FORMULATION AND EVALUATION OF TICAGRELOR SUBLINGUAL TABLETS

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Submitted By

C.A.MUNIYASAMY

(Reg.No: 261611303)

Under the guidance of

Dr. A.ABDUL HASAN SATHALI, M.Pharm., Ph.D.,

Department of Pharmaceutics

COLLEGE OF PHARMACY

MADURAI MEDICAL COLLEGE

MADURAI – 625 020

MAY-2018

CERTIFICATE

CERTIFICATE

This is to certify that the dissertation entitled **"FORMULATION AND EVALUATION OF TICAGRELOR SUBLINGUAL TABLETS"** is a bonafide work done by **Mr.C.A.MUNIYASAMY (Reg.No:261611303), Department of Pharmaceutics, College of Pharmacy, Madurai Medical College** in partial fulfillment of The TamilNadu Dr.M.G.R Medical University rules regulations for award of **MASTER OF PHARMACY IN PHARMACEUTICS** in under my guidance and supervision during the academic year 2017–2018.

Name & Signature of the Guide

Name & Signature of the Head of Department

Name & Signature of the Dean/Principal

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LIST OF ABBREVIATIONS

%	:	Percentage
^{0}C	:	Celsius
cm	:	Centimeter
FT-IR	:	Fourier transform infrared
gm	:	Gram
Hrs	:	Hours
IP	:	Indian Pharmacopoeia
KBr	:	Potassium Bromide
Log	:	Logarithm
mg	:	Milligram
ml	:	milliliter
mm	:	Millimeter
nm	:	Nanometer
µg	:	Microgram
pH	:	Potential of Hydrogen
RH	:	Relative Humidity
Rpm	:	Revolution per Minute
UV	:	Ultra Violet
DSC	:	Differential Scanning Colorimetry
PXRD	:	Powder X ray Diffraction
IR	:	Infra red
λmax	:	Maximum Absorbance
BCS	:	Biopharmaceutical Classification System
Conc.	:	Concentration

CDR	:	Cumulative Drug Release
e.g.	:	Example
Etc.	:	Excetra
FDA	:	Food and Drug Administration
mts	:	Minutes
ppm	:	Parts Per Million
SD	:	Standard Deviation

CHAPTER I

INTRODUCTION

INTRODUCTION

Development of a formulation involves a great deal of study and experimental work to get optimum results. While doing so we have to keep in mind various factors are considered like choice of excipients, drug bioavailability, drug stability in required dosage form, cost effectiveness, manufacturing aspects.

Now a day's formulation research is breaking barriers of conventional methods. Present day's drugs can be delivered with a convenience manner, performance and bioavailability.

The oral route of drug administration is the most convenient for patients, with tablets emerging as the most popular solid oral dosage form used today. Standard compressed, controlled-release and coated tablets are the most common form of solid oral dosages. A wide range and diversity of ingredients are often included in tablet formulations. A knowledge of the difference between tablet and capsule formulations should enable nurses to improve patient compliance with respect to solid oral dosage forms.

Oral administration is a route of administration where a substance is taken through the mouth. Many medications are taken orally because they are intended to have a systemic effect, reaching different parts of the body via the bloodstream. Tablets are solid dose pharmaceutical preparation containing drug substances usually prepared with the aid of suitable pharmaceutical excipients. They may vary in size, shape, weight, hardness, thickness, disintegration and dissolution characteristics and in other aspects, depending on their intended use and method of manufacture. Tablets constitute approximately 90% of all dosage forms clinically used to provide systemic

administration of therapeutic agents. This wide spread use of tablets have been achieved as a result of their convenience and also the diversity of tablet types***. (Ruchita jaiswani et al.,2014)***

Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. According to the Indian Pharmacopoeia Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drugs or a mixture of drugs, with or without diluents. They vary in shape and differ greatly in size and weight, depending on amount of medicinal substances and the intended mode of administration. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of Tablet. All medicaments are available in the Tablet form except where it is difficult to formulate or administer. Tablets are intended for oral administration. Some are swallowed whole or after being chewed, some are dissolved or dispersed in water before being administered and some are retained on mouth where the active medicament is liberated.

Solid medicaments may be administered orally as powders, pills, cachets, capsules or tablets. These dosage forms contain a quantity of drug which is given as a single unit and they are known collectively as solid unit dosage forms, even in the case of sustained action preparations which, technically, contain the equivalent of several normal doses of drug. Tablet that disintegrates or dissolve rapidly in the patients mouth are convenient for young children, elderly patients, mentally retarded and bedridden patients who used to suffer most probably with the problem of dysphagia and hand tremors. ***(Ruchita jaiswani et al.,2014)***

Oral route is the most desirable and preferred method of administering therapeutic agents for their systemic effects, but poorly solubility of drug is major challenge in pharmaceutical industry.

Up to 40% of orally administered drugs suffer from formulation difficulties related to their water insolubility. Dissolution rate, absorption, distribution and excretion of a moiety depend upon its solubility characteristics. Solubility is the phenomenon of dissolution of solid in liquid phase to give a homogenous system**.** Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration.

Low aqueous solubility is the major problem encountered with formulation development of new chemical entities. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. Water is the solvent of choice for liquid pharmaceutical formulations. Most of drugs are weakly acidic and weakly basic with poor aqueous solubility. ***(Kadam S.V et al., 2013)***

The solubility is defined as a maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature and the solubility increase bioavailability increases. **(*Sandeep Kumar et al.,2016)***

Solubility defines as:

Table-1. Definition of solubility

Definition	Parts of solvent required one part of solute
Very soluble	<1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10000
Insoluble	>10000

On the basis of solubility, drugs are classified into four classes of the BCS classification. Solubility challenges are faced in the Class II and Class IV of the BCS system. BCS classification is a scientific framework which deals in classification of drug substance based on its aqueous solubility and permeability. **(*Sandeep Kumar et al., 2016)***

Table-2. Biopharmaceutical drug classification system

Class	Solublility	Permeability	Examples
I	High	High	Metoprolol
II	Low	High	Neteglinide
III	High	Low	Cemetidin
IV	Low	Low	Ticagrelor

To improve solubility and bioavailability of poorly soluble drug we use various methods or techniques like solid dispersion, complexation, liquidsolid, hydrotropy, sonocrystallization, self-emulsifying method, micronization, chemical modification, pH adjustment, co-solvency, micellar solubilization etc. The purpose of this review article is to describe the techniques of solubilizaton for the attainment of effective absorption and improved bioavailability***.*** ***(Kadam S.V et al., 2013)***

FACTOR AFFECTING THE SOLUBILITY

1. **Nature of solute and solvent:**

   The nature of solute and solvent depends on concentration of solute in specific quantity of solvent at specific temperature. Example: at room temperature in 100gm of water only 1gm of lead (II) chloride can be dissolved while 200 grams of zinc chloride can be dissolved.

2. **Particle size:**

   Particle size affect on solubility. As article size decreases, the surface area to volume ratio increases. As the surface area of particle increases it causes greater interaction with solvent. The effect of particle size on solubility can be described by,

$$\text{Log } (S/S_0) = \frac{2\ \gamma\ V}{2.303\ R\ T\ r}$$

   Where,

   S is the solubility of fine particles

   S_0 is the solubility of large particles

   V is molar volume

γ is the surface tension of the solid

r is the radius of the fine particle.

T is absolute temperature

R is gas volume

3. **Molecular size:**

   Solubility affected by molecular size of particle. The solubility of the substance is decreased when molecules have higher molecular weight and higher molecular size because larger molecules are more difficult to surround with solvent molecules in order to solvate the substance.

4. **Temperature:**

   Solubility affected by temperature. If the solution process absorbs energy then the solubility will increase with increasing temperature. If the solution process releases energy then the solubility will decrease with increasing temperature

5. **Pressure:**

   For solids and liquid solutes, solubility not affected by change in pressure but for gaseous solutes, solubility increases as pressure increases and decrease as pressure decrease.

SOLUBILITY ENHANCEMENT METHOD *(Kadam S.V et al., 2013)*

Various techniques have been used in attempt to improve solubility and dissolution rates of poorly water soluble drugs.

which include as following:

A. Particle Size Reduction
B. Nanonization
C. Cosolvency
D. Hydrotropy
E. pH Adjustment
F. Sonocrystallization
G. Supercritical Fluid (SCF) Process
H. Solid Dispersion
I. Inclusion Complexation
J. Self-Emulsifying Or Self-Micro Emulsifying Systems
K. Liquisolid Methods

A. PARTICLE SIZE REDUCTION

The solubility of drug is often intrinsically related to drug particle size; as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows greater interaction with the solvent which causes an increase in solubility. Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. Particle size reduction is thus permitting an efficient, reproducible, and economic means of solubility enhancement. However, the mechanical forces inherent to comminution, such as milling and grinding, often impart significant amounts of physical stress upon the drug product which may induce degradation. The thermal stress which may occur during comminution and spray drying is also a concern when processing thermo sensitive or unstable active compounds. Using traditional

approaches for nearly insoluble drugs may not be able to enhance the solubility up to desired level.

