2	Soluble
Phosphate Buffer pH6.8	12.8	Sparingly soluble
Distill Water	0.0118	Insoluble

Table 14: Assay of Formulation of Clopidogrel ODTs.

Formulation Code	WT Average	Absorbance	Conc (mcg/ml)	Total Amount Clopidogrel (mg)	Yield %
F1	235mg	0.5811	15.46	77.3	103
F2	232mg	0.5580	14.86	74.3	99
F3	233mg	0.5391	14.36	71.8	95.7
F4	230mg	0.5824	15.49	77.45	103.2
F5	230mg	0.5532	14.73	73.65	98.2
F6	232mg	0.5567	14.83	74.15	98.8
F7	233mg	0.5607	14.93	74.65	99.53
F8	231mg	0.5773	15.36	76.8	102.4
F9	231mg	0.5672	15.10	75.5	100.6

The assay of Clopidogrel Orodispersible tablets were found to be in the acceptable limit of Clopidogrel content as per USP is 90 to 110%. The results revealed that the assay of Clopidogrel was within the acceptable limit as shown in Table 14.

In-Vitro Dissolution Studies

The *in-vitro* drug release of Clopidogrel ODTs were shown in Tables 15 and 16.

Table 15: Drug Release Percentage of Formulation of Clopidogrel ODTs in Phosphates Buffer pH 6.8.

Formulation Code	Drug Release %			
	5 min	10 min	15 min	20 min
F1	47.46	52.32	70.31	74.92
F2	56.61	67.45	73.71	77.53
F3	56.17	62.31	74.37	80.31
F4	31.23	39.52	45.66	56.76
F5	34.75	41.97	49.23	54.88
F6	32.11	39.87	49.69	55.83
F7	26.33	33.86	42.73	49.21
F8	13.41	30.65	43.94	50.35
F9	69.70	73.53	84.67	90.32
PLAVIX®	13.32	21.52	31.81	41.31

Table 16: Drug Release Percentage of Formulation of Clopidogrel ODTs in 0.1N HCl.

Formulation Code	Drug Release %			
	5 min	10 min	15 min	20 min
F1	84.63	87	88	91.14
F2	92.34	95.21	95.3	98.93
F3	91.8	92.77	96.37	97.07
F4	12.22	52.35	69.2	81.9
F5	24.6	47.23	81.93	94.91
F6	25	83.12	86	88.4
F7	17.46	69.6	81.13	84.1
F8	12.84	40.24	68.84	86.34
F9	45.9	66.7	85.14	92.2
PLAVIX®	11	23.7	31.2	40.8

The drug release in phosphates buffer pH 6.8 of formulations F1, F2 and F3 were found to be 47.46%, 56.61% and 56.17% at 5 minutes. The drug release of formulations F4, F5 and F6 were found to be 31.23%, 34.75% and 32.11% at 5 minutes. The drug release of formulations F7, F8 and F9 were found to be 26.33%, 13.41% and 69.70% while PLAVIX® 13.32% at 5 minutes. The highest dissolution rate and the maximum drug release was observed in formulation F9, which was 69.70% in 5 minutes. The drug release in 0.1N HCl of

formulations F1, F2 and F3 were found to be 84.63%, 92.34% and 91.8% at 5 minutes. The drug release of formulations F4, F5 and F6 were found to be 12.22%, 24.6% and 25% at 5 minutes. The drug release of formulations F7, F8 and F9 were found to be 17.46%, 12.84% and 45.9% while PLAVIX®11% at 5 minutes. The highest dissolution rate and the maximum drug release was observed in formulation F2, which was 92.34% in 5 minutes.

CONCLUSION

Clopidogrel bisulfate, an P2Y12 inhibitor, was selected as a model for preparation of Orodispersible tablets by direct compression technique. Orodispersible tablets were prepared by adding different concentrations of superdisintegrants and several formulations of Clopidogrel bisulfate ODTs have been prepared by utilizing different excipients. Masking taste of bitterness characters of Clopidogrel bisulfate has been done to increase compliance for formulated tablets. All prepared ODTs were evaluated for weight variation, thickness uniformity, friability, hardness, wetting time, dispersion time, disintegration time, and dissolution time. A total of nine formulations of Orodispersible tablets of Clopidogrel were formulated by direct compression using superdisintegrants like sodium starch glycolate, croscarmellose sodium and crospovidone, then evaluated. Among the nine formulations the drug release of F2 and F3 formulations were found to be 92.34% and 91.8% at 5 minutes in 0.1NHCl medium while the drug release of F9 formulation were found to be 69.7% at 5minutes in phosphate buffer. The formulations F2 and F9 were the best formulations as it showed a drug release percentage 92.34% and 69.7% at 5 minutes and the assay of Clopidogrel was within the acceptable limit.

