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FORMULATION AND EVALUATION OF TICAGRELOR ORODISPERSIBLE TABLETS

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ABSTRACT

Orodispersible drug-delivery system server major benefit over the conventional dosage forms because the drug disintegrate rapidly and dissolve in saliva without the use of water. Ticagrelor is one of the most recent antiplatelet agents used to inhibit platelet aggregation via blocking the Adenosine diphosphate (ADP) receptors of the subtype P2Y12, it used in patients with a history of myocardial infarction or with acute coronary syndrome (ACS) to prevent future myocardial infarction, stroke and cardiovascular death. Ticagrelor is used to prevent a serious or life-threatening heart attack or stroke, or death in people who have had a heart attack or who have acute coronary syndrome (ACS; blockage of blood flow to the heart). The present study is directed towards the development of formulation and evaluation of Ticagrelor Orodispersible tablets to improve the bioavailability of ticagrelor which shows 36% as ticagrelor is classified as a biopharmaceutics classification system (BCS) class IV drug with highly lipophilic having poor aqueous solubility and permeability increasing the solubility, improve the bioavailability and onset of action Ticagrelor has been done. The ODTs of various batches were prepared by using various concentrations of various superdisintegrants like sodium starch glycolate, crospovidone and croscarmellose sodium by direct compression and wet granulation method. In the initial preparation of formulation, we initially used the direct compression method for preparing F1 and F2, but its flowability was found to be weak. Therefore, we adopted the wet granulation method. In this study eleven formulations were prepared using certain selective excipients. All the prepared ODT formulations were

evaluated for physical characteristics, disintegration, *in-vitro* dissolution, The hardness and the friability. The *in-vitro* dispersion time of all the formulation was done and in-*vitro* dissolution study of all the formulations was carried out for 5, 15 and 30 minutes according to the results formulation F11 was found as the best formulation which showed 101.45% drug release at 5 minutes and minimum disintegration time of 18 sec. It was concluded that F11 is the best formulation of Ticagrelor Orodispersible tablets in order to enhance the bioavailability of drug.

KEYWORDS: Ticagrelor, Drug delivery system, Orodispersible tablets, Superdisintegrants.

INTRODUCTION

Oral drug delivery is currently the gold standard in the pharmaceutical industry where it is regarded as the safest, the most convenient and most economical method of drug delivery with the highest patient compliance. Oral route is the most preferred route of administration and tablet and capsules are the most preferred dosage forms, but several limitations of that kind of dosage forms like chocking and swelling discomfort in geriatric and pediatric patients. Orodispersible tablets have been developed and new ODTs technologies compensate many pharmaceuticals and patients' needs, ranging from enhanced life-cycle management to convenient dosing for pediatric, geriatric, and psychiatric patients with dysphasia. Over the past three decades, Orodispersible tablets (ODTs) have gained considerable attention as a preferred alternative to conventional tablets and capsules due to better patient compliance.[1-4]

Ideal Characteristics of Orodispersible Tablets[2-5]

ODTs should depict some ideal characteristics to distinguish them from traditional conventional dosage forms. Important desirable characteristics of these dosage forms include: Require no water for oral administration, easily dissolve or disperse in saliva within a few seconds, have a pleasing taste, leave negligible or no residue in the mouth when administered, Portable and easy to transport, able to be manufactured in a simple conventional manner within low cost, permit the manufacture of tablet using conventional processing and it should be compatible with taste masking.

Advantages of Orodispersible Tablets[1-5]

ODTs provide advantageous dosage forms for the oral drug delivery of certain drugs, which have limited bioavailability such as protein and peptide-based therapeutics, ODTs usually offers many biopharmaceutical advantages such as faster onset of action, improved efficiency

over conventional dosage forms, less side effects etc. Low drug dose is required and is found to be more effective than conventional dosage forms like tablets and capsules, and it is observed that this small dose shows better bioavailability and improved dissolution profiles. Achieve increased bioavailability/rapid absorption through pre-gastric absorption of drugs from mouth, pharynx and esophagus as saliva passes down. Rapid disintegration of tablet results in quick dissolution and rapid absorption, which provide rapid onset of action. Pregastric absorption of drugs avoids hepatic metabolism, which reduces the dose and increase the bioavailability. Free from risk of suffocation due to physical obstruction when swallowed, thus offering improved safety. Not requirement of water or other liquid to swallow. It has acceptable taste and pleasant mouth feeling, no residue in the mouth after oral administration. Administration to the patients who cannot swallow, such as the elderly, stroke victims, bedridden patients, patients affected by renal failure and patients who refuse to swallow such as pediatric, geriatric and psychiatric patients. ODTs are stable for long time, as the drug is in solid dosage form till patient consumes it. Accurate dosing as compared to liquids. ODTs opened new business opportunity like product differentiation, product promotion, patent extension and life cycle management. Suitable during traveling where water may not be available. No specific packaging required can be packaged in push through blisters. Conventional manufacturing equipment. Cost effective. Good chemical stability as conventional oral solid dosage form. Rapid drug therapy intervention and adaptable and amenable to existing processing and packaging machinery.

Challenges in Formulation of Orodispersible Tablets[4-7]

The following are some of the challenges involved in formulation of Orodispersible tablets: Mechanical strength and disintegration time: Mechanical strength of the tablets should be maintained, as it is accepted that on increasing the mechanical strength, disintegration time is delayed. To allow good disintegration in oral cavity, ODTs should be made with very low compression force.

Taste masking: In case of unpalatable drugs, taste masked form of medicament for rapid drug delivery is preferred. Drug delivery system releases active ingredients by disintegrating or dissolving in the oral cavity. Hence, taste masking is very critical step to provide patient compliance. Aqueous solubility: Water soluble drugs forms eutectic mixtures, so they form glassy solid which may break on drying due to lack of supporting structure during sublimation method, so this presents various formulation challenges for manufacturers.

Mouth feel: ODTs should be disintegrated into smaller fragments in the patient's oral cavity. For patient's palatability, generated fragments should not be large as well as the taste of drug should not be too bitter.

