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COMPATIBILITY STUDIES WITH PHARMACEUTICAL EXCIPIENTS OF CLOPIDOGREL FOR THE DEVELOPMENT OF NOVEL DELIVERY SYSTEMS

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ABSTRACT

In the present study that the 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, sodium starch glycolate, 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. Preformulation, formulation and evaluation of Clopidogrel to avoid problems associated with conventional delivery system such as limited permeation, low dissolution and bioavailability and also to improve bioavailability were evaluated for preformulation studies parameters and one of the most recent antiplatelet agents. It was concluded that the drug Clopidogrel was found to be compatible with various excipients which were selected for the formulation development of the Clopidogrel ODTs. Formulation scientist from his experience and knowledge have to significantly in the preformulation study stage and is an important factor in the ADDS (Advanced Drug Delivery Systems) product development process.

KEYWORDS: Clopidogrel, Compatibility, Excipients, Development, Preformulation, Formulation, Antiplatelet agent.

INTRODUCTION

Preformulation studies[1-150]

Preformulation is essentials of pharmaceutical science that utilizes biopharmaceutical principles in the determination of physicochemical properties of the drug substance. Prior to the development of any dosage form new drug, it is essential that certain fundamental physical and chemical properties of drug powder are determined. This information may dictate many of subsequent event and approaches in formulation development. The safety, efficacy, quality and stability of a formulation are major concepts of any API development process. In API development process, a detailed characterization of the API and other formulation components is usually carried out during the preformulation stage. Formulation scientist from his experience and knowledge have to significantly in the preformulation study stage and is an important factor in the ADDS (Advanced Drug Delivery Systems) product development process.

One of the objectives of this study is to development of drug delivery systems by building scientific pharmaceutical research information depend on formulation scientists to join the knowledge and experience as well as experimental and practical results of this study with regard to information in previous studies, and approved references. It was found to be that the most important concepts and basics of preformulation studies such as definitions, methods, conclusion, idea, and types of pharmaceutical analysis techniques using in evaluation of preformulation studies parameters, in this study that we focused on developing drug delivery systems and linking the formulation development to establish the basics of pharmaceutical research in studying the drug-excipient compatibility, dug with various excipients, which is important for the safety, effectiveness, quality, formulation, stability, bioavailability, and pharmacokinetics of the drug etc.

Determination of physical chemical properties of API substance with the goal of developing a new drug which is safe stable and efficacious, each API, has intrinsic chemical and physical properties that were considered prior to the development of pharmaceutical formulation, the purpose of preformulation study is to generate useful information for the formulator in the development of stable and bioavailable dosage form, inappropriate preformulation study results in poor stability of active ingredients increase the overall cost of development and increased development time, preformulation studies help to fortify the pharmaceutical scientific foundation of the guidance, provide regulatory relief and conserve resources in the

drug development and evaluation process, enhance public safety standards, improve product quality, promote the implementation of new technologies, aids policy development and regulatory decision making and after compiling all data it is transferred to the development pharmacist and for the day work on formulation of dosage form.

Preformulation study objectives: To establish the Physico-chemical parameters of a new API entity, determine its kinetics and stability, establish its compatibility with common excipients, it provides insights into how drug products should be processed and stored to ensure their quality, estimate problem may arise during formulation that is stability problem poor *in-vivo* dissolution, poor bioavailability, to interpret BCS classification of drugs and its significance and develop optimal drug delivery system.

Drug-Excipient compatibility study: The primary objective of this investigation was to identify a stable storage condition for API in solid state and identification of compatible excipients for its formulation. Incompatibilities are major concerns in formulation development. Selection of the proper excipient during preformulation studies is of prime importance.

Dosage forms: DF contain API and pharmaceutical excipients, which are intended to generate an ideal formulation and manufacturability of pharmaceutical products, thereby enabling a much safer and more effective administration. Pharmaceutical excipients are ideally inactive and have no impact on the stability or therapeutic effect of the active ingredient. On the other hand, there are studies that have presented that some pharmaceutical excipients are just allegedly described as inactive ingredient. Some pharmaceutical excipients have the capacity to affect API, efficacy by affecting its pharmacokinetics. Excipients can affect the physical and chemical form of pharmaceuticals by several factors such as hydrogen bond interaction, polymorphic conversion, and others. Accordingly, drug-excipient compatibility should be conducted so as to determine any drug-excipient interactions that may obstruct the stability, bioavailability, and manufacturability of pharmaceutical dosage forms.

Importance of Drug-Excipient Compatibility

Studies of active pharmaceutical ingredient (API)-excipient compatibility represent an important study in the preformulation stage of the development of new dosage forms, stability of the dosage form can be maximized, any physical or chemical interaction between API, and excipient can affect bioavailability and stability of drug, it helps to avoid the

surprise problem, by performing drug excipient compatibility studies (DECS) we can know the possible reaction before formulating final dosage form, DECS data is essential for IND (investigational new drug) submission, and now, USFDA has made it compulsory to submit DECS data for any new coming formulation before its approval.

The potential physical and chemical interactions between an API, and the excipients can affect the chemical nature, the stability and bioavailability of the former and, consequently, its therapeutic efficacy and safety, solid dosage forms are generally less stable than their API components and despite the importance of API-excipient compatibility testing, there is no universally accepted protocol to assess such interactions.

Pharmaceutical excipients: Excipients are additive substances used to improve the bulkiness, disintegration, dissolution rate, and bioavailability of a formulation etc. Different dosage forms like powders, granules, capsules, tablets, oral liquids, injectable products, implants, eye products, nasal products, inhalers, topical creams, ointments, gels, transdermal patches and suppositories etc, contains different types of excipients. To make it acceptable and compatible various pharmaceutical excipients are added in pharmaceutical dosage form for their direct therapeutic action, manufacturing process, to protect, support or enhance stability, for bioavailability or patient compliance. These must be physiologically and chemically stable, must not have any incompatibility with the API, and must meet the standards of regulatory requirements.

Evaluation of Drug-Excipient Compatibility

The compatibility study of API and excipients is important to predict the stability of the API, in the final pharmaceutical product. It's the first time that API was compatible with excipients promoted physical and chemical compatibility studies was achieved by thermal and non-thermal methods. As a part of preformulation study, a compatibility study of API with the other excipients was carried out using physical blends in analytical techniques for the evaluation of drug-excipient interactions. The most commonly used pharmaceutical analytical techniques include, thermal techniques such as Differential Scanning Calorimetry (DSC), Thermogravimetric Analysis (TGA), Isothermal Microcalorimetry (IMC) and Hot stage microscopy (HSM) etc, and non-thermal techniques such as UV-Visible Spectrophotometric (UV), Infrared, Near-Infrared and Raman Spectroscopy (FT-IR), (NIR), Powder *X*-Ray Diffraction (PXRD), Solid-State Nuclear Magnetic Resonance Spectroscopy (ssNMR), Microscopic techniques: Scanning Electron Microscopy (SEM), Chromatographic

techniques: Thin Layer Chromatography (TLC), and High-Performance Liquid Chromatography (HPLC) etc.