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REFERENCES

1. Kavitha K, Subramaniam K, JiaHui B, Santhi K, Dhanaraj SA, Rupesh KM. Potential Drug Candidates for Fast Dissolving Drug Delivery - A Review. Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2013; 4(4): 1510-1526.
2. Sehgal P, Gupta R, Umesh Kumar S, Chaturvedi A, Gulati A, Sharma M. Fast Dissolving Tablets. Am. J. Pharm Tech Res., 2012; 2(4): 252-279.
3. MdNehal S, Garima G, Pramod KS. Fast Dissolving Tablets: Preparation, Characterization and Evaluation: An Overview, International Journal of Pharmaceutical

Sciences Review and Research, 2010; 4(2): 87-96.

4. Rajeev soni, Galividyasagar. Design and Development of Quick Dissolving Tablet Containing Loratadine by Direct Compression Method. International Journal of Pharmaceutical, Chemical and Biological Sciences, 2013; 3(3): 771- 800.
5. Gunda RK, Kumar JS, Jayakumari S, Vijayalakshmi A, Satyanarayana V. Formulation Development and Evaluation of Risperidone Fast Dissolving Tablets. Journal of Pharmacy Research, 2016; 10(9): 579-88.
6. RedyaNaik R, et al.Formulation and Evaluation of Oral Dispersible Tablets of Clopidogrel Bisulfate by Solid Dispersion Method. Indo American Journal of Pharmaceutical Research, 2014; 4(7): 3152-3162.
7. Jain H, Arora V, Gupta J, Bhandari A. Formulation Optimization of Immediate Release Tablet of Clopidogrel Bisulphate Free from Surface Irregularities. International Journal of Pharmaceutical Sciences and Research, 2011; 2(12): 3243-3246.
8. Prasad SB, Tamilselvan A, Subramanian SN. Formulation and Evaluation of Clopidogrel Bisulfate Immediate Release Tablets. Journal of Global Trends in Pharmaceutical Sciences, 2014; 5(4): 2154 – 2166.
9. Kumar GR, Kumar JNS, Satyanarayana V, Swarupa Rani G, Prasad BS. Formulation Development and Evaluation of Clopidogrel Fast Dissolving Tablets. Iranian Journal of Pharmaceutical Sciences, 2016; 12(2): 61-74.
10. Kuccherkar BS, Badhan AC, Mahajan HS. Mouth Dissolving Tablets: A Novel Drug Delivery System. Phrma Times, 2003; (35): 3-10.
11. Masaki K. Intrabuccal Disintegrating Preparation and Production thereof, US Patent No.5, 466, 464, 1995.
12. Pebley WS, Jager NE, Thompson SJ. Rapidly Disintegrating Tablets, US Patent No. 5,298,261, 1994.
13. Arya Arun, Chandra Amrish. Fast Drug Delivery Systems: A Review. Der Pharmacia Lettre, 2010; 2(2): 350-361.
14. Renon JP, Corveleyn S. Freeze-Dried Rapidly Disintegrating Tablets, US Patent No. 6,010,719, 2000.
15. European pharmacopeia. 2010.
16. Raymond CR, Paul JS, Marian EQ. Handbook of Pharmaceutical Excipients, 6th Edition. Pharmaceutical Press and American Pharmacists Association, 2009; S48-S760.
17. Nikam et al. Mouth Dissolving Tablets: an overview. Pharmacology online, 2011; 3: 562-58.