Hygroscopicity: Orodispersible tablets should have less sensitivity to humidity. This might be challenging task for manufacturer as various hydrophilic excipients are added in the formulation in order to get faster dissolution. Hence, ODTs usually need higher protection from humidity. Amount of drug: Amount of drug that has to be incorporated in each unit dose can be a limitation factor for development of ODTs. Quantity of drug in lyophilization technology should be less than 400mg and 60mg for insoluble drugs and soluble drugs respectively.

Size of tablet: Tablet size should be selected by considering its ingestion as well as handling. Reported size of tablet to swallow is 7-8 mm, but for handling purpose it should be larger than 8 mm. So, the tablet size which is easy to take and handle is difficult to achieve. Environmental conditions: ODTs are meant to dissolve in minimum quantity of water, so many excipients are added which may be sensitive to environmental condition such as temperature and humidity.

Mechanisms of ODTs[2-6]

ODTs involve the following mechanisms to achieve the desired fast dissolving characteristics: Water must quickly enter into the tablet matrix to cause rapid disintegration and instantaneous dissolution of the tablet. Incorporation of an appropriate disintegrating agent or highly water-soluble excipients in the tablet formulation. There are some under mentioned mechanisms by which the tablet is broken down into the smaller particles and then subsequently result a solution or suspension of the drug. The mechanisms are high swellability of disintegration, chemical reaction and capillary action.

Drug Selection Criteria for Orodispersible Tablets Formulation[1-7]

There are several factors that should be considered while selecting an appropriate drug candidate in formulation of Orodispersible tablets. For example, the drug should have the ability to permeate the oral mucosa with good solubility in water and saliva. Dose of the drug should be lower in ODTs (preferably less than 50 mg). It should be partially non-ionized at oral cavity pH. It should possess the ability to diffuse into the epithelium of the upper GIT. Drugs which need frequent dosing.

Techniques for Preparation of ODTs[2-21]

The techniques used to manufacture ODTs can be classified as: Conventional techniques and patented techniques.

Conventional Techniques

The various conventional technologies are developed for the preparation of Orally Disintegrating drug delivery system that are Freeze drying, spray drying, molding, Phase transition process, melt granulation, sublimation, mass extrusion, cotton candy process, direct compression. Detail of all these conventional techniques as given in Table 1.

Patent Techniques

Rapid-dissolving characteristic of ODTs is generally attributed to fast penetration of water into tablet matrix resulting in its fast disintegration. Several technologies have been developed on the basis of formulation aspects and different processes and resulting dosage forms vary on several parameters like mechanical strength, porosity, dose, stability, taste, mouth feel, dissolution rate and overall bioavailability. Table 2 represents the list of unique patent technologies, their advantages and disadvantages.

Table 1: Conventional Techniques used for the Preparation of ODTs.

S. NO	Techniques	Method and characteristics of prepared ODTs
1	**Disintegrant Addition**	Involves the addition of superdisintegrants in optimum concentration to the formulation to achieve rapid disintegration/dissolution. For e.g. MCC and sodium starch glycolate are used in formulation of Efavirenz, Crystalline cellulose (AvicelPH-102) and low substituted HPEC used in oxybutinin and pirenzepine formulation. Crospovidone used in galanthamine HBr. Crospovidone (3%w/w) and crosscarmellose Na (5%w/w) used in prochlorperazine maleate formulation.
2	**Freeze Drying or Lyophilization**	**Characteristics:** similar to conventional tablets with higher % of disintegrants, lower hardness and higher % of friability 2. Freeze Drying or Lyophilization The drug is dissolved or dispersed in an aqueous solution of a carrier. The mixture is poured into the wells of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze drying. Finally, the blisters are packaged and shipped. The preparations are highly porous, have high specific surface area, dissolve rapidly and ultimately show improved absorption and bioavailability. Dose incorporated: insoluble 400mg. Water soluble drug loading: 60mg

		Advantages of Freeze drying • Tablets produced by this technique possess very low disintegration time. • Render tablets with great mouth feel due to fast melting effect. • Provides immediate dissolution (5 sec). • Increases absorption and bioavailability of drug. • Lyophilization is useful for heat a sensitive drug that is thermolabile substances. • Tablets prepared by lyophilization disintegration rapidly in less than 5 secs due to quick penetration of saliva in pores when placed in oral cavity. **Disadvantages of freeze drying** • Relatively expensive and time-consuming process. • The product obtained is poorly stable and fragile, sensitive to humidity rendering conventional packaging unsuitable. • Very poor physical resistance, • High cost of production, • Low dose of water-soluble drugs
3	**Moulding**	Water-soluble ingredients with a hydro alcoholic solvent is used and is molded into tablets under pressure lower than that used in conventional tablet compression. **Characteristics:** Molded tablets are very less compact than compressed tablet porous structure that enhances disintegration/dissolution and finally absorption increased. **Advantages** • Very rapid dissolution (5–15 s) **Disadvantages** • High cost of production, • Weak mechanical strength • Possible limitations in stability.
4	**Sublimation**	Inert solid ingredients that volatilize rapidly like urea, camphor ammonium carbonate, ammonium bicarbonate, and hexamethylenetetramine were added to the other tablet ingredients and the mixture is compressed into tablets. The volatile materials were then removed via sublimation, which generates porous structure. **Characteristics:** Porous structure that enhances dissolution by using volatile material or solvent e.g. cyclohexane, benzene etc. **Advantages:** Good physical resistance & highly porous structure **Disadvantages:** Harmful residual adjuvant, Extra equipments for heating, Not applicable to volatile and heat sensitive drugs.
5	**Spray-Drying**	By hydrolyzed and non hydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate or crosscarmellose sodium as disintegrating agent and an acidic material (e.g. citric acid) and / or alkali material (e.g. Sodium bicarbonate) to enhance disintegration /dissolution.(Mishra DN.et al) Characteristics: Prepared tablet disintegrates within 20 seconds when immersed in an aqueous medium.
6	**Mass Extrusion**	Involves softening the active blend using the solvent mixture of