Preformulation parameters: According to dosage form of API, mainly solid state, particle size, shape, pKa, pH determination, common ion effect, temperature, partition coefficient, solubility studies, dissolution rate, melting point, powder flow properties, crystallinity, polymorphism, hygroscopicity, stability study and drug-excipient compatibility etc. While other dosage forms according to important of preformulation parameters used in study before start in development of formulation.

Drug-excipient compatibility and formulation stability is not depended on API only but also its affected by excipient. Excipient play important role in dosage form but side by side it also increases compatibility problem so proper selection of excipient is very important in development of formulation. Incompatibility can be result mainly in any of following changes: Changes in organoleptic properties, changes in dissolution performance, decrease in potency, and increase in degradation rate etc.

Drug excipient physicochemical characterization is a systematic approach towards design of therapeutically active and stable dosage forms. The rapid advancements in novel drug delivery systems development have led to an interest by formulation scientists in the role and functionality of the excipients.

In the present study, it was proposed to Clopidogrel-excipient compatibility studies of the safety, efficacy, quality and stability of a formulation are major concepts of any API development process. In API development process, a detailed characterization of the API and other formulation components is usually carried out during the preformulation stage, with commonly different excipients using for formulation development of Orodispersible tablets ODTs.

MATERIALS AND METHODS

As shown in Table 1.

Table 1: List of Materials Used.

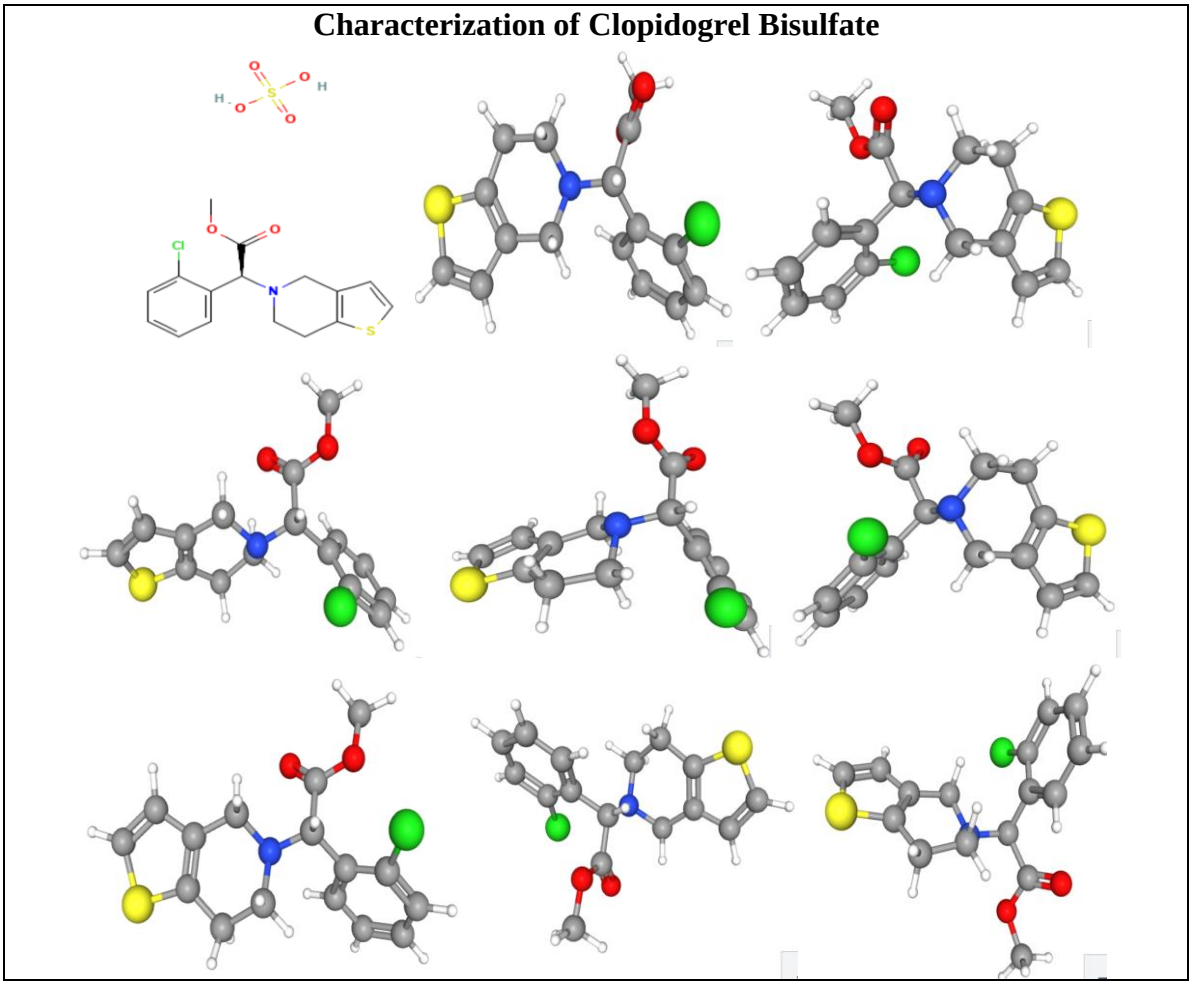
NO	Materials
1	Clopidogrel Bisulfate
2	Avicel PH101
3	Crospovidone

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)
All materials were gift from (Shaphaco Pharmaceutical Industry Company-Yemen).	

Evaluation of Drug-Excipient Compatibility Studies Methods [50-182]

Table 2: Clopidogrel bisulfate data.