18. Sastry SV, Nyshadham JR, Fix JA. Recent Technological Advances in Oral Drug Delivery - A Review. Pharm Sci Technol Today, 2000; 3(4): 138-145.
19. Sravani M. Formulation and Evaluation of Mouth Dissolving Tablets of Nebivolol HCl for Treatment of Hypertension. Int J Pharma Chem Res., 2017; 3: 200-212.
20. Gandhi L, Akhtar MS. Comparative Study on Effect of Natural and Synthetic Superdisintegrants in the Formulation of Orodispersible Tablets. J Drug Deliv Ther., 2019; 9(2): 507-513.
21. Sandhyarani G, Sarangapani M. Formulation and Evaluation of Orodispersible Tablets of Domperidone. IOSR J Pharm., 2016; 6(9): 39-47.
22. Upadhyay P, et al. A Review on Formulation and Evaluation Approaches for Fast Release Tablet. Mathews J Pharma Sci., 2023; 7(1): 15.
23. Ramu S, Kumar YA, Rao DS, Ramakrishna G. Formulation and Evaluation of Valsartan Oral Dispersible Tablets by Direct Compression Method. Am J Adv Drug Deliv., 2014; 1: 2321-547X.
24. Pandy P, Dahiya M. Oral disintegrating Tablets: A Review. Int J Pharma Res., 2016; 5(1): 51.
25. Bhowmik D, Chiranjib B, Krishnath P, Chaandira RM. Fast Dissolving Tablet: an Overview. J Chem Pharm Res., 2009; 1(1): 165.
26. Arora P, Sethi VA. Orodispersible Tablet: a Comprehensive Review. Int J Res Drug Dev Pharm Life Sci., 2013; 2(2): 271-272.
27. Jassem NA. Orodispersible Tablets: a Review on Recent Trends in Drug Delivery. IJDDT, 2022; 12: 433.
28. Alburyhi MM, Saif AA, Noman MA. Stability Study of Six Brands of Amoxicillin Trihydrate and Clavulanic Acid Oral Suspension Present in Yemen Markets. Journal of Chemical Pharm Research, 2013; 5(5): 293-296.
29. Saif AA, Alburyhi MM, Noman MA. Evaluation of Vitamin and Mineral Tablets and Capsules in Yemen Market. Journal of Chemical Pharma Research, 2013; 5(9): 15-26.
30. Alburyhi MM, Saif AA, Noman MA, Al-Ghorafi MA. Comparative Study of Certain Commercially Available Brands of Paracetamol Tablets in Sana'a City, Yemen. European Journal of Pharmaceutical and Medical Research, 2018; 5(12): 36-42.
31. Alburyhi MM, Saif AA, Saif RM. Preformulation Study of Ceftriaxone and Ciprofloxacin for Lipid Based Drug Delivery Systems. EJUA-BA, 2022; 3(4): 339-350.
32. Alburyhi MM, Saif AA, Noman MA, Yahya TA. Formulation, Development and Evaluation of Famotidine Orodispersible Tablets. European Journal of Pharmaceutical

and Medical Research, 2023; 10(10): 56-62.

33. Bary AA, El-Gazayerly ON, Alburyhi MM. Formulation of Immediate Release Lamotrigine Tablets and Bioequivalence Study. Journal of Chemical Pharm Research, 2013; 5(10): 266–271.
34. Alburyhi MM, Saif AA, Noman MA, Saif RM. Recent Innovations of Delivery Systems for Antimicrobial Susceptibility Study of Ciprofloxacin Biodegradable Formulations for Post-Operative Infection Prophylaxis. European Journal of Pharmaceutical and Medical Research, 2023; 10(9): 32-36.
35. Saif AA, Alburyhi MM, Noman MA, Almaktari AM. Formulation and Evaluation of Trimetazidine Hydrochloride and Clopidogrel Bisulphate Multi-unit Solid Dosage Forms. Journal of Chemical Pharm Research, 2014; 6(2): 421-426.
36. Alburyhi MM, Saif AA, Noman MA, Saif RM. Recent Innovations of Delivery Systems for Antimicrobial Susceptibility Study of Ceftriaxone Biodegradable Formulations for Post-Operative Infection Prophylaxis. European Journal of Pharmaceutical and Medical Research, 2023; 10(8): 95-99.
37. Alburyhi MM, Saif AA, Noman MA, Al khawlani MA. Formulation and Evaluation of Bisoprolol Fast Dissolving. World Journal of Pharmaceutical Research, 2023; 12(16): 01- 10.
38. Noman MA, Alburyhi MM, El-Shaibany A, Alwesabi NA. Formulation and Evaluation of Pandanus Odoratissimus L Extract for Treatment of Nocturnal Enuresis as Orodispersible Tablets Delivery System. World Journal of Pharmaceutical Research, 2024; 13(5): 56-71.
39. Alburyhi MM, Saif AA, Noman MA. Formulation and Evaluation of Ticagrelor Orodispersible Tablets. World Journal of Pharmaceutical Research., 2024; 13(5): 26-55.
40. Alburyhi MM, Noman MA, Saif AA, Salim YA, Abdullah JH. Formulation and Evaluation of Domperidone Orodispersible Tablets. World Journal of Pharmacy and Pharmaceutical Sciences, 2024; 13(3): 49-68.
41. Aboghanem A, Alburyhi MM, Noman MA. Effect of Different Excipients on Formulation of Immediate Release Artemether/Lumefantrine Tablets. Journal of Chemical Pharm Research, 2013; 5(11): 617-625.
42. Alburyhi MM, El-Shaibany A. Formulation and Evaluation of Anti-peptic Ulcer Capsules of Curcuma Longa Herbal Product. World Journal of Pharmaceutical Research, 2023; 12(22): 76-96.
43. Alburyhi MM, Saif AA, Noman MA, Saeed SA, Al-Ghorafi MA. Formulation and