B. COSOLVENCY

The solubility of poorly soluble drugs in water can be increased by mixing it with some water miscible solvent in which the drug is readily soluble. This process is known as cosolvency and the solvent used in combination are known as cosolvent. Cosolvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute. It is also commonly known as solvent blending. There is a dramatic change in the solubility of drugs by addition of organic co-solvent into the water. The cosolvents are having hydrogen acceptor or donor groups with a small hydrocarbon region. The hydrophobic hydrocarbon region usually interferes with the hydrogen bonding network of water which consequently reduces the intermolecular attraction of water while the hydrophilic hydrogen bonds ensures water solubility. Currently, the water-soluble organic solvents are polyethylene glycol 400 (PEG 400), ethanol, propylene glycol, and glycerin. . For example, Procardia (nifidipine) was developed by Pfizer contains glycerin, peppermint oil, PEG 400 and sodium saccharin in soft gelatin capsules. The water insoluble solvents include long-chain triglycerides (i.e. peanut oil, corn oil, soybean oil, sesame oil, olive oil, peppermint oil, hydrogenated vegetable oil and hydrogenated soybean oil), medium-chain triglycerides (Miglyol 812), beeswax, d-α- tocopherol (vitamin E) and oleic acid.

C. SURFACTANTS

Conventional approach to solubilize a poorly soluble substance is to reduce the interfacial tension between the surface of solute and solvent for

better wetting and salvation interaction. A wide variety of surfactants like Polyglycolized glyceride, Tweens, Spans, Polyoxyethylene stearates and synthetic block copolymers like Poly (propylene oxide)-poly (ethylene oxide)-poly (propylene oxide) like Poloxamers based micelles, Poly (beta-benzyl-L-aspartate)-b-poly (ethylene oxide), Poly (caprolactone)-b-poly (ethylene oxide) etc are very successful as excipient and carrier for dissolution enhancement. Improvement of drug solubility by using the amphiphilic surfactants is due to lowering surface tension between drug and solvent, improvement of wetting characteristics and micellar solubilization.

D. POLYMERIC ALTERATION:

Different crystalline forms of a drug that may have different properties are known as Polymorphs. Polymorphs may differ in physicochemical properties such as physical and chemical stability, shelf-life, melting point, vapor pressure, intrinsic solubility, dissolution rate, morphology, density and biological activities as well as bioavailability. Amongst the stable, unstable and metastable crystalline polymorphs, metastable forms are associated with higher energy with increased surface area, subsequently solubility, bioavailability and efficacy. With regard to bioavailability, it is preferable to change drug from crystal forms into metastable or amorphous forms. However, the possibility of a conversion of the high energy amorphous or metastable polymorph into a low energy crystal form having low solubility cannot be ruled out during manufacture and storage. It is preferable to develop the most thermodynamically stable polymorph of the drug to assure reproducible bioavailability of the product over its shelf-life under a variety of real-world storage conditions.

E. SOLID DISPERSION METHOD *(Kadam S.V et al., 2013)*

Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid stage to achieve an increased dissolution rate or sustained release of drug, altered solid state properties and improved stability.

CLASSIFICATION OF SOLID DISPERSION

Solid dispersion classified in 3 groups;

- **First generation solid dispersions:** In first generation solid dispersion, formulation of eutectic mixtures or molecular dispersion improved the rate of drug release which in turn increases the bioavailability of poorly water soluble drugs. Disadvantage related formulation of crystalline solid does not release drug quickly. Example: Crystalline carriers: Urea, Sugars and Organic acids.
- **Second generation solid dispersion:** In second generation we use amorphous state of carrier which improves drug release; likes fully synthetic polymers include povidone (PVP), polyethyleneglycols (PEG) and polymethacrylates. Natural product based polymers are mainly composed by cellulose derivatives, such as hydroxypropyl methylcellulose (HPMC), ethylcellulose or hydroxypropyl cellulose or starch derivates, like cyclodextrins.
- **Third generation solid dispersion:**

  In third generation we use carrier which have surface activity and self emulsifying property. The surfactants decrease the recrystallisation of drug and thus improve the solubility of drug. Example: Surface active self-emulsifying carriers: Poloxamer 408, Tween 80, and Gelucire 44/14.

MECHANISM OF SOLUBILITY ENHANCEMENT

a) **Particles with Reduced Particle Size**

Preparation of solid dispersions results in particles with reduced particle size and thus the surface area is improved and increased dissolution rate is attained. The ultimate result is improved bioavailability.

b) Particles with Improved Wettability

Wettability is improved during solid dispersion production. It has been suggested that the presentation of particles to the dissolution medium as physically separate entities may reduce aggregation. In addition, many of the carriers used for solid dispersions may have some wetting properties; hence, improved wetting may lead to reduced agglomeration and increased surface area.

c) Particles with Higher Porosity

Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity also depends on the carrier properties; for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release profile.

d) Drugs in Amorphous State:

Poorly water-soluble crystalline drugs, when in the amorphous state tend to have higher solubility. Drug in its amorphous state shows higher drug release because no energy is required to break up the crystal lattice during the dissolution process. In solid dispersions, drugs are presented as

supersaturated solutions after system dissolution, and it is speculated that, if drugs precipitate, it is as a metastable polymorphic form with higher solubility than the most stable crystal form.

e) **Solubilization Effect:**

The carrier material, as it dissolves, may have a solubilization effect on the drug. Enhancement in solubility and dissolution rate of poorly soluble drugs is related to the ability of carrier matrix to improve local drug solubility as well as wettability

SELECTION OF CARRIER:

One of the most important steps in the formulation and development of solid dispersion for various applications is selection of carrier. The properties of carrier have a major influence on dissolution characteristics of the drug. A material should possess following characteristics to be suitable carrier for increasing dissolution.

- Freely water soluble with intrinsic rapid dissolution properties.
- Non-toxic and pharmacologically inert
- Thermal stability preferably with low melting point especially for melt method
- Solubility in variety of solvents and should pass through a vitreous state upon solvent evaporation for the solvent method.
- Ability to increase aqueous solubility of drug.
- Chemical compatibility and not forming a strongly bonded complex with drug.

POLYMERS USED IN SOLID DISPERSIONS

A variety of polymers is offered as carriers for formulation of solid dispersion. Table 2.1 represents various categories and examples of carriers. Some polymers used in solid dispersions are as follows:

A) Polyethylene glycol (PEG):

The term polyethylene glycols refer to compounds that are obtained by reacting ethylene glycol with ethylene oxide. PEGs are commonly termed as polyethylene oxides, with a molecular weight (MW) usually falling in the range 200-3,00,000. For the manufacture of solid dispersions and solutions, PEGs with molecular weights of 1500-20,000 are usually employed. As the MW rises, so does the viscosity of the PEG. At MW of up to 600, PEGs are fluid, in the range 800 -1500 they have a consistency that is best described as vaseline-like, from 2000 to 6000 they are waxy and those with MW of 20,000 and above form hard, brittle crystals at room temperature. Their solubility in water is generally good, but reduces with MW. A meticulous advantage of PEGs for the solid dispersions is that they have good solubility in numerous organic solvents. The melting point of the PEGs of interest lies under 65 0C in every case (e.g. the m.p. of PEG 1000 is 30-40^{0}C, the m.p. of PEG 4000 is 50- 58^{0}C and the m.p.of PEG 20,000 is 60-63^{0}C .Additional attractive features of the PEGs include their ability to solubilise some compounds and also to improve compound wettability. Even the dissolution rate of a relatively soluble drug like aspirin can be improved by formulating it as a solid dispersion in PEG 6000.

B) Polyvinyl Pyrrolidone (PVP):

PVPs have molecular weights ranging from 10,000 to 700,000. It is soluble in solvents like water, ethanol, chloroform and isopropyl alcohol. PVP is not suitable for preparation of solid dispersions prepared by melt method because it melts at a very high temperature above 275ºC, where it gets decomposed.

C) Polymers and Surface Active Agent Combinations:

The addition of surfactants to dissolution medium lower s the interfacial tension between drug and dissolution medium and promotes the wetting of the drug thereby they enhance the solubility and dissolution of drug. Ternary dispersion systems have higher dissolution rates than binary dispersion systems.

D) Cyclodextrins:

Cyclodextrins are primarily used to enhance solubility, chemical protection, taste masking and improved handling by the conversion of liquids into solids by entrapment of hydrophobic solute in hydrophilic cavity of CD. Advantages of CD include increasing the stability of the drug, release profile during gastrointestinal transit through modification of drug release site and time profile, decreasing local tissue irritation and masking unpleasant taste.

E) Phospholipids:

Phospholipids are major structural components of cell membranes. Phosphotidylcholine was first isolated from egg yolk and brain. In phosphatidyl ethanolamine and phosphatidyl serine, the choline moiety is replaced by ethanolamine and serine respectively. Other phospholipids that occur in

tissues include phosphotidyl ethanolamide, phosphotidyl serine and phosphotidyl glycerol. Naturally occuring lecithins contain both a saturated fatty acid and unsaturated fatty acids with some exceptions.

Methods of preparation of solid dispersions

Various methods used for preparation of solid dispersion system. These methods are given bellow.