Characterization of Clopidogrel Bisulfate



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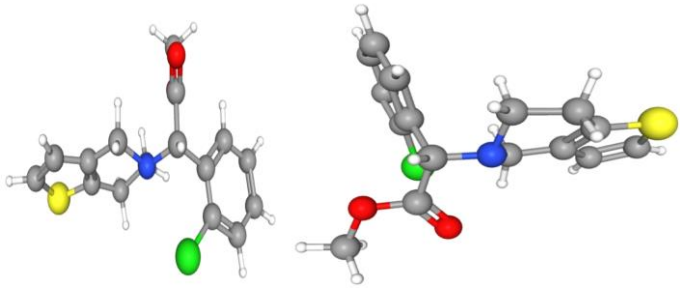
<tr><td colspan="4"> 
Clopidogrel Bisulfate Structure and 3D Conformer</td></tr>
<tr><td>Chemical Structure</td><td>(S)-methyl (2-chlorophenyl) (6, 7-dihydro-4H-thieno [3, 2-c] pyridin-5-yl) acetate hydrogensulfate.</td><td>Appearance</td><td>White to off white powder.</td></tr>
<tr><td>Chemical Formula</td><td>C16H18CINO6S2</td><td>Drug Solubility</td><td>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.</td></tr>
<tr><td>Molecular Weight</td><td>419.9 g/mol</td><td>BCS</td><td>Class-II Drug</td></tr>
<tr><td>Drug Action and Use</td><td colspan="3">P2Y12 inhibitor, Anti-platelets.
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 300-mg is followed by 75 mg once daily). The active metabolite has an elimination half-life of about six hours and acts by forming a disulfide bridge with the platelet ADP receptor. Present for treatment with a myocardial infarction with ST-elevation including a loading dose given in advance of percutaneous coronary intervention (PCI), followed by a full year of treatment for those receiving a vascular stent. A loading dose given in advance of fibrinolytic therapy, continued for at least 14 days .</td></tr>
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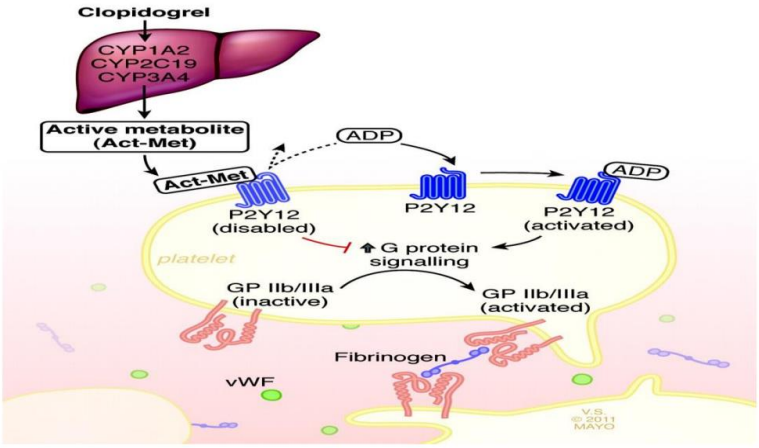
<tr><td></td><td colspan="3"> 
</td></tr>
<tr><td colspan="4">Clopidogrel Pharmacokinetics</td></tr>
<tr><td>Drug Absorption</td><td>Bioavailability: >50%
Clopidogrel is rapidly absorbed after oral administration of repeated doses of 75-milligram clopidogrel (base), with peak plasma levels (about 3 mg/l) of the main circulating metabolite occurring around one hour after dosing.</td><td>Drug Distribution</td><td>Protein binding: 94–98%</td></tr>
<tr><td>Drug Metabolism</td><td>Metabolism: Hepatic
Clopidogrel is a prodrug and activated in the liver by cytochrome P450 enzymes, including CYP2C19. Clopidogrel (top left) being activated: The first step is an oxidation mediated (mainly) by CYP2C19, unlike the activation of the related drug prasugrel.
The active metabolite has an elimination half-life of about six hours and acts by forming a disulfide bridge with the platelet ADP receptor.</td><td>Drug Excretion</td><td>Excretion: 50% renal and 46% biliary.</td></tr>
<tr><td>The Elimination Half-Life (T1/2)</td><td>The elimination half-life is 7–8 hours (inactive metabolite)</td><td>Availability</td><td>Tablets</td></tr>
</table>

Table 3: Pharmaceutical excipients data.

Nonproprietary Name	Chemical Name	Functional Category	Concentration %	Solubility	Incompatibilities	Notes
Sodium Starch Glycolate (Explotab)	Sodium carboxymethyl starch	Tablet and capsule disintegrant.	2–8%	Gives a translucent suspension in water	Incompatible with ascorbic acid.	Very hygroscopic
Croscarmellose Sodium (Ac-Di-Sol)	Cellulose, carboxymethyl ether, sodium salt, crosslinked	Tablet and capsule disintegrant.	0.5-5% 10-25%	Insoluble in water	Incompatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.	White or grayish-white powder
Microcrystalline Cellulose (Avicel)	Cellulose	Adsorbent, suspending agent, tablet and capsule diluent; tablet disintegrant.	5–20% 20–90%	Practically insoluble in water	Incompatible with strong oxidizing agents.	Crystalline powder
Crospovidone (PVPP)	1-Ethenyl-2-pyrrolidinone homopolymer	Tablet disintegrant.	2–5%	Practically insoluble in water	Compatible with most organic and inorganic pharmaceutical ingredients.	Hygroscopic powder
Mannitol (Emprove)	Mannitol	Diluent, plasticizer, sweetening agent, tablet and capsule diluent, therapeutic agent, tonicity agent.	10–90%	Freely soluble in water	Incompatible with may be salted out by potassium chloride or sodium chloride. Sodium cephapirin. xylitol infusion and may form complexes with some metals such as aluminum, copper, and iron.	Crystalline powder

Magnesium Stearate (magnesium salt)	Octadecanoic acid magnesium salt	Tablet and capsule lubricant.	0.25 - 5.0%	Practically insoluble in water	Incompatible with strong acids, alkalis, and iron salts.	Greasy
Talc	Altalc, E553b, hydrous magnesium calcium silicate, hydrous magnesium silicate, Luzenac Pharma, magnesium hydrogen metasilicate. Mg6(Si2O5)4(OH)4.	Anticaking agent, glidant, diluent, lubricant.	1.0–10.0% 5.0–30.0%	Practically insoluble in dilute acids and alkalis, organic solvents, and water.	Incompatible with quaternary ammonium compounds.	is a very fine, white to grayish-white, crystalline powder.
Lactose Anhydrous (Anhydrous Lactose)	O-b-D-Galactopyranosyl-(1!4)-b-D-glucopyranose]	Directly compressible tablet excipient, dry powder inhaler carrier, lyophilization aid, tablet and capsule diluent, tablet and capsule filler.	widely used in pharmaceutical formulations	Soluble in water	incompatible with strong oxidizers. When mixtures containing a hydrophobic leukotriene antagonist. -hydrolysis of the ester and amidine groups.	white to off-white crystalline particles or powder.
Saccharin Sodium	1,2-Benzisothiazolin-3-one 1,1-dioxide, sodium salt, Crystallose, E954, gendorf 450, sucaryl sodium	Sweetening agent. Saccharin can be used to mask some unpleasant taste characteristics or to enhance flavor systems. Its sweetening power is approximately 300–600 times that of sucrose.	0.02–0.5% w/w.	Readily dissolved by dilute ammonia solutions, alkali hydroxide solutions, or alkali carbonate solutions. 1 in 290 water.	Saccharin can react with large molecules. Saccharin sodium does not undergo Maillard browning.	White crystals or a white crystalline powder.
PVP K30	E1201, Kollidon, Plasdone,	Disintegrant, tablet binder.	2.0–5.0	Greater than 10% solubility in	Compatible in solution with a wide	White to yellowish-white

	polyvidone, polyvinylpyrrolidone, PVP;1vinyl-2-pyrrolidinone polymer.			water, methanol, PG.	range of inorganic salts, natural and synthetic resins, and other chemicals.	amorphous powder.