		water soluble polyethylene glycol, methanol and expulsion of softened mass through the extruder or syringe to get a cylindrical shape of the product into even segments using heated blade to form tablets. Characteristics: The dried product can be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.
7	**Direct Compression**	Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. **Characteristics:** It is most cost-effective tablet manufacturing technique. **Advantages** • Requires fewer unit operations compared with wet Granulation (shorter processing time and lower energy consumption). • Fewer stability issues for actives that are sensitive to heat or moisture. • For certain compounds, faster dissolution rates may be generated from tablets prepared by direct compression compared with wet granulation; for example, Norfloxacin. • Fewer excipients may be needed in a direct compression Formula. **Disadvantages** • Issues with segregation – these can be reduced by matching. • The particle size and density of the active drug substance with excipients. • In general, the drug content is limited to approximately 30% or approximately 50 mg. • Not suited for poorly flowing drug compounds. \• Static charges may develop on the drug particles or excipients during mixing, which may lead to agglomeration of particles producing poor mixing.
8	**Cotton Candy Process**	Involves the formation of matrix of polysaccharides by simultaneous action of flash melting and spinning. This candy floss matrix is then milled and blended with active ingredients and excipients after re-crystallization and subsequently compressed to FDT. **Characteristics:** It can accommodate high doses of drug and offers improved mechanical strength.
9	**Compaction a) Melt Granulation**	Prepared by incorporating a hydrophilic waxy binder (super polystate) PEG-6-stearate. Super polystate not only acts as binder and increase physical resistance of tablet but also helps the disintegration of tablet. **Characteristics:** It melts in the mouth and solubilizes rapidly leaving no residue.
	b) Phase-Transition Process	Prepared by compressing a powder containing two sugar alcohols with high and low melting points and subsequent heating at a temperature between their melting points. The tablet hardness was increased after hearing process due to increase of inter particle bond induced by phase transition of lower melting point sugar alcohol. **Characteristics:** The compatibility increased and so sufficient

		hardness gained by the formulation.
10	**Nanonization**	Involves size reduction of drug to Nano size by milling the drug using a proprietary wet-milling technique. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into ODTs. **Characteristics:** It is used for poorly water soluble drugs. It leads to higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional 999durability and wide range of doses (up to 200 mg of drug per unit).
11	**Fast Dissolving Films**	Involves size reduction of drug to Nano size by milling the drug using a proprietary wet-milling technique. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into ODTs. **Characteristics:** It is used for poorly water soluble drugs. It leads to higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability and wide range of doses (up to 200 mg of drug per unit).
12	**Tableting (Standard)**	**Advantages** • Low cost of production. • Use of standard equipment/materials. • High dose. • Good physical resistance. **Disadvantages** • Significant effects of the size and hardness of the tablets on disintegration property.
13	**Tableting (Effervescent)**	**Advantages** • Use of standard equipment. • High dose Good physical resistance. • Pleasant effervescent mouth feels. **Disadvantages** • Operating in controlled low humidity. • Need of totally impermeable blister.
14	**Tableting (Humidity Treatment)**	**Advantages** • Good physical resistance. • Pleasant mouth feels. **Disadvantages** • Extra equipment for humidification and drying. • Possible limitations in stability. • High cost of production. • Not suitable for moisture sensitive compounds. • Fragile before humidity treatment.

Table 2: Different Patent Techniques for Preparation of ODTs.

S.NO	Technique	Advantages	Disadvantages
1	**Zydis**	Quick dissolution, Self-preserving and increased bioavailability.	Expensive process, poor stability at higher Temperature and humidity.
2	**Orasolv**	Taste-masking is twofold, quick Dissolution.	Low mechanical strength
3	**Durasolv**	Higher mechanical strength than Orasolv, Good rigidity.	Inappropriate with larger dose.
4	**Flashtab**	Only conventional tableting technology	----------
5	**Wow tab**	Adequate dissolution rate and hardness.	No significant change in bioavailability
6	**Oraquick**	Faster and efficient production, appropriate for heat-sensitive drugs	----------
7	**Ziplet**	Good mechanical strength, satisfactory properties can be obtained at high dose (450 mg) and high weight (850 mg).	As soluble component dissolves, rate of water diffusion in to tablet is decreased because of formation of viscous concentrated solution.
8	**Flash Dose**	High surface area for dissolution.	High temperature required to melt the matrix can limit the use of heat-sensitive drugs, sensitive to moisture and humidity.

Ticagrelor Drug Profile[8-20]

Ticagrelor is a platelet aggregation inhibitor. It is used for the Prevention of thrombotic events like stroke, heart attack in people with acute coronary syndrome or myocardial infarction with ST elevation.

Therapeutic category: Antithrombotic agent. Chemical name:(1S,2S,3R,5S)-3-[7-[[(1R,2S)-2-(3,4-difluorophenyl) cyclopropyl] amino]5-Propylsulfanyltriazolo[4,5-d] pyrimidin-3-yl]-5-(2-hydroxyethoxy) cyclopentane-1,2-diol. As shown in Figure 1.

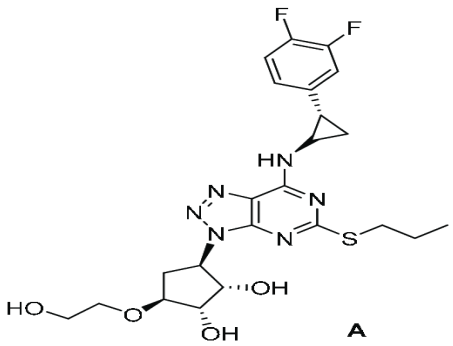

Fig. 1: Chemical Structure of Ticagrelor.

Empirical Formula: C23H28F3N6O4S. Molecular Weight: 522.57 g/mol. Pharmacologic Class P2Y12 receptor antagonist. Adenosine Diphosphate (ADP) receptor inhibitor.

Preparations: Tablets 90mg, 60mg. Description: Physical State: Solid. Color: white or off-white to pale pink crystalline powder. Nature: The molecule has no pKa values within physiological range and does not demonstrate pH dependent solubility. It is non-hygroscopic, exhibiting no significant increase in water content after exposure at 40°C/75% RH. Melting Point: 140-142°C. Log P: The log P (octanol/water) has been measured to > 4.0 at pH 7.4. Bioavailability: 36%. Solubility: Soluble in methanol, ethanol, DMSO, dimethyl Formamide (DMF). It does not exhibit pH dependent solubility in aqueous buffers. Water solubility: The drug substance has low water solubility (0.016 mg/mL at 20 ±5°C). Dose: 60 to 180 mg twice a day orally for one year. Usual strength: 60mg; 90 mg. BCS Class: Ticagrelor is classified as Class IV compound (low solubility, low permeability). Boiling point: 777.6±70°C.