1. Melting method
2. Solvent method
3. Melting solvent method (melt evaporation)
4. Melt extrusion methods
5. Lyophilization techniques
6. Melt agglomeration Process
7. The use of surfactant
8. Electrospinning
9. Super Critical Fluid (SCF) technology

1. Melting method

The melting or fusion method is the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved.

2. Solvent method

In this method, the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The main advantage of the solvent

method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents

3. Melting solvent method (melt evaporation)

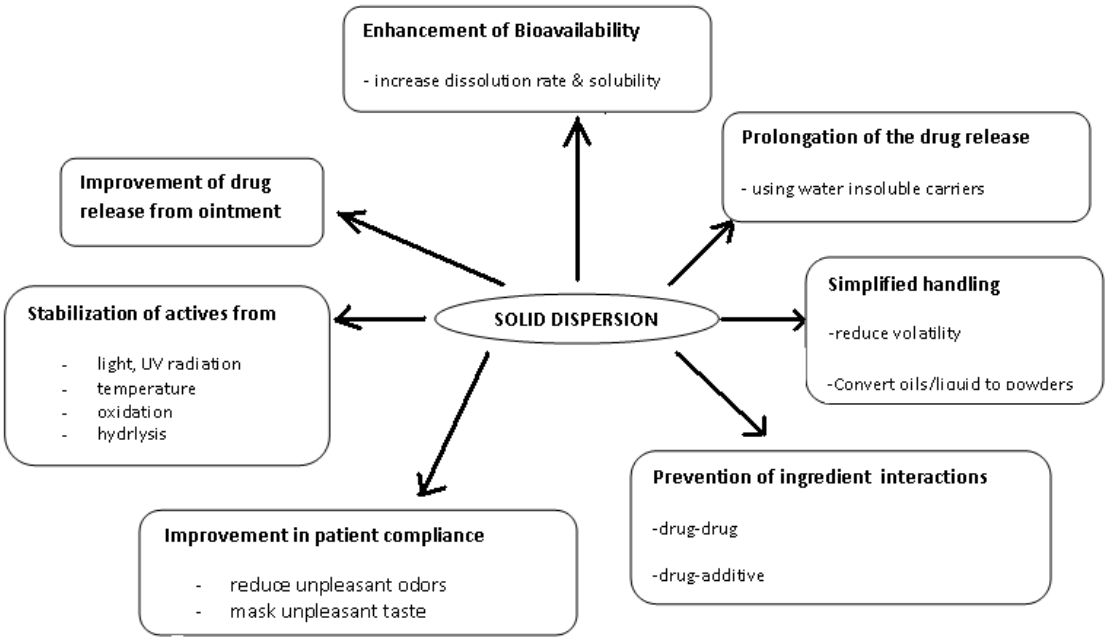
It involves preparation of solid dispersions by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt ofpolyethylene glycol, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The 5 –10% (w/w) of liquid compounds can be incorporated into polyethylene glycol 6000 without significant loss of its solidproperty. It is possible that the selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. Also the liquid solvent used may affect the polymorphic form of the drug, which precipitates as the solid dispersion. This technique possesses unique advantages of both the fusion and solvent evaporation methods. From a practical standpoint, it is only limited to drugs with a low therapeutic dose e.g. below 50 mg.

ADVANTAGES OF SOLID DISPERSIONS:

Generally, solid dispersion is mainly used

- To reduced particle size.
- To improve wettability.
- To improve porosity of drug.
- To decrease the crystalline structure of drug in to amorphous form.

- To improve dissolvability in water of a poorly water-soluble drug in a pharmaceutical.
- To mask the taste of the drug substance.
- To prepare rapid disintegration oral tablets.
- To obtain a homogenous distribution of small amount of drugs at solid state.
- To stabilize unstable drugs.
- To dispense liquid or gaseous compounds.
- To formulate a faster release priming dose in a sustained release dosage form.
- To formulate sustained release dosage or prolonged release regimens of soluble drugs using poorly soluble or insoluble carriers



CHAPTER II

SUBLINGUAL TABLETS – A REVIEW

SUBLINGUAL TABLETS – A REVIEW

Drugs have been applied to the mucosa for topical application for many years. However, recently there has been interest in exploiting the oral cavity as a portal for delivering drugs to the systemic circulation.

Drug delivery through the sublingual route had emerged from the desire to provide rapid onset of pharmacological effect. Dysphasia (difficulty in swallowing) is a common problem of all age groups, especially geriatrics, pediatric, and patients who are mentally retarded, uncooperative, nauseated or on reduced liquid intake/diets have difficulties in swallowing these dosage forms. Sublingual drugs are administered under the tongue and reached directly in to the systemic circulation through the ventral surface of the tongue and floor of the mouth. The drug is rapidly absorbed into the reticulated vein that lies underneath the oral mucosa, and transported through the facial veins, internal jugular vein, and braciocephalic vein and then drained in to systemic circulation. Considering the oral cavity sublingual area is the most permeable part of the buccal cavity. The decreasing order of permeability in the buccal cavity is the sublingual, the buccal area (cheek), then the palatal area. The order is generally based upon the relative thickness and the extent of blood supply to the specific part***. (Patil Vaishali A et al., 2015)***

The sublingual route usually produces a faster onset of action than the orally ingested tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolic processes

The sublingual tablets are usually small and flat, compressed lightly to keep them soft. The tablets must dissolve quickly allowing the API to be absorbed quickly and It is designed to dissolve in small quantity of saliva; after

the tablet is placed in under the tongue, the patient should avoid eating, drinking, smoking and possibly talking in order to keep the tablet in place. Systemic drug delivery through the sublingual route had emerged from the desire to provide immediate onset of pharmacological action.

Sublingual products have been designed for numerous indications ranging from migraine (for which rapid onset of action is important) to mental illness(for which patient compliance is important for treating chronic indications such as depression and schizophrenia) . Sublingual route provides 3-10 times greater absorption of the drug than oral route and is only surpassed by hypodermic injection. Sublingual route is very much appropriate for short-acting drugs.

Most of the sublingual drugs, which are absorbed by simple diffusion; here the sublingual area acts like a litmus paper readily soaking up the substances; however not all the substances are permeable and accessible to oral mucosa. Majority of drugs which are administered through sublingual route falls in the category of antianginal drug. Systemic drug delivery through the sublingual route had emerged from the desire to provide immediate onset of pharmacological effect.

By selecting the appropriate pharmaceutical excipients in the correct proportion, in combination with optimal manufacturing techniques the sublingual tablets could be prepared effectively.

ORAL MUCOSA

The oral mucosal lining offers a preferable route for the local and systemic administration of certain drugs and for the treatment of some diseases. This route has several distinct advantages over the enteral and

parenteral routes of drug delivery due to its rich blood supply, rapid onset of action, enhanced bioavailability, avoidance of the first pass and food effects, increased patient compliance, and ease of self-medication.

Oral mucosal drug absorption is governed by (a) the permeability of the oral mucous membrane and the anatomy of the underlying tissues, (b) the physicochemical properties of the drugs, and (c) the formulation design. The focus of this review is on the latter two points, as an understanding of these elements enables the selection of drug candidates suitable for oral mucosal delivery and optimizes drug delivery.

ANATOMICAL STRUCTURE OF THE ORAL MUCOSA

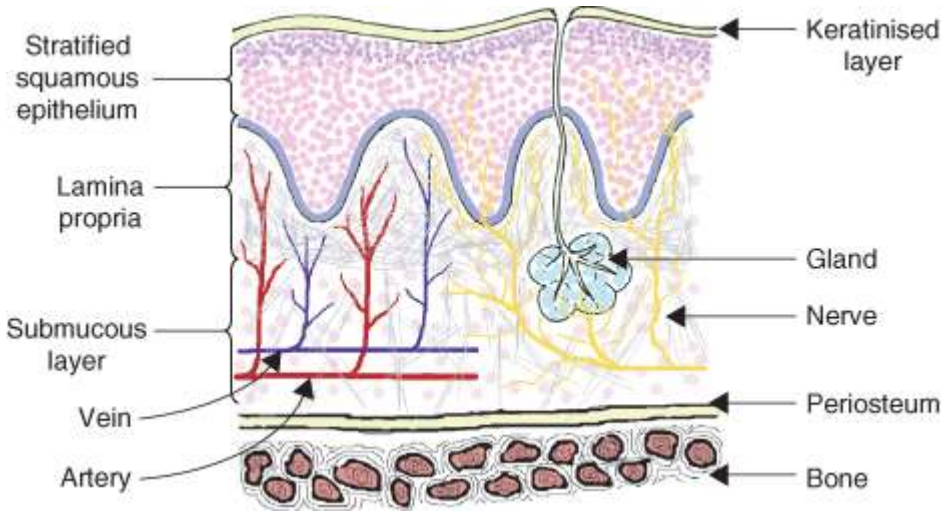


Figure-1: Anatomical structure of oral mucosa

The oral cavity has four distinct regions that can absorb drugs through the sublingual, buccal, gingival, and palatal regions. These regions differ from one another in histological structure and biochemical composition of the mucosal membrane, and their ability to retain the dosage form long enough to allow complete drug absorption. The sublingual membrane on the floor of the

mouth under the tongue and the buccal membrane lining the cheeks are commonly used for systemic drug delivery.