According to Clopidogrel and excipients data as shown in Tables 2 and 3, it was selected that the different excipients to preformulation study with Clopidogrel in the present study, the equipments used as shown in Table 4.

Table 4: List of Equipment's Used.

NO	Equipment's
1	Balance (Sartorius).
2	Oven (Incubator) by STUART scientific.
3	PH Meter (HANNA)
4	Fourier Transform Infrared Spectrometer (FT/IR-4200) made by JASCO
5	UV/VIS –Spectrophotometer (V-530). made by JASCO
6	Melting Point Tester. (automatic melting point) SMP40
7	Tablet Machine (CIP machineries PVT.LTD). Table machine (Rimek)
8	Digital Over Head Stirrer

Preformulation studies

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. Solubility specification of drugs as shown in Table 5.

Table 5: Solubility specification of drugs.

Solubility	Approximate Volume of Solvent in ml per gm of Solute
Excellent	Less than 1
Very soluble	1 to 10
Freely soluble	10 to 30
Soluble	30 to 100
Sparingly soluble	30 to 100

Slightly soluble	1000 to 10000
Very slightly soluble	1000 to 10000
Practically insoluble/ Insoluble	More than 10000

UV-Visible Spectrophotometric Method

UV Scanning of Clopidogrel in 0.1 N HCl and Phosphate Buffer at H 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 curve: 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.

Preformulation studies

Preformulation studies are initiated to define the physical and chemical properties of the agent. The key goals of preformulation studies are to ensure the delivery of drug product with acceptable stability, bioavailability, and manufacturability.

Melting point determination of clopidogrel

The most common and most basic method of determination is the capillary method. Melting point of the Clopidogrel was determined by capillary method; one sided closed capillary filled with drug and put into the Melting Point Apparatus. Temperature was noted at which solid drug changed into liquid.

Drug-Excipient compatibility studies

A physical mixture including Clopidogrel and excipient was created in a 1:1 ratio, and it was subjected to analytical techniques such as FTIR spectroscopy. FTIR, of both pure drug and physical mixes were obtained, and the spectra of the both drug and mixture of excipient with drug were compared to look for any incompatibilities.

FTIR Spectroscopy Study

FTIR study KBr-disc method was used to record the FTIR spectra and KBr pellets were made in 1:100 ratio of sample and KBr. FTIR spectra was recorded using FTIR spectrum in a range of 4000-400cm^{-1}. Different functional groups of test compound for distinctive vibrational frequencies are identified using FTIR spectroscopy. FTIR spectra were used for the investigation of interaction in the physical mixture of API and excipient through shifting of peaks to lower or higher wavenumbers and appearance or disappearance of characteristic peaks of functional groups for pure API in physical mixture. FTIR spectroscopic study was performed to check the compatibility between API, and different excipients in amount (5mg:5mg) as ratio (1:1) as shown in Table 6. The FTIR spectra of a API alone and API with excipients were obtained by KBr method and compared with the standard FTIR spectrum of the pure API. Infrared spectrophotometer is not only used for determining the compatibility of excipients with the APIs, but also for API identification.

Infrared spectral study of samples in room condition

Compatibility studies were performed by preparing blend of different excipients with Clopidogrel in room condition as shown in Table 6.

Table 6: Samples of Clopidogrel and Different Excipients for Compatibility Studies.

No	Component(s)	Amount(5mg:5mg)
1	Clopidogrel	1
2	Clopidogrel and Avicel PH 101	(1:1)
3	Clopidogrel and SSG	(1:1)
4	Clopidogrel and Lactose	(1:1)

5	Clopidogrel and Mannitol	(1:1)
6	Clopidogrel and Crospovidone	(1:1)
7	Clopidogrel and PEG	(1:1)
8	Clopidogrel and CCS	(1:1)
9	Clopidogrel and Saccharin Sodium	(1:1)
10	Clopidogrel and Mg. Stearate	(1:1)
11	Clopidogrel and PVPK30	(1:1)
12	Clopidogrel and Calcium Carbonate	(1:1)
13	Clopidogrel and Talc	(1:1)
14	Clopidogrel and All Excipients	(1:1)

Formulation of Orodispersible Tablets ODTs

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 7 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 7: 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	5.2	5.2	5.2	5.2	5.2	5.2	5.2	5.2	12.27

Sodium									
PEG	----	----	----	----	----	----	----	----	30
Calcium Carbonate	----	----	----	----	----	----	----	----	39.35
PVP K30	----	----	----	----	----	----	----	----	6.13
Mannitol	----	----	----	----	----	----	----	----	6.13
Flavor (Peppermint)	2	2	2	2	2	2	2	2	2

Evaluation of Pre-Compression Parameters of Formulations

Bulk density

Bulk density (ρb) was determined by placing pre sieved drug excipients mixture into a graduated cylinder and measuring the volume (Vb) and weight (M).

ρb = M/Vb.

Tapped density

The measuring cylinder containing a known quantity of blend was tapped for a fixed number of taps. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the drug excipients mixture was measured. The tapped density (ρt) was calculated using the following formula. ρt = M/Vt.

Angle of repose

Angle of repose (**θ**) was determined using funnel method. The drug excipients mixture was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the pile (r) was measured and the angle of repose was calculated. **θ** = tan -1 (h/r). As shown in Table 6.

Carr's index

Carr's Index or % compressibility is helpful to determine flow properties of powder mixtures, which is calculated as follows:

C = (ρt–ρb)/ρt X 100 Where, ρt - Tapped density, ρb -Untapped bulk density.

Hausner's ratio

Hausner's ratio is an index of ease of powder flow; it is calculated by the following formula.

Hausner's ratio = ρt\ ρb Where, ρt - Tapped density ρb - Bulk density. As shown in Tables 8 and 9.

Table 8: Powder flow properties.

Description of flow	Angle of Repose (θ)
Excellent	≤25
Very Good	25 – 30
Good	31 – 35
Fair	36 – 40
Passable (But flow aid might be needed)	41 – 45
Poor (Agitation or vibration needed)	46 – 55
Very Poor	>56

Table 9: Powder flow properties.

Description of flow	Carr's Index (%)	Hausner Ratio
Excellent	≤10	1.00 – 1.11
Good	11 – 15	1.12 – 1.18
Fair	16 – 20	1.19 – 1.25
Passable	21 – 25	1.26 – 1.34
Poor	26 – 31	1.35 – 1.45
Very Poor	32 – 39	1.46 – 1.59
Very, Very Poor	>40	>1.60

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 45C° 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).