Pharmacokinetics Data: Ticagrelor demonstrates dose proportional pharmacokinetics, which are similar in patients and healthy volunteers. Absorption of drug bioavailability: 36%, peak plasma time Tablets: 1.5hr (Ticagrelor). Distribution of drug: The steady state volume of distribution of ticagrelor is 88 L. Ticagrelor and the active metabolite is extensively bound to human plasma Protein (>99.0).

Metabolism of drug CYP3A is the major enzyme responsible for Ticagrelor metabolism and the formation of the active metabolite and their interactions with other CYP3A substrates ranges from activation through to inhibition. Ticagrelor and the active metabolite are P-glycoprotein weak inhibitors. The major metabolite of Ticagrelor is AR-C124910XX, which is also active as assessed by in vitro binding to the platelet P2Y12ADP-receptor. The systemic exposure to the active metabolite is approximately 30-40% of that obtained for ticagrelor. Excretion of drug.

The primary route of Ticagrelor elimination is hepatic metabolism. When radiolabeled Ticagrelor is administered, the mean recovery of radioactivity is approximately 84% (58% in feces, 26% in urine). Recoveries of Ticagrelor and the active metabolite in urine were both less than 1% of the dose. The primary route of elimination for the major metabolite of Ticagrelor is most likely to be biliary secretion. The mean t1/2 is approximately 7 hours for Ticagrelor and 9 hours for the active metabolite.

Drug Clearance: The systemic clearance of Ticagrelor is 14.2 L/h. Drug Interactions: Avoid use with strong CYP3A inhibitors and strong CYP3A inducers. Ticagrelor is metabolized by CYP3A4/5. Strong inhibitors substantially Increase Ticagrelor exposure and so increase the risk of adverse events. Strong inducers of CYP3A substantially reduce Ticagrelor exposure and so decrease the efficacy of Ticagrelor. Patients receiving more than 40 mg per day of simvastatin or lovastatin May be at increased risk of statin-related adverse events because these Drugs are metabolized by CYP3A4. Ticagrelor inhibits the P-glycoprotein transporter; monitor digoxin levels with initiation of or change in Ticagrelor therapy. Use of Ticagrelor with aspirin maintenance doses above 100 mg reduced the effectiveness of Ticagrelor.

Difficulty in swallowing (dysphagia) is a common problem of all age groups, especially the elderly and pediatrics. Orodispersible drug delivery systems are extensively used to improve bioavailability and patient compliance. The development of Orodispersible tablets (ODTs) has been done for pediatric, geriatric, bedridden and for those patients who may not have access to water. Basically, swallowing problems also are happening in young individuals because of their under developed muscular and nervous systems. In some cases, such as motion sickness, coughing, and unavailability of water, swallowing of conventional tablets may become difficult or improper. ODTs that dissolve or disintegrate rapidly in oral cavity result in solution, and presents an ultimate remedy for this problem. In addition, they give pleasing mouth feeling.

Oral administration of Ticagrelor is associated with bioavailability problem. Bioavailability of the drug is 36% of orally administered dose. In Acute Coronary Syndrome there is increase in blood pressure which may lead to sudden heart attack. Ticagrelor is the drug of choice in Acute Coronary Syndrome. So, the aim of present work was to develop and characterize Orodispersible tablet of Ticagrelor with improved bioavailability.

Develop a formulation of Ticagrelor 90 mg tablets that is equivalent to the reference product using similar excipients to match the in-vitro dissolution profile. A compressed coated tablet was formulated consisting of Ticagrelor and excipients conforming to the USP/BP monograph and below maximum amount allowed per unit dose. The physical characteristics of powder blends were evaluated.[6]

In the present study, it was proposed to formulate Orodispersible tablets of Ticagrelor by using wet granulation and direct compression technique methods, 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.

MATERIALS AND METHODS

Ticagrelor**,** Crospovidone**,** Mannitol**,** Microcrystalline Cellulose (Avicel 102), Croscarmellose Sodium**,** Sodium Starch Glycolate**,** Polyethylene Glycol 6000**,** Sodium Saccharin**,** Magnesium Stearate**,** Hydroxypropyl Cellulose**,** Sodium Lauryl Sulfate (SLS)**,** Tween, Aerosil 200(Colloidal Silicon Dioxide)**,** Poloxmer and Betacyclodixtrin (BCD) were gift from (Global Pharmaceutical Industry Company-Yemen).

Evaluation of Ticagrelor[8-47]

Organoleptic Properties

Organoleptic properties like color, odour and taste of ticagrelor were studied. Color: a small amount of Ticagrelor was taken in paper and investigated by the eye in well-illuminated place. Taste and odour: Very small amount of Ticagrelor was used to assess the taste with the help of tongue as well as smelled to get odor.

Melting Point Determination

The most common and most basic method of determination is the capillary method. Melting point of the Ticagrelor 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.

Solubility Test

Solubility is defined as the number of grams of substance which will dissolve in 100 ml of solvent at a stated temperature. The solubility of drug was studied in different solvents such as methanol, acetate buffer, phosphate buffer, HCL by measuring how many parts of solvent is required for one part of solid. Then analyzed by spectrophotometer. Solubility specification of drugs as shown in Table 3.

Table 3: Solubility Specification of Drugs.

Solubility	Approximate Volume of Solvent in ml per gm of Solute
Very Soluble	Less than 1
Freely Soluble	1 to 10
Soluble	10 to 30
Sparingly Soluble	30 to 100
Slightly Soluble	100 to 1000
Very Slightly Soluble	1000 to 10000
Practically Insoluble	More than 10000

Preparation of Working Solutions

Ticagrelor solubility test is performed in methanol, buffer phosphate pH6.8, acetate buffer pH4.5 and HCl pH1.2.

Preparation of Phosphate Buffer pH 6.8

Dissolving 3.40g of potassium dihydrogen phosphate and 0.45g of hydroxide sodium (NaOH), then complete the volume to 500ml with purified water. Taken 200ml of buffer phosphate and then dissolving 10mg of active ingredient Ticagrelor and shake the volumetric flask by sonicator device. Let the volumetric flask sit undisturbed for several hours to allow any undissolved particles to settle. Filtration of solution that contains the active ingredient, then measure the solubility under UV spectrophotometer.