The mucosal lining consists of three distinct layers. The outermost layer is the epithelial membrane, which consists of stratified squamous epithelial cells and has a protective barrier function. The innermost layer of the epithelial membrane is called the basement membrane that replenishes the epithelium. Below the epithelium lies the lamina propria followed by the submucosa. The lamina propria is a hydrated and less dense layer of connective tissue containing collagen and elastic fibers. The oral submucosa is also richly supplied with blood vessels.

SUBLINGUAL GLANDS

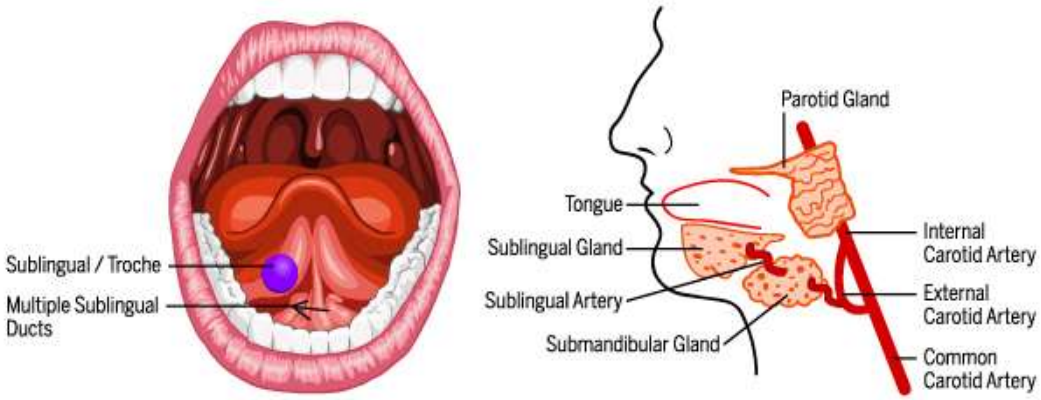


Figure-2: Sublingual glands

Salivary glands which are present in the floor of the mouth underneath the tongue. They are also known as sublingual glands. They produce mucin in turn produces saliva. The interior area of the mouth remains lubricated due to production of the saliva by the glands, which is necessary for chewing and food swallowing. The fluid which is produced by the glands gets mix with the food, so the food gets easily chewed. Due to low secretion of the saliva it can

create problem in swallowing the food and potential for food lodge in the throat increases. The absorption is transfer of the drug from its site of administration into systemic circulation, so it can be said that absorption is directly proportional layer thickness.

The absorption of the drug following this way Sublingual > Buccal > Gingival >Palatal. Due to high permeability and rich blood supply, the sublingual route can produce rapid onset of action so the drug with short delivery period can be delivered and dose regimen is frequent. The drug gets diluted in the saliva and from there the drug is adsorbed across the oral cavity. For example: Glyceryl nitrate-a potent coronary vasodilator which is used for rapid symptomatic relief of angina. After administration, its gets pharmacologically active after 1-2 minutes. Oral spray was found to provide rapid relief of symptom with first class metabolism. The extent of first class metabolism when compared to the sublingual spray decreased to 48% with sublingual tablets and 28% with the oral dose. ***(Neha Narang et al., 2011)***

MECHANISM OF SUBLINGUAL ADMINISTRATION:

Following sublingual administration, the drugs are absorbed across the mucous membrane by one of the following mechanisms:

- Passive diffusion
- Active or carrier-mediated transport
- Endocytosis.

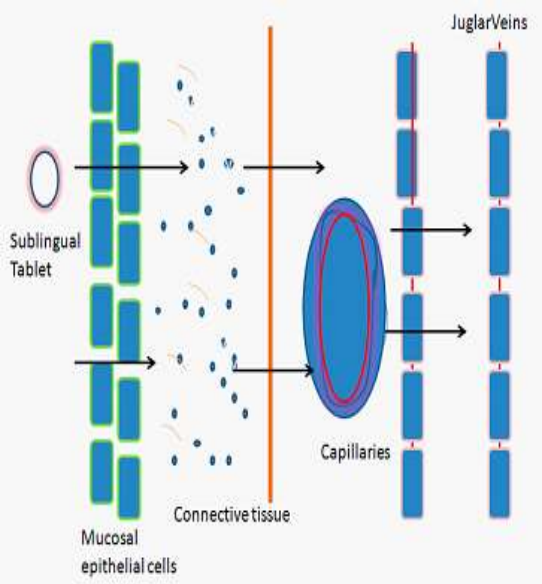


Figure-3: Mechanism of drug absorption

Although the process of passive diffusion is spontaneous, the rate of diffusion is dependent on the molecular weight and solubility of the drug, concentration gradient, temperature, the surface area of the membrane, and the proximity of the molecule to the membrane. When a drug exists in its unionized form in saliva, it is absorbed by passive diffusion. Physical models have been proposed to describe drug absorption from saliva through the lipid bilayer of the mucous membrane into systemic circulation. The rate of drug absorption across the mucous membrane is directly related to its partition coefficient. Some compounds, such as glutamic acid, L-ascorbic acid, nicotinic acid, and thiamine, are transported via a carrier-mediated process.

The absorption is effected by the lipid solubility and hence the permeability of the solution commonly known as osmosis, the ionization, and the molecular weight of the drug. The cells of oral epithelium adsorb the drug by the process of endocytocis. It is unlikely that the same mechanism is observed throughout the stratified epithelium. However, it is believed that

acidic stimulation of the salivary glands, with the accompanying vasodilatation, facilitates absorption and uptake into the circulatory system.

The mouth is lined with a mucous membrane which is covered with squamous epithelium and contains mucous glands. The sublingual mucosal tissue is similar to that of buccal mucosa. The salivary glands consist of lobules of cells which secrete saliva through the salivary ducts into the mouth.

The three pairs of salivary glands are the parotid, the submandibular and the sublingual which lies on the floor of the mouth. The more acidic the taste is, greater the stimulation of salivary output; serving to avoid potential harm to acid-sensitive tooth enamel by bathing the mouth in copious neutralizing fluid. The sublingual artery travels forward to the sublingual gland, it supplies the gland and branches to the neighboring muscles and to the mucous membranes of the mouth, tongue and gums. Two symmetrical branches travel behind the jawbone under the tongue to meet and join at its tip. Another branch meets and anastomoses with the submental branches of the facial artery. The sublingual artery stems from the lingual artery – the body's main blood supply to the tongue and the floor of the mouth – which arises from the external carotid artery. The proximity with the internal carotid artery allows fast access to its route supplying the greater part of the cerebral hemisphere.

Lipids present in the oral mucous membrane offer the main barrier to the permeability of hydrophilic drugs. On the other hand, well-hydrated connective tissues provide resistance to lipophilic drugs. Thus, the potential transport path across the oral mucous membrane may be either polar or non-polar. Non-polar molecules cross through the lipid regions of the epithelium,

while polar molecules travel through ionic channels present in the intercellular spaces of the epithelium, or aqueous pores present in the epithelial cells. For this reason, an understanding of a drug's lipophilic or hydrophilic nature during the developmental stage of the drug product appears to be the most useful index for evaluating its suitability for absorption across the oral mucosa. permeation and diffusion, and so are able to move freely between the tissues of the body. Active transportation into cells leads to rapid metabolisation of the substances. Molecules such as glucose (fructose) and amino acids are essential for cell metabolism and special mechanisms have evolved to facilitate their rapid diffusion and permeation across cell membranes***. (Neha Narang et al., 2011)***

SUITABILITY OF DRUG FOR PREPARATION OF SUBLINGUAL TABLET

- No bitter taste.
- Dose lowers than 20 mg, e.g. nifedipine.
- Small to moderate molecular weight.
- Good stability in water and saliva.
- Partially no ionized at the oral cavities pH.
- Under going first pass effect e.g. ketotifen fumarate.
- Many drug properties could potentially affect the performance of sublingual tablets like solubility, crystal morphology, particle size, hygroscopicity, compressibility and bulk density of drug.
- Some drugs undergoes extensive first pass metabolism which results in poor bioavailability of its oral dosage forms, that kind of drugs are suitable for sublingual dosage form.

- Drugs that are unstable in parenteral preparation are suitable for sublingual dosage form.
- Many pharmaceuticals are designed for sublingual administration, including cardiovascular drugs, steroids, barbiturates, enzymes, antiemetics, vitamins, minerals and vaccines Able to saturate the oral mucosa.
- Should have lower bio availability are good candidates for sublingual tablets
- Frequent dosing of drugs unsuitable for sublingual tablets.
- Ability to permeate oral muosa.

FACTORS AFFECTING THE SUBLINGUAL ABSORPTION

(Somya Sah et al., 2016)

- **Lipophilicity of drug:** For a drug to be absorbed completely through sublingual route, the drug must have slightly higher lipid solubility than that required for GI absorption is necessary for passive permeation.
- **Solubility in salivary secretion:** In addition to high lipid solubility, the drug should be soluble in aqueous buccal fluids i.e. biphasic solubility of drug is necessary for absorption.
- **pH and pKa of the saliva:** As the mean pH of the saliva is 6.0, this pH favors the absorption of drugs which remain unionized. Also, the absorption of the drugs through the oral mucosa occurs if the pKa is greater than 2 for an acid and less than 10 for a base.
- **Binding to oral mucosa:** Systemic availability of drugs that bind to oral mucosa is poor.