RESULTS AND DISCUSSION

Preformulation studies

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 10.

Table 10: 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

Characterization of Clopidogrel by UV Spectroscopy

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 were shown in Table 11, Figure 1, and Table 12, Figure 2.

Table 11: Calibration Curve Results of Clopidogrel Bisulfate in 0.1N HCl.

NO	Concentration µg/ml	Absorbance
1	2.5	0.0781
2	5	0.1682
3	10	0.3683
4	15	0.5712
5	20	0.7546

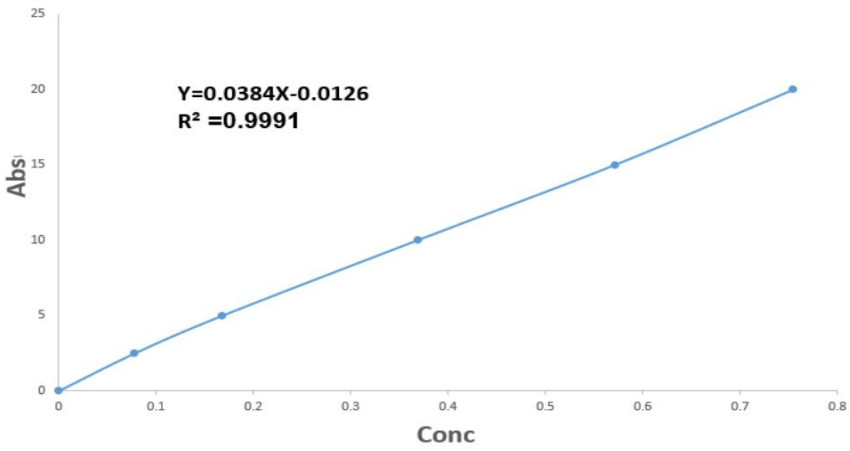


Fig. 1: Calibration Curve of Clopidogrel Bisulfate in 0.1N HCl.

Table 12: Calibration Curve Results of Clopidogrel Bisulfate in Phosphate Buffer at pH 6.8.

NO	Concentration µg/ml	Absorbance
1	5	0.0921
2	10	0.2120
3	15	0.3199
4	20	0.4355
5	25	0.5522
6	30	0.6597

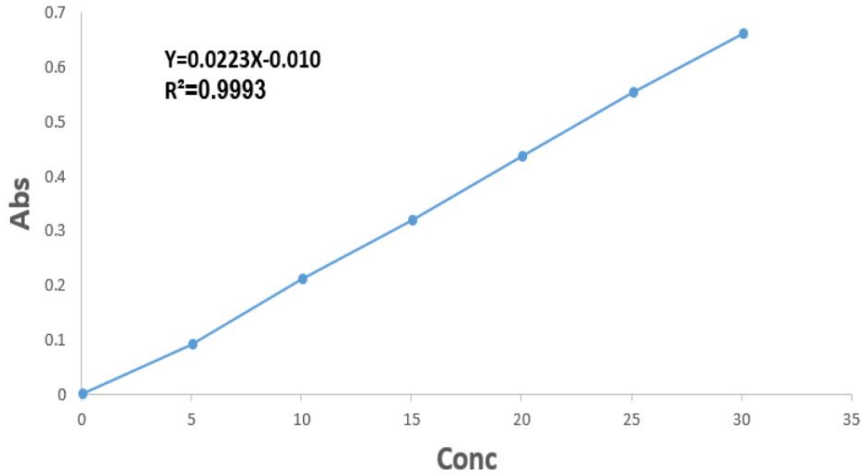


Fig. 2: Calibration Curve Clopidogrel Bisulfate at Phosphate BufferpH6.8.

Melting point determination of clopidogrel

Melting point of pure Clopidogrel was determined by open capillary method. The capillary tube was closed at one end by fusion and was filled with Clopidogrel by repeated tapings. The capillary tube was placed in a digital melting point apparatus. The instrument was set to automatically increase the temperature of the heating bath. The rise in temperature was viewed through screen. The temperature at which the drug started d melting was recorded. The melting point range of Clopidogrel was identical to reference melting point stated in MP (178.5 -179.4°C). The sample started to melt at 178.5°C, and turned into liquid at 178.95°C, indicating that the sample used is pure. That reading has stated in melting point tester.as shown in Table 13.

Table 13: Results of melting point of clopidogrel.

Test	Temp Rang Analyzed (Melting)	Results
Test I Clopidogrel	(178.5 -179.4°C)	178.95°C
Test II Clopidogrel	(178.5 -179.4°C)	178.95°C

Characterization of Clopidogrel by FTIR

FTIR spectrum studies indicated that major functional groups present in Clopidogrel show characteristic peaks in IR spectrum. Figures (3) to (14) show peaks observed at different wave numbers and the functional group associated with these peaks for drug and drug with different excipients. The major peaks are identical to functional group of Clopidogrel. Hence, it was confirmed that there was compatibility between drug and various excipients, thus conforming that no interaction of drug occurred with the components of the formulation excipients.

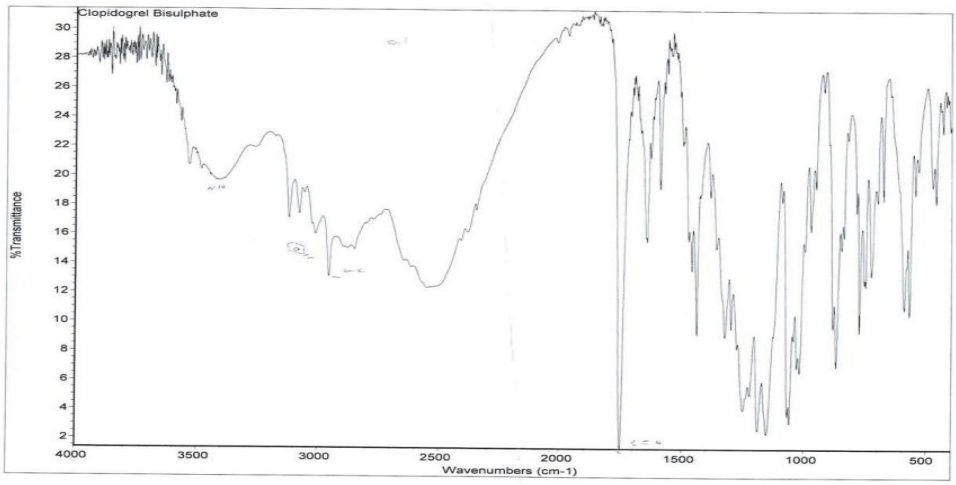


Fig. 3: FTIR Spectrum of Pure Clopidogrel.