Preparation of Acetate Buffer pH 4.5

Dissolving 1.495g of sodium acetate trihydrate into 500ml Volumetric flask, add amount of water and add 7ml of 2N of acetate buffer, dilute to volume with purified water and mix. Taken 200ml of acetate buffer and then dissolving 10mg of active ingredient Ticagrelor and shake the volumetric flask by sonicator device. Let the volumetric flask sit undisturbed for several hours to allow any undissolved particles to settle. Filtration of solution that contains the active ingredient, then measure the solubility under UV spectrophotometer.

Preparation of 0.1N HCl

Taken 0.05ml of 0.1N HCl in volumetric flask and complete the volume with purified water to 500ml. Taken 200ml of buffer HCl and then dissolving 10mg of active ingredient Ticagrelor and shake the volumetric flask by sonicator device. Let the volumetric flask sit undisturbed for several hours to allow any undissolved particles to settle. Filtration of solution that contains the active ingredient, then measure the solubility under UV spectrophotometer.

UV Visible Spectrophotometer

UV Scanning of Ticagrelor in 0.1 N HCl

The sample was scanned with UV-V spectrophotometer in the range 200-800nm against 0.1N HCl as blank and the wavelength corresponding to maximum absorbance was noted.

UV Scanning of Ticagrelor in Phosphate Buffer pH 6.8

The sample was scanned with UV-V spectrophotometer in the range 200 -800nm against phosphate buffer pH 6.8 as blank and the wavelength corresponding to maximum absorbance was noted.

UV Scanning of Ticagrelor in Acetate Buffer pH 4.5

The sample was scanned with UV-V spectrophotometer in the range 200_800nm against acetate buffer pH 4.5 as blank and the wavelength corresponding to maximum absorbance was noted.

Formulation of Ticagrelor ODTs

Orodispersible tablets containing 60 mg of Ticagrelor drug were prepared. Considering the preformulation studies achieved and the literature survey conducted the excipients were selected and an attempt to produce Orodispersible tablets.

Formulation of Different Batches[8-47]

Design Processes

Direct Compression and wet granulation techniques was employed for the preparation of Orodispersible tablets. Ticagrelor Orodispersible tablets were prepared in eleven formulations F1 to F11 using the ingredients given in the Table 4. Orodispersible tablets of Ticagrelor were prepared as per the formulation given in Table 4. Accurately weighed quantities of Ticagrelor, mannitol, crospovidone and other excipients were passed through sieve number 25 and mix properly by using geometric mixing. The above blend was granulated with a solution Hydroxylpropyl-cellulose EXF HPC (dissolve HPC in 30 % P.W) then dry in oven. These granules are blended with aerosil 200 and blend properly. After that it was lubricated with magnesium stearate. Then each mixture has compressed by using rotary tablet compression machine of punch size (7.1mm) and (8.5mm) to prepare tablets.

Table 4: Composition of Ticagrelor Formulations ODTs.

Ingredients	Quantity Per Tablet										
	Formulation Code										
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Ticagrelor	60	60	60	60	60	60	60	60	60	60	60
Microcrystalline Cellulose (Avicel 102)	45.75	30	30	45.75	45.75	44.55	43.05	43.05	46.05	46.05	46.69
Mannitol	30	45.75	45.75	30	30	30	30	30	20	20	30
Sodium Starch Glycolate	7.5	7.5	—	—	—	—	—	—	—	—	—
Croscarmellose Sodium	—	—	7.5	7.5	—	5	—	—	5	5	—
Crospovidone (XL)	—	—	—	—	7.5	2.5	7.5	7.5	2.5	2.5	4.5
Hydroxylpropyl - Cellulose EXF	3	3	3	3	3	2.7	2.7	2.7	2.7	2.7	3
Sodium Saccharin	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25
Magnesium Stearate	1	1	1	1	1	1	1	1	1	1	1
Aerosil 200 (Colloidal Silicon Dioxide)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sodium Lauryl Sulfate SLS	—	—	—	—	—	1.5	—	—	—	—	1.5
Tween SD	—	—	—	—	—	—	3	—	—	—	—
Poloxmer	—	—	—	—	—	—	—	3	—	—	—
Polyethylene Glycol PEG 6000	—	—	—	—	—	—	—	—	60	—	—
Beta Cyclodextrin (BCD)	—	—	—	—	—	—	—	—	—	60	—

Evaluation of Ticagrelor Precompression

Micrometric Properties

Angle of Repose (θ)

Angle of repose is determined using fixed funnel method. The blend is poured through a funnel that can be raised vertically until a maximum cone height (h) is obtained. Radius of the heap(r) is measured and angle of repose is calculated using formula: $\theta = \tan^{-1}(h/r)$ Where, θ = angle of repose, h=height of pile, r=radius of the base pile. The relationship between the angle of repose and powder flow is as shown in the Table 5.

Table 5: Flow Properties and Corresponding Angle of Repose.

Flow Property	Angle of Repose
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very Poor	56-65
V-very Poor	>66

Bulk Density

Apparent bulk density (LBD) is determined by pouring blend into a graduated cylinder. The bulk volume (v) and weight of powder (m) is determined. The bulk density is calculated using the formula

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

Tapped Density

The measuring cylinder containing known mass of blend is tapped for a fixed time. The minimum volume (vt) occupied in the cylinder and weight of powder blend (m) as measured. The tapped density (TBD) is calculated using the formula

$$TBD = \frac{\text{Weight of the powder (m)}}{\text{Tapped volume of the packing (v t)}}$$

Compressibility Index

The compressibility index is measure of the propensity of a powder to consolidate. As such, it is a measure of the relative importance of inter-particulate interactions. In a free-flowing powder, such interactions are generally less significant and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interactions bridging between particles often results in lower bulk density and a greater difference between the bulk and tapped densities. These differences in particle interactions are reflected in the compressibility index. Compressibility index was calculated from the bulk and tapped density using the following formula,

Compressibility index (%) = [TD – BD/TD] × 100

Where, TD = Tapped density, BD = Bulk density

Hausner Ratio

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

$$\text{Hausner Ratio} = \frac{\text{TBD (density Tapped)}}{\text{LBD (density Bulk)}}$$

Where TBD is tapped density and LBD is bulk density. Lower Hausner ratios (<1.25) indicate better flow properties than higher ones (>1.25). Scale of flowability as shown in Table 6.