- **Thickness of oral epithelium:** As the thickness of sublingual epithelium is 100-200 μm which is less as compared to buccal thickness. So the absorption of drugs is faster due to thinner epithelium and also the immersion of drug in smaller volume of saliva.

IDEAL CHARACTERISTICS OF SUNLINGUAL TABLETS

MOUTH FEEL

Mouth-feel is critical, and patients should receive a product that feels pleasant. Any large particles from the disintegrating tablet that are insoluble or slowly soluble in saliva would lead to an unpleasant gritty feeling. This can be overcome by keeping the majority of the particles below the detectable size limit. In some cases, certain flavors can improve mouth-feel perception, resulting in a product that is perceived as being less gritty, even if the only change is the flavor. Effervescence can be added to aid disintegration and improve mouth-feel by reducing the “dryness” of a product.

HYGROSCOPICITY

Several fast dissolving dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence they need protection from humidity, which calls for specialized product packaging.

FRIABILITY

In order to allow fast dissolving tablets to dissolve in the mouth, they are made of either very porous or soft molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle which are difficult to handle, often requiring specialized peel off

blister packing. To overcome this problem, some companies introduced more robust forms of fast dissolving tablets, such as Wowtab by Yamanouchi Shadlee and Dura Solve by CIMA labs.

DRUG SELECTION CRITERIA

- Able to saturate the oral mucosa.
- At least moderately non-ionized at oral cavity PH.
- Have the ability to diffuse and partition into the epithelium of upper GIT.
- Small to moderate molecular weight.
- Low dose drugs mostly less than 20 mg.
- Should have good stability in saliva and water.
- Should have lower bio availability are good candidates for sublingual tablets.
- Frequent dosing drugs are unsuitable for sublingual tablets.
- Ability to permeate oral mucosal tissue

Advantages

- Rapid onset of action is achieved as compared to the oral route.
- Liver is bypassed and also drug is protected from metabolism due to digestive enzymes of the middle gastro intestinal tract
- Improved patient compliance due to the elimination of associated pain with injections; administration of drugs in unconscious or incapacitated patients; convenience of administration as compared to injections or oral medications.
- Low dosage gives high efficacy as hepatic first pass metabolism is avoided and also reduces the risk of side effects.

- The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.
- Due to rapidity in action these sublingual dosage forms are widely used in emergency conditions e.g. asthma.
- Rapid absorption and higher blood levels due to high vascularization of the region and therefore particularly useful for administration of antianginal drugs.
- They also present the advantage of providing fast dissolution or disintegration in the oral cavity, without the need for water or chewing.

Disadvantages

- Since sublingual administration of drugs interferes with eating, drinking, and talking, this route is generally considered unsuitable for prolonged administration.
- Although this site is not well suited to sustained-delivery systems.
- Sublingual medication cannot be used when a patient is uncooperative.
- The patient should not smoke while taking sublingual medication, because smoking causes vasoconstriction of the vessels. This will decrease the absorption of the medication.
- Various types of sublingual dosage forms are available but tablets, films and sprays are in trends these days. For the preparation of these dosage forms different methods are described depends upon the feasibility and advantages over the others.

Requirements of sublingual tablets

- Rate of absorption from the saliva solution
- Drug and dosage form stability
- Mechanical strength of final product
- Taste, mouth feel, swallowing ability
- Exhibit low sensitivity to environmental conditions such as humidity and temperature
- Allows the manufacture of tablet using conventional processing and packaging equipment at low cost
- Overall bioavailability
- Require no water for oral administration, yet dissolve/disintegrate in mouth in a matter of seconds
- Leave minimal or no residue in mouth after administration.

TECHNIQUES FOR PREPARATION OF SUBLINGUAL TABLETS

(Somya Sah et al. 2016)

The formulation of sublingual tablets involves the selection of suitable excipients of bland taste that shall ultimately resulting in a rapid disintegrating tablet their by enhancing the dissolution of active ingredient. There are different types of techniques used for preparation of sublingual Tablets.

1. **COMPRESSION MOLDING:**

Tablets manufactured by the compression molding process exhibit rapid disintegration and dissolution, which is usually within 5–10 seconds. These tablets pose special challenges during handling and shipping, because of the poor mechanical strength, and may require special packaging.

Alternatively, the mechanical strength of the tablets may be enhanced by employing a suitable binder. However, the binder level should be optimized to avoid any deleterious effects on disintegration and dissolution of the tablets.

The formulations for the compression molding process typically contain soluble excipients to impart quick and complete dissolution, and taste modifiers for patient compliance. Molded tablets have also been prepared directly from a molten matrix, in which the drug is dissolved or dispersed (heat molding), or by evaporating the solvent from a drug solution or suspension at room pressure (no vacuum lyophilization).

The compression molding process involves moistening of the formulation blend with a solvent (usually hydro-alcoholic), followed by molding into tablets under low pressure. The moist tablets are finally dried. The lower compression pressure employed for molding and drying of the moist tablet produces a highly porous tablet structure with enhanced dissolution. The choice, ratio, and amount of granulating solvents are critical to the physicochemical characteristics, performance, and stability of the tablets, and should be optimized. Several patented technologies are also available for commercial manufacture of compression molded tablets.

2. DIRECT COMPRESSION:

The direct compression method is commonly used for commercial manufacture of sublingual tablets. It is a simple and cost-effective process, as it employs ingredients that can be mixed well and do not require further granulation steps prior to lubrication and compression. Sublingual tablets manufactured by the direct compression method exhibit good mechanical strength and acceptably fast disintegration.

The directly compressible sublingual tablet formulation contains directly compressible soluble excipients, a super disintegrant, and lubricant. It may also contain microcrystalline cellulose, dry binder, buffers, surface-active agents, sweeteners, and flavors. Sugar-based excipients are widely used as bulking agents because of their high aqueous solubility, sweetness, pleasant feeling in the mouth, and good taste-masking. Nearly all sublingual formulations incorporate some saccharide-based material. The choice of a suitable disintegrant and its amount are critical for achieving a fast disintegration and dissolution rate. Sometimes effervescent agents are used to increase disintegration and dissolution of sublingual tablets.

Several novel approaches of incorporating disintegrants and other soluble and/or insoluble excipients to obtain rapid dissolution and adequate mechanical strength are reported. One example is the Flashtab technology of multiparticulate actives (coated crystals and uncoated or coated microgranules). In these tablets, the simultaneous presence of a disintegrant with a high swelling or disintegrating force, defined as “disintegrating agent,” and a substance with a low swelling force (starch, cellulose, and direct-compression sugar), defined as “swelling agent,” was claimed as the key factor for the rapid disintegration of a tablet. The tablet manufactured by this technology is reported to have adequate mechanical strength.

Advantages

- Low labor input
- A dry process
- Fewest processing steps.

Disadvantages

- Stratification may occur due to differences in particle size and bulk density which results poor content uniformity.
- A large dose drug may cause problem in direct compression. It requires diluents. The tablet becomes large in size which is difficult to swallow and also costly.
- During handling of dry materials static charge may form which may present uniform distribution of drug.
- Direct compression diluents may interact with the drug. For example, amine drug with Lactose produce discoloration of tablet.

3. **FREEZE DRYING (LYOPHILIZATION):**

The process of freeze drying (lyophilization) is expensive, time-consuming, and produces tablets of poor mechanical strength. For these reasons, it is not commonly used to manufacture sublingual tablets. However, it does have advantages over the other processes, as the tablets made by this process have high porosity, and when placed under the tongue disintegrate and dissolve immediately. It is a process of choice for products that are unstable or are heat sensitive. The process involves lowering the temperature of the product in an aqueous medium to below freezing, followed by applying a high-pressure vacuum. To extract the water in the form of a vapor, which is collected as ice on a condenser, a gradual temperature rise is applied during the drying process. The product temperature at the ice sublimation interface and the formulation collapse temperature are critical to obtain a freeze-dried cake of quality structure. This process retains the physical structure and

preserves the material for storage or transport.The resulting tablets are usually light and have highly porous structures that allow rapid dissolution or disintegration. The freeze-drying process may result in a product with an amorphous structure, leading to an enhanced dissolution rate. However, tablets manufactured by freeze drying process have poor stability at a higher temperature and humidity.

4. SPRAY DRYING:

In spray drying process, highly porous and fine powder can be produced and processing solvent is evaporated during process. Spray dryers are widely used in pharmaceuticals and biochemical process. Spray drying can be used to prepare rapidly disintegrating tablets by using support matrix such as hydrolyzed and non hydrolyzed gelatin and other components like Mannitol as bulking agent, sodium starch glycolate, Crosscarmellose sodium as disintegrants, acidic material like citric acid and alkali like sodium bicarbonate to enhance disintegration and dissolution. The tablet manufactured from this process, disintegrated in less than 20 seconds in an aqueous medium.