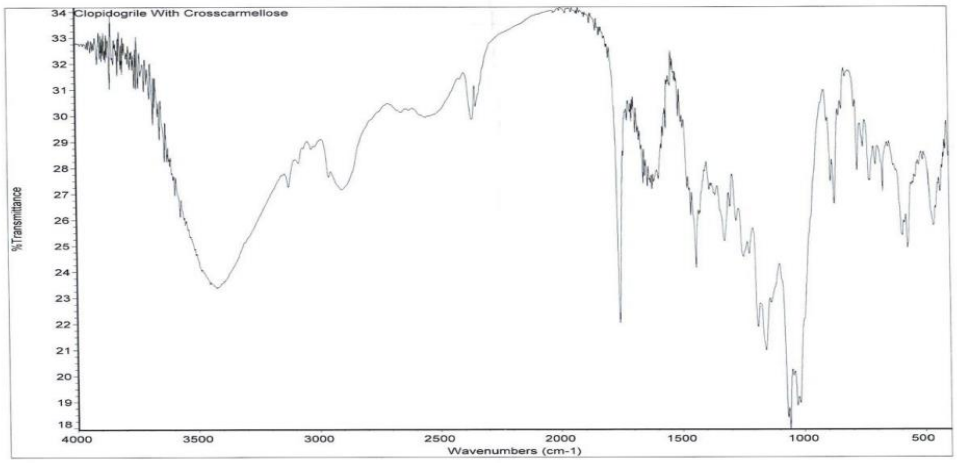


Fig. 4: FTIR Spectrum of Physical Mixture Clopidogrel and CCS.

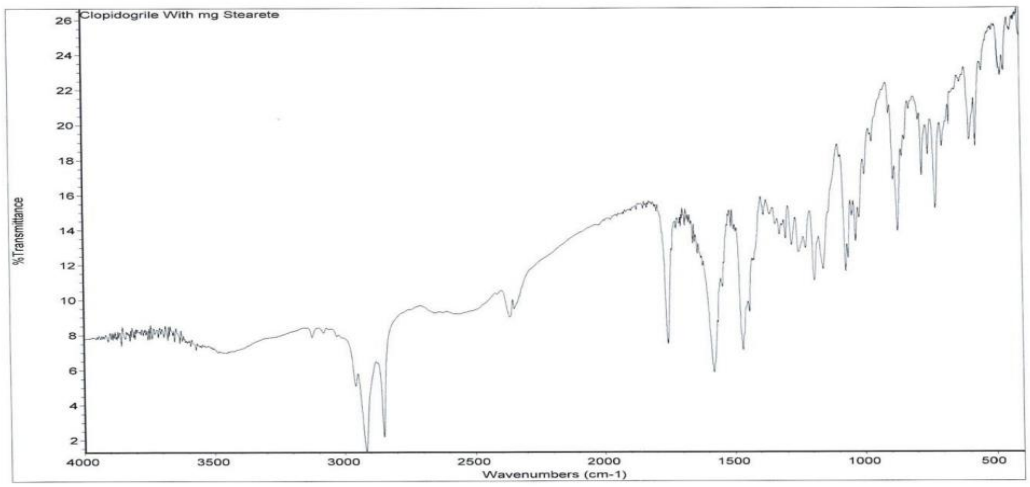


Fig. 5: FTIR Spectrum of Physical Mixture Clopidogrel and Mg Stearate.

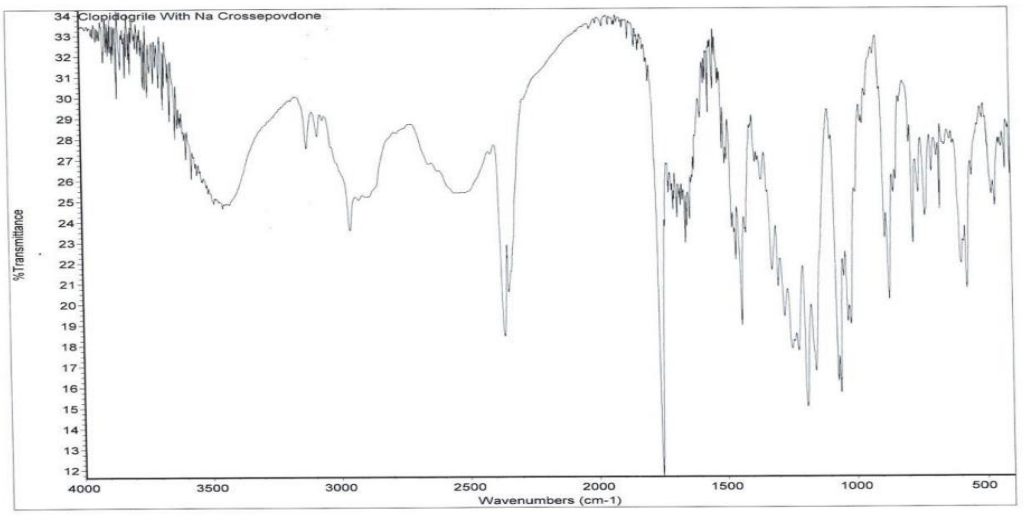


Fig. 6: FTIR Spectrum of Physical Mixture Clopidogrel and Crospovidone.

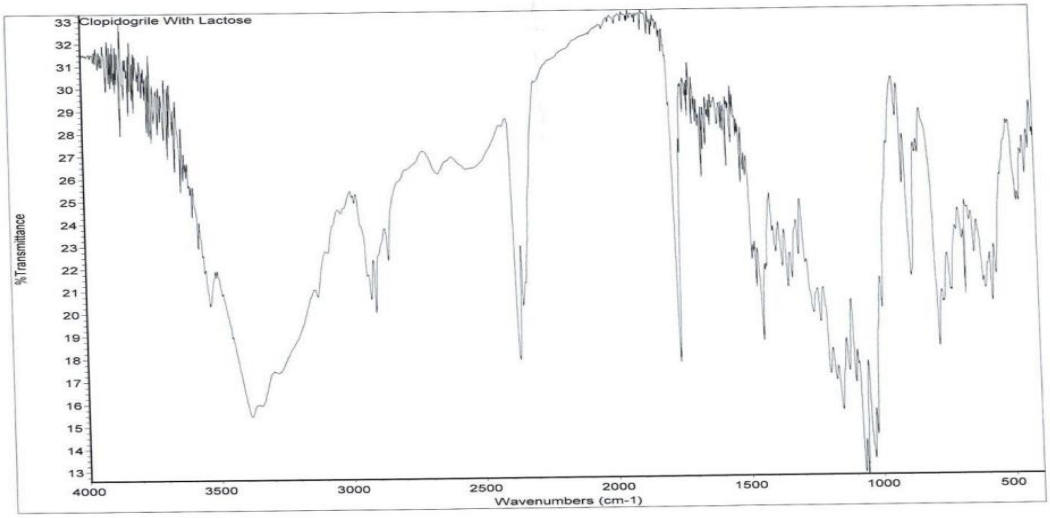


Fig. 7: FTIR Spectrum of Physical Mixture Clopidogrel and Lactose.