Table 6: Grading of the Powders for Their Flow Properties According to Carr's Index.

Flow Character	Compressibility 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 – 37	1.46 – 1.59
Extremely Poor	>38	>1.60

Post Compression Parameters

The compressed tablets were evaluated for the following parameters.

General Appearance

Physical appearance of drug was examined by various organoleptic properties. The general appearance of tablets, its visual identity and overall 'elegance' is essential for consumer acceptance. The control of general appearance involves measurement of attributes such as a tablet's size, shape, color presences or absence of odor, taste, surface texture, physical flaws and consistency.

Hardness Test

The hardness of tablet is an indication of its strength. Measuring the force required to break the tablet across tests it. The force is measured in kg and the hardness of about 2-5 kg/cm^2 is considered to be satisfactory for Orodispersable tablets. Hardness of 10 tablets from each formulation is determined by hardness tester, etc.

Weight Variation Test

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. First the total weight of 20 tablets from each formulation is determined and the average is calculated. The individual weight of each tablet is also determined to find out the weight variation. USP specification for uniformity of weight as shown in Table 7.

Table 7: **Limits According to USP Specification for Uniformity of Weight.**

S.No	Average Weight of Tablets(mg)	Maximum % difference allowed
1.	**130 or less**	10
2.	**130 – 324**	7.5
3.	**More than 324**	5

Friability Test

Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling and transport. Roche friabilator is employed for finding the friability of the tablets. Weigh the 20 tablets from each batch and place in Roche friabilator that will rotate at 25 rpm for 4 minutes or run up to 100 rounds. the tablets were weighed again.

The percentage of friability can be calculated using the formula

% Friability = [(W1-W2)100]/W1

Where, W1= Weight of tablet before test, W2 = Weight of tablet after test

Friability of the Tablets less than 1 % was considered acceptable.

Moisture Content Determination

Moisture content (MC) is a reference to the amount of moisture present in a material. This value is often represented as a percentage of the material's mass (such as X% MC). The amount of moisture in an object can be measured in several different ways, such as with oven-dry tests or moisture meters. Take more than 500mg of powder of drugs and then placed in a moisture analyzer balance. This process continues for 15 minutes at a temperature of 105℃.

Disintegration Time Test

Disintegration test was carried out at 37℃ ±2℃ in 900ml of distilled water. The disintegration time of tablets from each formulation were determined using disintegration test

apparatus. One tablet was placed in each of the six tubes of the apparatus containing distilled water. One disk was added to each tube. The time taken in seconds for complete disintegration of the tablets with no palpable mass remaining in the apparatus was measured.

Assay of Ticagrelor by HPLC Method

Chromatographic Conditions

Column: Luna C18, 15cm Mobile phase: Buffer: Acetonitril (50:50). Buffer: Potassium dihydrogen orthophosphate (0.01M) weight 0.6804g of (KH2PO4) to 500ml of water and adjust (pH 3). Injection volume: 20µl., Wavelength: 255nm. Temperature: 40^{o}C.

Preparation of Mobile Phase

Potassium dihydrogen orthophosphate (0.01M) weight 0.6804g of (KH2PO4) to 500ml of water and adjust (PH 3) by phosphoric acid. mix, filter, and degas. Make adjustments if necessary.

Preparation of Standard Solution

Weight equivalent (60 mg) to 100 ml V.F and dissolve with methanol. Sonicate, if necessary, let it to cool and complete the volume with methanol, take 4 ml to 25 ml V.F complete with mobile phase. (0.096 mg/ml).

Preparation of Sample Solution

Weight equivalent one tablet (60mg) to 100 ml V.F and dissolve with methanol. Sonicate for 10 min let it to cool and complete the volume with methanol, take 4ml to 25ml V.F complete with mobile phase. (0.096 mg/ml).

Sample Injection Procedure**:** Separately inject equal volumes (about 20 µl) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the area responses for the major peaks. Calculate the quantity, in mg, of ticagrelor in each tablet taken by formula

(L/D) C (r_u/r_s) where, L:is labeled quantity, in mg of in each tablet. D: is concentration, in mg/ml of Ticagrelor of sample preparation. C: is the concentration calculate on the anhydrous basis of USP Ticagrelor in standard preparation. r_u and r_s: are the peak area responses obtained from standards and sample preparation.

In-Vitro Dissolution Studies

Dissolution Parameters

Apparatus: dissolution Tester (RC-80C). Medium: % 0.2 w/v tween 80; 900ml. RPM:75. Temperature: 37°C ± 0.5°C. Sampling interval: 5, 15, 30 minutes. Sample withdrawn: 5ml Wavelength: 255nm. Instrument: HPLC.

Preparation of Mobile Phase

Mobile phase: Buffer: acetonitrile (50:50): Buffer potassium dihydrogen orthophosphate (0.01M). Weight 0.6804g of (H2KO4) to 500ml of water and adjust (pH3) by phosphoric acid.

Preparation of the Standard

Weight equivalent (60.32mg) to 100 ml V.F and dissolve with methanol. sonicate, if necessary, let it to cool and complete the volume with methanol, Take 10ml to 100 ml V.F complete with medium (0.06 mg /ml).

Preparation of Sample Solution

Weight equivalent one tablet (60 mg) to 900 ml of medium. Preparation of medium: Take 11.2 ml of tween 80 by V.F to 6L of water.

Procedure: The in vitro dissolution studies of Ticagrelor Orodisipersible tablets were performed using dissolution Tester (I-RDA-15). The volume of dissolution medium tween 80 used was 900 ml and the temperature was maintained at 37°C±0.5°C. The speed of the basket was set at 75rpm. One tablet was placed in each jar of dissolution apparatus. 5ml of sample from each jar was withdrawn at every 15 minutes interval up to 1 hour and same volume of tween 80 was replaced to each dissolution jar, so that volume of dissolution medium was maintained to 900 ml. Then the sample was filtered and the amount of Ticagrelor released from ODTs was determined spectrophotometrically at 299 nm using tween 80 as blank.