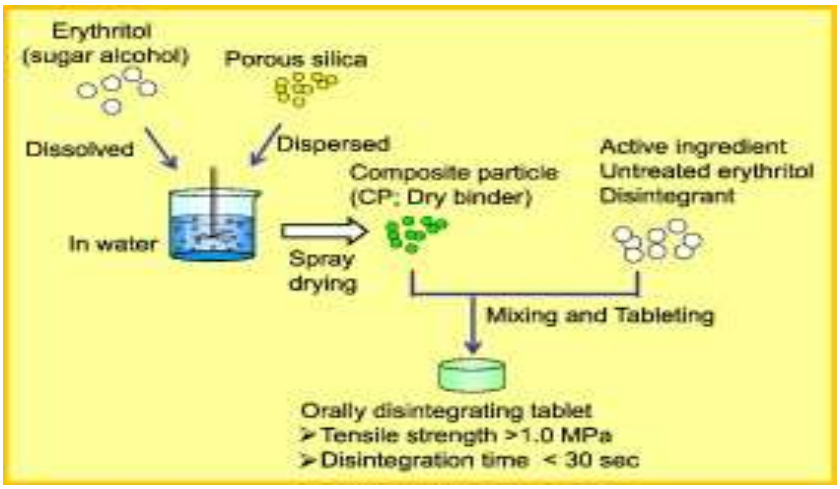


Figure-4: Spray Drying Process

5. SUBLIMATION:

The key to rapid disintegration for mouth dissolving tablet is the presence of a porous structure in the tablet matrix. Conventional compressed tablet that contain highly water-soluble ingredients often fail to dissolve rapidly because of low porosity of the matrix. Hence, to generate porous matrix, volatile ingredients are used that are later subjected to a process of sublimation. The volatile material was then removed by sublimation and that result in formation of a porous matrix (approximately 30%).

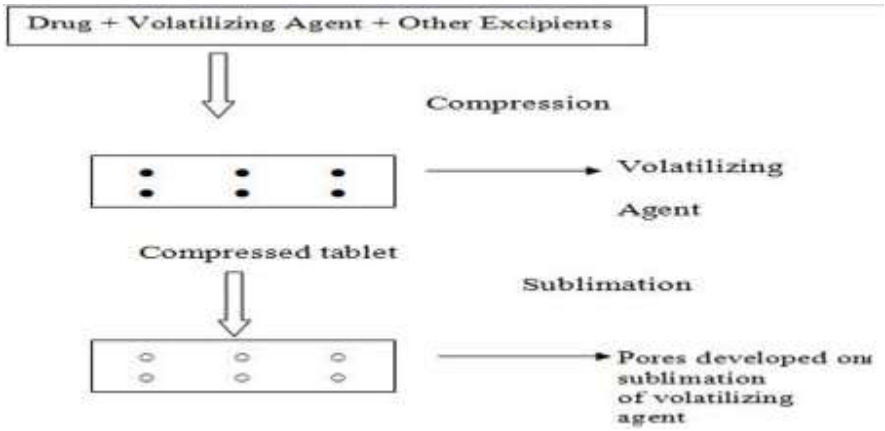


Figure-5: Sublimation process

6. MASS EXTRUSION:

This technology involves softening of the active blend using the solvent mixture of water soluble polyethylene glycol and methanol and expulsion of softened mass through the extruder or syringe to get a cylindrical shaped extrude which are finally cut into even segments using heated blade to form tablets. This process can also be used to coat granules of bitter drugs to mask their taste.

7. DISINTEGRATE ADDITION:

Disintegrate addition technique is one popular technique for formulating Fast-dissolving tablets because of its easy implementation and cost-effectiveness. The basic principle involved in formulating Fast-dissolving tablets by disintegrates addition technique is addition of superdisintegrants in optimum concentration so as to achieve mouth dissolving along with the good mouth feel.

Mechanism of Superdisintegrants

There are four main mechanisms for tablets disintegration as follows

1. Swelling

The most accepted general mechanism of action for tablet disintegration is swelling. The tablets with high porosity nature show poor disintegration due to have lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. Note if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

2. Porosity of capillary action (Wicking)

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. The water up take by tablet mainly depends upon hydrophilicity of the drug/excipients and tableting conditions.

3. Disintegrating particle due to repulsive forces

The another mechanism of tablet disintegration attempts to explain the swelling of tablet made with 'non-swellable' disintegrants. Particle repulsion theory based on the observation that non swelling particle also cause disintegration of tablets. Water is required for The electric repulsive forces between particles are the mechanism of disintegration. Wicking is secondary.

4. Due to deformation

During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. The swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet.

COMERCIALLY AVAILABLE SUBLINGUAL TABLETS


ALWAYS DISPENSE WITH
PATIENT PACKAGE INSERT
Pfizer
NDC 0071-0418-13
Nitrostat®
(Nitroglycerin Sublingual
Tablets, USP)
0.4 mg / tablet
Rx only


SUMATRIPTAN
Tablets USP
50 mg*

CHAPTER III

LITERATURE REVIEW

LITERATURE REVIEW

Siji C et al (2018) prepared carvedilol sublingual tablets which is an oral antihypertensive agent by direct compression using different superdisintegrants like crosscarmellose sodium, crosspovidone, sodium starch glycolate and the solubility enhanced by solid dispersion method. Prepared tablets evaluated for thickness, uniformity of weight, hardness, friability, wetting time, invitro disintegration time, drug content, invitro drug release. The formulation F7 consist of superdisintegrant crosscarmellose sodium 5% and drug polymer in the ratio 1:4 shows the maximum drug release.

Harmanpreet singh et al (2017) prepared rizatriptan sublingual tanblets by direct compression method using different bioadhesive polymers such as sodium carboxy methyl cellulose, HPMC-K4M and chitosan at various concentration ranging from 0.5-5% w/w along with sodium starch glycolate or cross carmellose sodium as superdisintegrants at different concentration ranging 2-8% w/w. The formulation batches containing 2% w/w chitosan along with 2% w/w sodium starch glycolate or cross carmellose sodium which disintegrate rapidly and slow high dissolution and *ex* vivo permeation. From this the formulation showed increased the bioavailability and directly enter into the systemic circulation.

Wafa Al Madhagi et al (2017) prepared glimepiride sublingual tablets gives rapid drug absorption that can be used in emergency. The were prepared by using different superdisintegrants like sodium starch glycolate, cross povidone, cross carmellose sodium, pre-gelatinized starch, maize

starch. The formulations contain binders like flulac and aerosil with disintegration time 21 seconds give the suitable sublingual tablets.

Saroj Makwana et al (2017) developed sublingual tablets of nicardipine hydrochloride used for the treatment of angina and it having low bioavailability about 10-40% orally attributed to the hepatic first pass metabolism. The solubility of nicardipine enhanced by carried solid dispersion of drug and beta cyclodextrin complex. The sublingual tablets were prepared direct compression method by using sodium starch glycolate, cross carmellose sodium, cross povidone as superdisintegrants. The optimized formulation showed in-vitro disintegration time was 41 seconds and 99.95% drug release within the 8 minutes. Formulation containing 4% crosspovidone and 2% PVP K-30 show highest disintegration time and ex-vivo permeation was 96.81% within the 14 minutes.

Bhanja SB et al (2017) developed a sublingual tablet of Perindopril which is an effective drug in the treatment of hypertension. Perindopril containing tablets were prepared by direct compression method using different ingredients such as Crospovidone, Sodium saccharin, Mannitol, Microcrystalline cellulose, Talc and Magnesium stearate. The tablets were evaluated for physical properties including Hardness, Weight variation, Thickness, Friability, Drug content, Wetting time, Water absorption ratio, *In-vitro* disintegration time, *In-vitro* dissolution study and also Drug release kinetic study. The Hardness, Weight variation, Thickness, Friability and Drug content of tablets were found to be acceptable according to pharmacopoeial limits. An optimized tablet formulation was found, which provided short wetting time of 45 sec, water absorption ratio of 55 and *In-vitro* disintegration time of

98 sec. because of the amount of superdisintegrant i.e. crospovidone was significantly affected the dependent variables like wetting time, Water absorption ratio and *In-vitro* disintegration time. The best *in-vitro* drug release was found to be in optimized formulation i.e.99.88% during the end of 12 min. The *in-vitro* drug release data of all Perindopril sublingual tablets were subjected to goodness of fit test by linear regression analysis according to Zero order equation, first order equation, Higuchi's equation and Krosmeyer-Peppas equation to ascertain the mechanism of drug release.

Mohd Abdul Hadi et al (2017) developed sublingual administration of felodipine (antihypertensive drug) offer suitable and practical approach in serving the desired objective of faster disintegration and dissolution characteristic with increase bioavailability and to know the effects of two synthetic superdisintegrants like crospovidone and sodium starch glycollate was done by taking different ratios. Prepared tablets were subjected to different evaluation parameters such as hardness, thickness, friability, weight variation, and drug content uniformity, in vitro disintegration time, wetting time, in vitro dissolution studies and stability studies are carried out by using best formulation. Thus, sublingual tablet of Felodipine could be an alternative route to avoid gastrointestinal side effect as well as bypass hepatic first pass metabolism. The formulated sublingual tablets may act as a potential alternate for the Felodipine oral tablet.