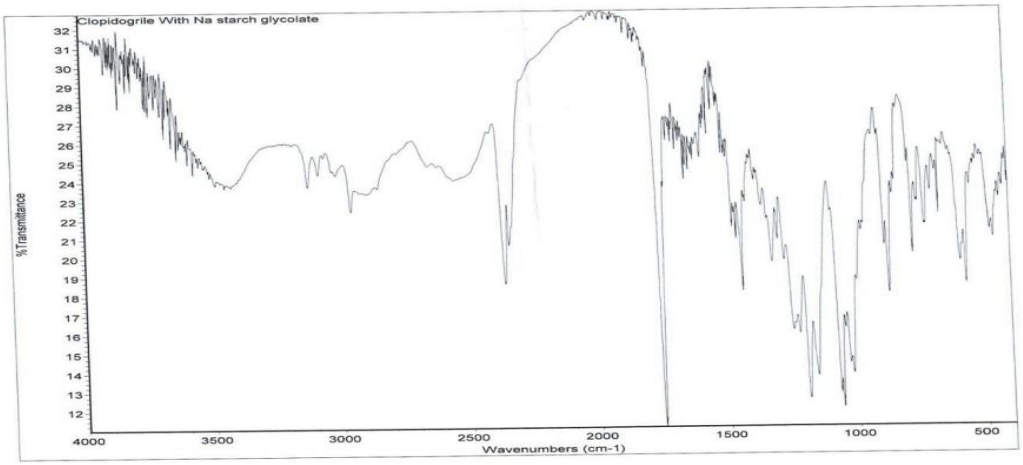


Fig. 8: FTIR Spectrum of Physical Mixture Clopidogrel and SSG.

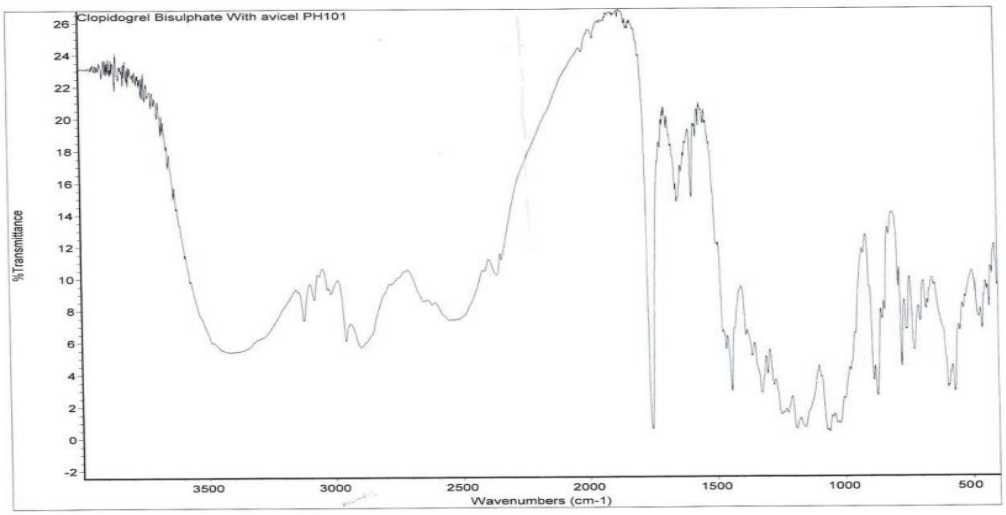


Fig. 9: FTIR Spectrum of Physical Mixture Clopidogrel and Avicel PH101.

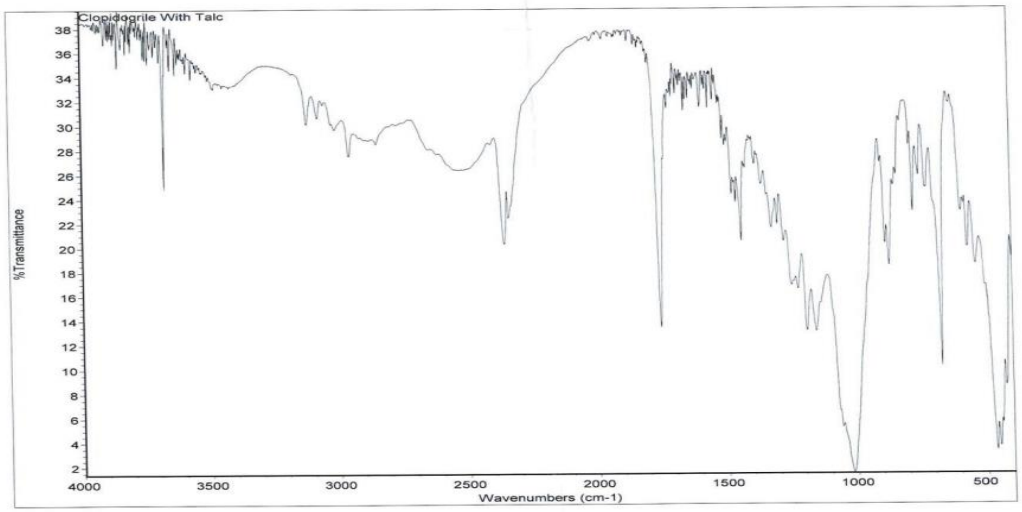


Fig. 10: FTIR Spectrum of Physical Mixture Clopidogrel and Talc.

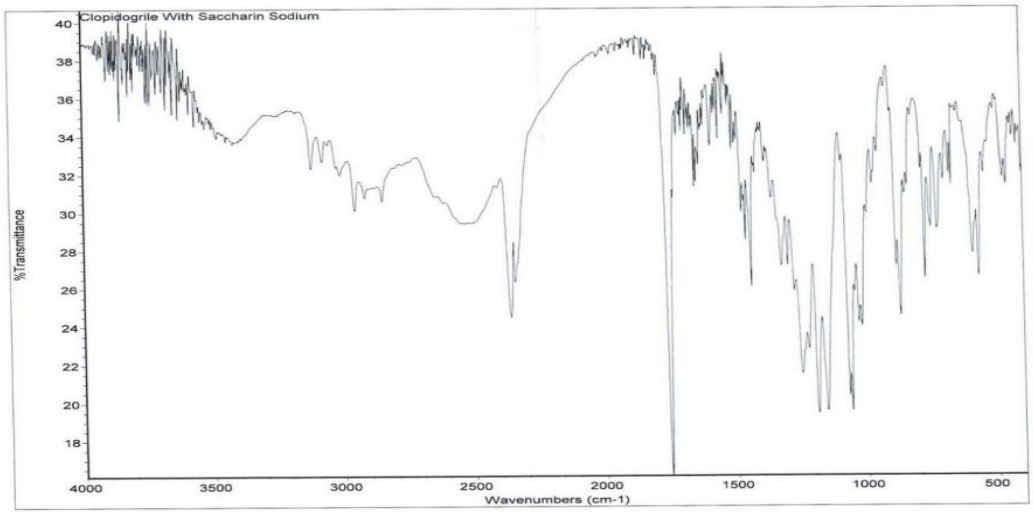


Fig. 11: FTIR Spectrum of Physical Mixture Clopidogrel and Saccharin Sodium.