Evaluation of Diclofenac Orodispersible Tablets. European Journal of Pharmaceutical and Medical Research, 2023; 10(9): 01-06.

44. Saif AA, Alburyhi MM, Noman MA. Formulation and Evaluation of Ketoprofen Fast Dissolving Tablets. International Journal of Sciences, 2018; 7(09): 27- 39.
45. Alburyhi MM, El-Shaibany A. Formulation and Evaluation of Effervescent Granules of Artemisia Arborescence Herbal Product for Foodborne Illness. World Journal of Pharmacy and Pharmaceutical Sciences, 2023; 12(12): 1429-1444.
46. Hamidaddin MA, Alburyhi MM, Noman MA, Saif AA. Formulation and Evaluation of Rosuvastatin Fast Dissolving Tablets. World Journal of Pharmacy and Pharmaceutical Sciences, 2023; 12(9): 2293-2303.
47. Alburyhi MM, Saif AA, Noman MA, Salim YA, Hamidaddin MA. Formulation and Evaluation of Lisinopril Orally Disintegrating Tablets. World Journal of Pharmacy and Pharmaceutical Sciences, 2023; 12(9): 357-369.
48. Alburyhi MM, El-Shaibany A. Formulation and Evaluation of Antitumor Activity of Artemisia Arborescence Extract Capsules as Dietary Supplement Herbal Product Against Breast Cancer. World Journal of Pharmaceutical Research, 2024; 13(3): 95-114.
49. Alburyhi MM, Hamidaddin MA, Saif AA, Noman MA. Formulation and Evaluation of Rivaroxaban Orodispersible Tablets. World Journal of Pharmacy and Pharmaceutical Sciences, 2024; 13(2): 2066-2092.
50. Noman MA, Alburyhi MM, El-Shaibany A, Alwesabi NA. Preformulation and Characterization Studies of Pandanus Odoratissimus L Extract Active Ingredient in Treatment of Nocturnal Enuresis. World Journal of Pharmacy and Pharmaceutical Sciences, 2024; 13(2): 1603-1620.
51. Alburyhi MM, El-Shaibany A. Formulation and Evaluation of Antibacterial Orodispersible Tablets of Artemisia Arborescence Extract Herbal Product. European Journal of Pharmaceutical and Medical Research, 2024; 11(2): 409-417.
52. Raweh SM, Noman MA, Alburyhi MM, Saif AA. Formulation and Evaluation of Anti-acne Gel of Azadirachta Indica Extract Herbal Product. European Journal of Pharmaceutical and Medical Research, 2024; 11(2): 427-433.
53. Alburyhi MM, Saif AA, Noman MA, Yassin SH. Formulation and Evaluation of Simvastatin Orodispersible Tablets. World Journal of Pharmaceutical Research, 2023; 12(16): 1033-1047.
54. Othman AM, Alburyhi MM, Al-Hadad GH. Formulation and Evaluation of Captopril Mouth Dissolving Tablets. European Journal of Pharmaceutical and Medical Research,

2024; 11(1): 18-28.

55. Alburyhi MM, El-Shaibany A. Formulation and Evaluation of Oral Pharmaceutical Solution of Pandanus Odoratissimus L Extract Herbal Product in Treatment of Nocturnal Enuresis. World Journal of Pharmacy and Pharmaceutical Sciences, 2024; 13(1): 1840-1851.
56. Alburyhi MM, Saif AA, Noman MA, Yahya TA, Al-Ghorafi MA. Formulation and Evaluation of Drotaverine Orally Disintegrating Tablets. World Journal of Pharmaceutical Research, 2023; 12(18): 66-79.