Syed Suhaib Ahemed et al (2017) developed fast dissolving sublingual tablets of gabapendin using superdisintegrants like crosscarmellose sodium, crosspovidone, sodium starch glycolate, PVP-K30.

All formulations were evaluated post compression parameters like hardness, friability, drug content uniformity, dissolution test and disintegration test.

Pawar P P et al (2016) developed sublingual tablets of ondansetron HCL is selective inhibiter of type 3 serotonin (5HT3) receptor & shows antiemetic action. it is easier route of administration, it is also used in patients of dysphasia (difficulty in swallowing). In the present study the research was done for the replacement of superdisintegrants that are Cross carmalose sodium & Sodium starch glycolate. The formulations were evaluated for preformulation & post-formulation studies. The disintegration time was within the range of 12 – 19 seconds & the results were satisfactory.

Somya Sah et al. (2016) Oral administration is one of the most convenient forms for the intake of drug due to ease of administration, painless, versatility, and paramount patient compliance. The demand of fast disintegrating tablets has been growing, during the last decades especially for geriatric and pediatric patients due to dysphasia. So the new drug delivery known as orally disintegrating tablets came to existence. As nowadays most of the people need effective relief within a short period of time so sublingual is the most suitable form of administration. These tablets disintegrate and dissolve rapidly in saliva due to interaction with our salivary enzymes.

Shailesh T Prajapath et al (2016) formulated sublingual tabets of zolmitriptan. It is a 5-HT receptor agonist (1B/1D) used in the acute treatment of migraine having low bioavailability about 40% orally due to hepatic first pass metabolism. Sublingual tablets were prepared using ispaghula husk powder, gellan gum, sodium alginate as super disintegrating polymers and citric acid, tartaric acid and camphor as permeation enhancers by direct

compressible technique and evaluated for weight variation, thickness, friability, content uniformity, hardness, disintegration time, wetting time, in-vitro drug release, in-vitro and ex-vivo permeation study. The in-vitro disintegration time of the optimized formulation was 9 ± 2 sec and all formulations showed 100% of dissolution within 6 ± 2 min. Formulation containing 4% of gellan gum showed highest disintegration and 2% of citric acid formulation showed highest permeation 88% within 30 min and ex-vivo permeation was 52% within 30 min. From this the sublingual tablet formulation gives better results using natural super disintegrant for fast onset of action.

Shailesh T Prajapati et al (2016) prepared sublingual tablets of sumatriptan succinate is a selective 5-hydroxytryptamine-1 receptor agonist effective in the acute treatment of migraine headaches, having low bioavailability of about 15% orally due to first-pass metabolism. The intensely bitter taste of Sumatriptan succinate was masked and to formulated fast-acting, taste-masked sublingual tablet formulation by solid dispersion method with mannitol and ion exchange with Kyron T 114 because it releases the drug in salivary pH. For a better feel in the mouth, menthol and sweetener Na saccharine were added to the tablet formulation. The tablets were prepared by direct compression and evaluated for weight variation, thickness, friability, drug content, hardness, disintegration time, wetting time, in vitro drug release, and in vitro permeation study. Optimized batches disintegrated in vitro within 28-34 s. Maximum drug release could be achieved with in 10 min for the solid dispersion batches and 14-15 min for the ion-exchange batches with Kyron T 114. The optimized tablet formulation showed better taste and the formulated

sublingual tablets may act as a potential alternate for the Sumatriptan succinate oral tablet.

Ahmed E Aboutlab et al (2016) formulated sublingual tablets of domperidone (DMP), anti emetic drug having a poor oral bioavailability (13-17%) due to extensive first pass metabolism. The solubility enhanced by solid dispersions of DMP with Pluronic F-68 were prepared in different weight ratios by fusion method and they were evaluated for their in vitro dissolution rate to select the best ratio for final formulation. Then, solid dispersions were formulated into sublingual tablets in combination with various soluble excipients. Sublingual tablets were prepared by direct compression technique and evaluated for their physical properties, in vitro dissolution rate and kinetics of drug release. The best formulae were selected for in vivo studies in rabbits in comparison with marketed oral tablets; Motinorm ®. Solid dispersions of DMP with Pluronic F-68 in a weight ratio of 1:7 (w/w) showed the highest dissolution rate and were selected for sublingual tablets formulation. Sublingual tablets formulae S16 (containing Fructose and 10% w/w Ac-Di-Sol) and S20 (containing Fructose and 10% w/w Explotab) showed the best results and were selected for in vivo studies in rabbits. The selected formulae showed marked enhancement of DMP bioavailability compared with the commercial oral tablets; Motinorm ® , with relative bioavailability values of 432.49±10.13% and 409.32±11.59 % for S16 and S20, respectively. From the results confirmed that sublingual tablets were an effective tool for DMP delivery with marked enhancement of bioavailability.

Sardarmal Yadav et al (2015) developed sublingual tablets of ramipril are most effective against hypertension and provide rapid onset of action with

rapid drug release. The sublingual tablets of ramipril avoid first pass effect so that provide complete utilization of drug and it provide maximum drug release (98.01%).

Baljinder Singh et al (2015) developed sublingual tablets of telmisartan to improve the solubility and bioavailability by encapsulating it inside the cavity of β-cyclodextrin. Sublingual tablets using polymers like CP and SSG and CCS by employing direct compression method and the prepared tablets were evaluated for thickness, uniformity of weight, hardness, friability within the IP limits. Out of 6 formulations, the tablets which contain 5% of CP had shown low wetting time 30.26, low in vitro disintegration time 26.08 sec, high water absorption ratio 95.66% and highest drug release profile i.e 80.33% which release the drug within the 3 minutes.

Mohmed Akbar et al (2015) prepared sublingual tablets of doxofylline using super disintegrant like sodium starch glycolate and crosscarmellose sodium with aview to obtain rapid disintegration when held beneath the tongue, permitting direct absorption of active ingredient by the oral mucosa and it also by passes first pass metabolism and improve the bioavailability. In-vitro release kinetic studies were carried out for zero order, first order, and Higuchi kinetic model. FTIR studies were carried out for pure drug doxofylline, MCC, PVPK30, SSG, crosscarmellose and optimized formulation to confirm that there is no interaction between drug and different excipients.DSC studies carried out to know the thermal stabilities of drug and optimized formulation.

Prathusha B et al (2015) developed and optimized sublingual tablets of Nifedipine for the treatment of angina and hypertension. The solubility of Nifedipine was improved by solid dispersion and FTIR studies confirmed the

absence of drug-excipients interactions. Sublingual tablets were prepared by direct compression method using various concentrations of superdisintegrant and diluents. The formulated tablets were evaluated for hardness, thickness, weight variation, friability, wetting time, *in-vitro* dispersion time, water absorption ratio, drug content, disintegration time and the results were within USP limits. The optimized formulation showed shorter wetting time 22 sec, *invitro* dispersion time of 41 sec and disintegration time 1 min 45 sec and showed 88 folds increase in solubility and *in vitro*-dissolution at 10 min compared to pure Nifedipine and 10 fold increase compared to marketed oral Nifedipine tablets. The drug releases from the sublingual tablets follow Higuchi release kinetics and diffusion was the main mechanism for drug release.

Narendra Yadav et al (2015) prepared sublingual tablets of terbutaline sulphate is a selective B2 bronchodilator which is used in the treatment of asthma. The conventional terbutaline sulphate tablets available in the market are not suitable for onset of action where quicker onset of action required. The tablets were prepared by using mannitol, microcrystalline cellulose pH102 (F1) and lactose monohydrate, microcrystalline cellulose pH102 (F4) as filler and its combination in different ratio, Crospovidone as superdisintegrant and sodium lauryl Sulphate as permeability enhancers by drug dispersion direct compression method. The formulation F1 found the 93.51% of % drug permeability, 8 seconds disintegration time and 96.95% drug release within one minute. The formulation F4 also found the 98.25% of drug permeability, 13 seconds disintegration time and 90.31% drug release within one minute. It was concluded that the sublingual tablet of Terbutaline sulphate can be

formulated for sublingual absorption of drug in emergency treatment of asthma by direct compression drug dispersion method.

Dipti Maheswari S and Pankaj H et al (2014) developed fast disintegrating sublingual tablets by solubility enhancement as Lercanidipine HCL undergoes first pass metabolism in liver and gut wall and it offers a fast relieve from angina pain and hypertension. For solubility enhancement screening of different polymers like povidone k-30, PEG-6000, poloxamer and HPMC3 were done using phase solubility study and Povidone k-30 was selected and solubility increased by solid dispersion by spray drying method was selected. Aspartame and mannitol were used as a sweetener. The preformulation studies showed no interaction between drug and polymer or with other additives. The optimized formulation containing Drug : Polymer ratio (1:3) and crosspovidone 5% showed grater dissolution (more than 95% within 20 min), satisfactory in vitro disintegration time (37 sec).