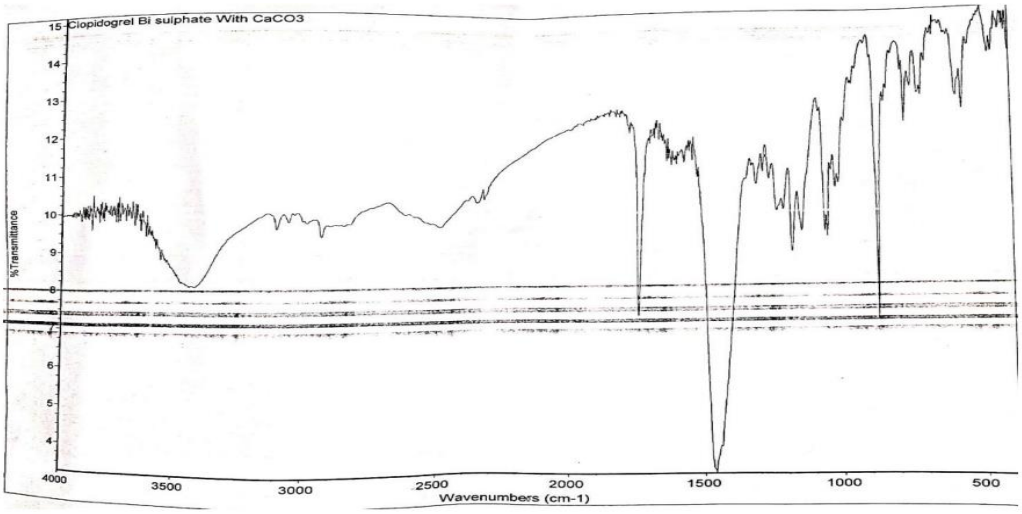


Fig. 12: FTIR Spectrum of Physical Mixture Clopidogrel and CaCO3.

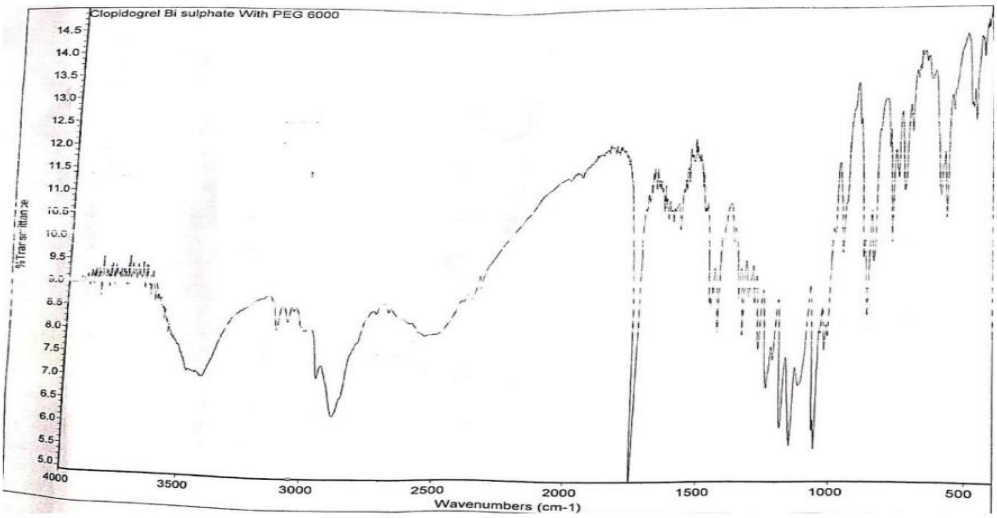


Fig. 13: FTIR Spectrum of Physical Mixture Clopidogrel and PEG6000.

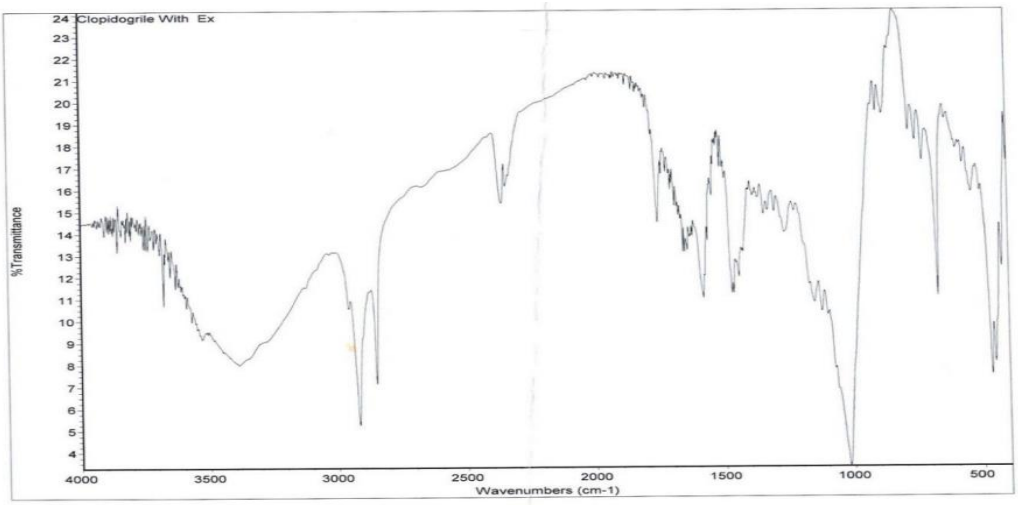


Fig. 14: FTIR Spectrum of Physical Mixture Clopidogrel and All Excipients.

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 14.

Table 14: 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

CONCLUSION

The compatibility studies of physical mixtures of Clopidogrel with different used excipients such as lactose, and avicel PH 101 as diluents, and sodium starch glycolate, croscarmellose sodium, and crospovidone as superdisintegrants were investigated by FTIR it was detected that there was no variation or minor deviation in the characteristic peaks in FTIR spectroscopy. The Clopidogrel formulations prepared were evaluated for precompression parameters and powder flow properties which were found to be within limits. It was

concluded that the drug Clopidogrel was found to be compatible with various excipients which were selected for the formulation development of the Clopidogrel ODTs. Formulation scientist from his experience and knowledge have to significantly in the preformulation study stage and is an important factor in the ADDS (Advanced Drug Delivery Systems) product development process.

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