RESULTS AND DISCUSSION

Evaluation of Ticagrelor

Organoleptic Properties

The organoleptic properties of Ticagrelor were shown in Table 8.

Table 8: Organoleptic Properties of Ticagrelor (API).

Tests	Specification	Observation
Color	White to off-white	White to off-white
Odor	Odorless	Odorless
Taste	Tasteless	Tasteless

The organoleptic properties like color, odor and taste of the API were evaluated. The color of Ticagrelor was found to be white to off-white powder, no characteristic odor and taste were observed in the study. Ticagrelor showed similar color, taste and odor.

Melting Point

Melting point of pure Ticagrelor was determined by open capillary method. The capillary tube was closed at one end by fusion and was filled with Ticagrelor 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 Ticagrelor was identical to reference melting point stated in MP (140-142°C). The sample started to melt at 140 °C, and turned into liquid at 142°C, indicating that the sample used is pure. That reading has stated in Melting point tester.

Solubility Test

The solubility profile of Ticagrelor was present in Table 9.

Table 9: Solubility Analysis of Ticagrelor (API).

Raw Material (API)	Solubility
Ticagrelor	Freely Soluble in Methanol
	Practically Insoluble in Water.
	Not Exhibits pH Dependent Solubility in Aqueous Buffers.

The solubility studies of drug (API) revealed that Ticagrelor was freely soluble in methanol, insoluble in water and not exhibits pH dependent solubility in aqueous buffers.

UV Scanning of Ticagrelor

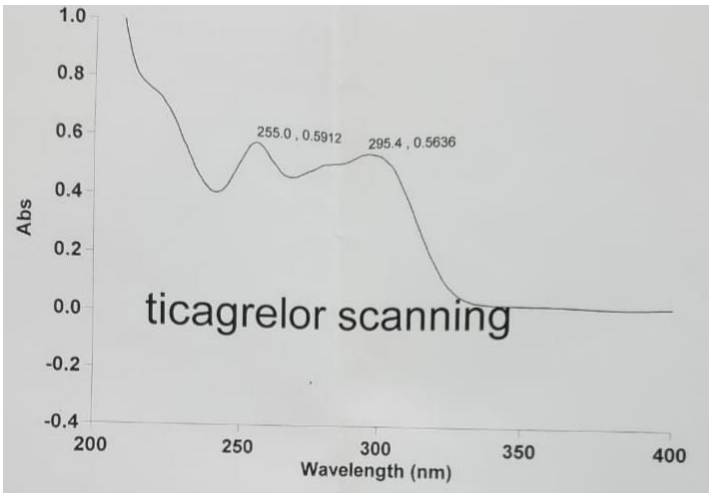

Fig. 2: Wave Length of Ticagrelor by UV Scanning.

The result show that wavelength of Ticagrelor is 255nm and 295nm as shown in Figure 2.

Evaluation of Ticagrelor

Micrometric Properties

The powder blends were evaluated for the following parameters such as angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The results were as shown in Table 10.

Table 10: Micrometric Properties of Ticagrelor.

Formulation code	Voids	Porosity (%)	Angle of Repose(θ)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Compressibility index (%)	Hausner Ratio	Evaluation of Angle of Repose
F11	0.177	17.7%	24.7	0.485	0.59	48.5	1.2	Exce

The angle of repose of F11 was found to be 24.7 which indicates excellent flow property. The bulk density was found to be 0.48 g/cm^3, the tapped density was found to be 0.59g/cm^3, the compressibility index was found to be 48.5% and the Hausner's ratio was 1.2.

Evaluation of Ticagrelor ODTs

General Appearance

The general appearance of all formulations were examined and found as follows: Color: White. Odor: odorless. Taste: all formula is sweet. Shape: Round. Surface texture: Biconvex and scored.

Post Compression Parameters

The prepared tablets were evaluated for various post compression parameters. The results are presented in Tables 11and 12.

Table 11: Post Compression Parameters of Ticagrelor Orodispersible Tablets ODTs.

Formulation	Friability	Hardness Mean	Average Weight	Disintegration Time (Sec)
F1	0.28%	2.05	146.73	37
F2	0.38%	4.675	157.415	307
F3	0.27%	3.425	154.01	29
F4	0.27%	2.55	151.29	29
F5	0.34%	2.4	145.325	34
F6	0.34%	1.75	144.155	36
F7	1.48%	2.625	150.525	52
F8	1.14%	4.2	156.025	59
F9	0.14%	4.35	213.19	1033
F10	0.54%	11.4	201.36	175
F11	0.084%	2.675	152.65	18

The hardness of the tablets was measured and the values were found in the range between 1.75 to 11.4 kg. The prepared tablets possessed good mechanical strength with sufficient hardness except F10 it has high hardness. Similarly, percentage friability values of the prepared Ticagrelor Orodispersible tablets showed less than 1% weight loss that is highly within the acceptable limit except F7 and F8 it showed more than 1% weight loss (present capping). Weight variation, all formulations of Ticagrelor Orodispersible tablets possessed the values are within the acceptable variation limit.

Disintegration time of Ticagrelor Orodispersable tablets ranges between 18 to 1033 seconds. All formulations of Ticagrelor Orodispersible tablets possessed the values are within the acceptable Disintegration time of the tablet except F2 and F9. The F11 showed the least disintegration time (18 sec) compared with all other formulations. From the above results, it was concluded that the F11 showed better tableting properties compared to the other formulations.

Table 12: Post Compression Weight Variation Results of Ticagrelor Orodispersible Tablets ODTs.

No	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
1	149.8	158.5	160.4	154.4	147.1	151.6	154	152.2	219.8	211.1	151
2	133.9	156.3	160.2	150	144.7	145.7	149.6	163.7	210.4	208.6	145
3	148.3	151.9	158	147.3	144.8	150.7	153.3	167.6	211.1	206.1	159
4	142.9	159.2	141.6	146.5	145.2	143.2	151.3	167.5	215	193.9	149
5	124.4	155.9	160.9	151.4	146.3	145.4	149.3	158.7	215.1	210	149
6	150.9	160.2	140.2	146.2	147.7	142.4	144.9	149.7	205.4	194	159
7	150.2	153.3	158.2	156	145.2	128.2	153.7	157.2	216.8	195	160
8	143.9	158.9	157	155.9	141.8	144.5	149.4	157.4	211	193.9	149
9	153	161	151.7	154.4	144.5	148.4	150.1	154.9	215.6	193.7	163
10	147.3	155.4	157	150.5	144.8	142.4	148.2	158	216.7	197.4	140
11	154.3	160.6	158.4	148.3	146.4	151.7	153.5	126.5	217.7	211.1	156
12	153.5	149.8	167.7	150.4	145.7	147.8	150.5	140.5	207.5	210.7	147
13	150.8	157.8	161.6	152.8	140.5	146.7	148.6	130	218.6	211.1	161
14	142.8	157.5	161.2	150.5	143.1	146.9	152.1	158.4	214.1	203.1	145
15	152	155.5	156.2	155.4	147	136.7	149.4	164.9	208.6	195.8	150
16	152.5	159.3	149.5	150.9	147.2	146.6	149	165.5	203	204.2	154
17	150.9	158.1	136.7	147	152.2	144.6	150.5	166.9	223.6	194.7	162
18	133.5	159.5	139.9	152.7	145.4	135	151.2	153.5	211.3	193.1	149
19	151.2	159	135.3	147.7	142.7	146.4	151.6	168.8	215.9	201.2	160
20	148.5	160.6	168.5	157.5	144.2	138.2	150.3	158.6	206.6	198.5	145
Total Weight	**2934.6**	**3148.3**	**3080.2**	**3025.8**	**2906.5**	**2883.1**	**3010.5**	**3120.5**	**4263.8**	**4027.2**	**3053.0**
Average Weight	**146.73**	**157.415**	**154.01**	**151.29**	**145.325**	**144.155**	**150.525**	**156.025**	**213.19**	**201.36**	**152.65**
%Error	**11.00**	**11.81**	**11.55**	**11.35**	**10.90**	**10.81**	**11.29**	**11.70**	**15.99**	**15.10**	**11.45**
Lower Limit	**135.73**	**145.61**	**142.46**	**139.94**	**134.43**	**133.34**	**139.24**	**144.32**	**197.20**	**186.26**	**141.20**
Higher Limit	**157.73**	**169.22**	**165.56**	**162.64**	**156.22**	**154.97**	**161.81**	**167.73**	**229.18**	**216.46**	**164.10**

Weight variation, all formulations of Ticagrelor Orodispersible tablets possessed the values are within the acceptable variation limit of the tablets.

Moisture Content

Moisture content, all formulations of Ticagrelor Orodispersible tablets possessed the values are within the acceptable limit was shown in Table 13.

Table 13: Moisture Content Results of Ticagrelor Orodispersible Tablets ODTs.

Formulation Code	Moisture Content %
F1	2.92%
F2	0.91%
F3	2.84%
F4	3.01%
F5	3.31%
F6	3.57%
F7	3.06%
F8	3.26%
F9	2.12%
F10	6.46%
F11	2.81%

Assay of Ticagrelor by HPLC Method

The assay was carried out by HPLC method as per the procedure given in methodology. The HPLC chromatogram of Ticagrelor standard and optimal sample formulation was shown in Table 14.

Table 14: HPLC Results of Ticagrelor Orodispersible Tablets ODTs.

S. No	Drug	RT*	Area
STD	Ticagrelor	4.320	1596801
F11	Formulation	4.310	1282721

***RT-Retention Tim**

Table 15: Results of Assay of Ticagrelor Orodispersible Tablets ODTs.

Formulation Code	Limit (%)	Assay (%)
F11	90-110%	108.94

The assay of Ticagrelor Orodispersible tablets (F11) was found to be 108.94%. The acceptable limit of Ticagrelor content as per USP is 90 to 110%. The results revealed that the assay of Ticagrelor was within the acceptable limit as shown in Table 15.

***In-Vitro* Dissolution Studies**

The *in-vitro* drug release of Ticagrelor ODTs were shown in Table 16.

Table 16: Comparative *In-Vitro* Drug Release Studies of Formulations of Ticagrelor Orodispersible Tablets ODTs.

Time (min)	Percentage of Drug Release (%)										
	Formulation Code										
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
5	82.92	96.58	81.47	67.04	80.13	94.58	100.76	87.84	44.26	94.28	101.45
15	89.46	99.81	90.27	88.61	89.83	99.81	103.65	93.07	75.18	101.31	104.46
30	96.60	103.78	98.67	96.27	98.39	101.21	104.33	93.94	91.60	103.41	105.07

Ticagrelor release was studied in tween 80 for up to 5, 15 and 30 minutes. The drug release at 5 minutes was between 44.26 to 101.45%. This indicates that F2, F6, F7, F10 and F11are the best formulas at a time of 5 minutes. The drug release at 15 minutes was between 75.18 to 104.46%. This also indicate that F2, F6, F7, F10 and F11are the best formulas at a time of 15 minutes. The drug release at 30 minutes was between 91.60 to 105.07%. This also indicates that F2, F6, F7, F10 and F11are the best formulas at a time of 30 minutes. The acceptable in vitro dissolution limit is not less than 80% of drug release at 30 minutes. The higher dissolution rates were observed in that F2, F6, F7, F10 and F11. So that the F2, F6, F7, F10 and F11are the best formulations. The drug release F11 at 5, 15 and 30 minutes was 101.45, 104.46 and 105.07% respectively. So that the F11 is the best formulation.

CONCLUSION

Ticagrelor Orodispersible tablets ODTs have a major benefit over the conventional tablets due to their rapid disintegration and dispersion, they also dissolve in the saliva without the use of water. Ticagrelor is mostly helpful to the patients for the treatment of acute coronary syndrome, cardiac angina. The ODTs of various batches were prepared by using various concentrations of various superdisintegrants like sodium starch glycolate, crospovidone and croscarmellose sodium by direct compression and wet granulation methods. Among the eleven formulations the disintegration time of F11 with crospovidone formulation to be as 18 sec and is almost better than other formulations. *In-vitro* dissolution studies were performed for all formulations, The F11 showed 101.45% drug release within the 5 minutes, minimum disintegration time of 18 sec and the assay of Ticagrelor was found to be within the acceptable limit.

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