Kundan P Chaudhari et al (2014) prepared fast disintegrating sublingual tablets of amlodipine besylate by using different disintegrant for the potential emergency treatment of angina and hypertension. The sublingual tablets were prepared by direct compression using Tulsion-671 and crospovidone as a superdisintegrants. The prepared batches of sublingual tablets were evaluated for hardness, friability, drug content uniformity, wetting time, water absorption ratio, and in-vitro disintegration time. All prepared tablets shows the disintegration time less than 1 minute which was within the Pharmacopoeial limit. From the results revealed that the tablets had acceptable hardness 3.15 – 3.59 kg/cm^2 and disintegration time 11 – 59 seconds. Optimum formulation of Tulsion-671 and crosspovidone in

combination showed disintegration time of 11 seconds and 95.89 % of drug release.

Balusu Haarika et al (2014) prepared fast disintegrating rizatriptan benzoate sublingual tablets for the treatment of migraine. The sublingual tablets were prepared by direct compression method using the superdisintegrants like sodium starch glycolate, croscarmellose sodium, cros povidone. The powder properties of all formulations were evaluated for diameter, thickness, weight variation, hardness, friability, wetting time, water absorption ratio, drug content, in-vitro and in-vivo disintegration time as well as in-vitro release. The optimized formulation was characterized by scanning electron microscopy (SEM), differential scanning calorimetry (DSC), powder x-ray diffraction (PXRD), and fourier transform infrared spectroscopy (FTIR). The optimized formulation containing crospovidone disintegrated very fast and very in-vitro drug release was very high.

Sheeba F R et al (2014) developed fast disintegrating sublingual tablets of nifedipine for the potential emergency for treatment of angina and hypertension. Nifedipine undergoes first pass metabolism in liver and gut wall which has oral bioavailability of 43-77%. But the sublingual tablets of nifedipine bypasses the metabolism and offers fast relieve from pain and hypertension. The tablets are prepared by direct compression using superdisintegrant like cros carmellose sodium, sodium sararch glycolate, cros povidone. The studied sublingual tablet group V shows a lesser T50% compared to conventional oral tablet. The group V also indicates the fast dissolution and disintegration rate of the optimized nifedipine sublingual tablet,

which is prerequisite for rapid management of angina and hypertension disease.

Brahmdutta raval et al (2014) prepared sublingual tablets ivabradine hydrochloride for reduction in ischemic condition in Stable Angina. Efficacy of sublingual administration, higher permeability of drug and improvement in bioavailability achievement for drug were the factors that lead to the development of the present work. Compatibility studies of drug and polymer were performed by FTIR and demonstrated no interaction between drug and excipients. Tablets were prepared by direct compression using different concentration of Croscarmellose sodium and Crospovidone. Pre-compression parameters for blend were in the range. Prepared tablets were evaluated for disintegration time, wetting time, Water absorption ratio, %CDR and Ex-vivo permeability study. Formulation F6 (3% CCS, 4.5% CP) was found to be the optimized and showed disintegration time of 25 sec. In vitro drug release was found within 7 minutes and maximum relative permeability from F6 was up to 21 minutes.

Brahmbhatt et al (2014) prepared sublingual tablets of Naratriptan used for the treatment of migraine and for pre and post Compression parameters was undertaken. The tablets were prepared by direct compression method using super disintegrates. After selection of superdisintegrants tablets were prepared by using polymer for reducing the flushing action of saliva and provide enough time for drug absorbed. The prepared tablets were evaluated for their physical and chemical property. The permeation study was performed on Goat mucosa for optimized batch. No interactions were found between drug and excipients. Formulation containing

Crosspovidone shows immediate drug release. Formulation containing Chitoson shows fast drug release as compared to superdisintegrants alone. Sublingual tablets were prepared by direct compression method using Crosspovidone as a superdisintegrants. But it is more effective in combination with Chitoson. As a result, sublingual tablet administration of Naratriptan formulated with appropriate excipients and especially with Chitoson seems promising alternative to traditional routes.

Jaleh Varshosaz et al (2014) prepared mucoadhesive sublingual tablets of Lorazepam, a benzodiazepine drug is used as an antianxiety, sedative, hypnotic, and anticonvulsant drug may accelerate the onset of its action. To optimize the formulation of the mucoadhesive sublingual tablets of lorazepam seven variables including: disintegrating agent type (Primojel or Kollidone), filler [Silicified microcrystalline cellulose (SMCC) or Avicel PH 101], carrier powder (mannitol or lactose), disintegrating agent content (5 or 10%), lubricant type (Mg-stearate or Aerosil), drug content (1 or 2 mg) and mixing time (12 or 24 h) were studied by the Taghuchi design and nine different formulations were prepared. The tablets were tested for their thickness, hardness, weight variation, drug content uniformity, assay, porosity, disintegration time, bioadhesion tensile strength and dissolution efficiency and the effect of different studied formulation parameters were studied on their properties. The formulation of tablets was optimized considering their dissolution efficiency within 10 minutes (DE10%). The optimum formulation obtained from 2 mg of the drug, 1.2 mg Mg-stearate, 6 mg of Primojel, 20.8 mg of Avicel, 90 mg of mannitol which was mixed for 12 hours with the drug. This tablet with the DE10% of 81.30±2.50%, bioadhesion of 34.15±0.15%,

and disintegration time of about 14 sec seems promising as a rapid disintegrating and mucoadhesive sublingual tablet for lorazepam.

Tejas B Parmar et al (2014) developed sublingual tablets of valsartan to overcome first pass metabolism and provide rapid onset of action. The solid dispersion of valsartan prepared with different carriers like β-cyclodextrin, poloxamer 407, PEG 6000, PEG 4000, poloxamer 188, pvp k-30. The proportion of drug and carrier was selected 1:1 due to dose limitation of drug and solubility study was performed to select the carrier, for β-cyclodextrin molar ratio(1:1) was selected. The tablets were prepared by direct compression method using different superdisintegrants like sodium starch glycolate, cross carmellose sodium, cross povidone. The formulation containing Drug-Beta cyclodextrin complex(1:1) and cross carmellose sodium(5%) showed greater drug dissolution and disintegration time(19 sec).

Karan kumar M et al (2014) developed sublingual tablets of Terazosin Hydrochloride, which is an effective drug in the treatment of Benign Prostate Hyperplasia, Hypertension. Sublingual tablets were prepared by direct compression method using different superdisintegrating agents such as Crosspovidone, Sodium starch glycolate and Crosscarmellose sodium. The tablets were evaluated for precompression studies like Bulk density, Tapped density, Carr's index, Hausner's ratio and post-compression studies like Thickness, Hardness, Weight variation, Friability, drug content, Wetting time, Water absorption ratio, in-vitro disintegration time, in-vitro dispersion time, in-vitro dissolution study and also drug release kinetic study. An optimized formulation i.e. F6 was found, which provided short wetting time of 67sec, water absorption ratio of 39.01 , in-vitro disintegration time of 61sec and in-

vitro dispersion time of 112sec. From the above results It indicated that the amount of superdisintegrant i.e. Crosspovidone was significantly affected the dependent variables like Wetting time, Water absorption ratio, in-vitro disintegration time and in-vitro dispersion time and the best in-vitro drug release in formulation F6 i.e. 102% during the end of 15min.

Balkrishna Prajapati et al (2014) developed mouth dissolving sublingual tablets of cimetidine to treat abdominal crampsby direct compression method using superdisintegrants like sodium starch glycolate, cross caarmellose sodium, cross povidone. Binders like PVP, MCC were used. The FT-IR study conducted for the no compatibility between drug and polymers. Th e tablet thickness ranged between 4.066-5.166 mm, hardness ranged between 3.04 - 4.2 kg/cm^2, friability ranged between 0.194-.302, the drug content was found be range of 96.02-99.54%. The stability study for three months at 40±20^0 C, 75±2% RH and results showed that the formulation was found to be stable.

Ajeet M Godbole et al (2014) developed sublingual tablets of ondansetran hydrochloride by direct compression method using different superdisintegrants like cros povidone, sodium starch glycolate and Ac-Di-Sol. The tablets contain ratio of mannitol : maltose : corn starch like 19:2:1 gave better tableting performace with respect to pre-compression and post-compression parameters. Formulation contain 4% cros povidone and PVP K-30 in ratio of 0.5% showed uniform release of drug over a period of 20 minutes with complete solubilization of tablet compared to that of gelatin and carbopol 934.

Aparna B et al (2014) prepared sublingual tablets of aripiprazole. It is an antipsychotic drug used for the treatment of schizophrenia. The sublingual tablets were prepared by direct compression method by using various ingredients such as Crospovidone, Crosscarmellose sodium, Sodium starch glycolate, Microcrystalline cellulose, Aspartame, Aerosil and Magnesium stearate. Fourier transform infrared spectroscopy was confirmed the absence of any drug- polymer interactions. Twelve formulations (F1-F12) of sublingual tablets were prepared by using the various concentrations of super disintegrate. The formulated tablets were evaluated for thickness, hardness, weight variation, friability, wetting time, water absorption ratio, disintegration time, drug content and *in-vitro* drug release studies. The optimized formulation was found, which provided short wetting time of 25 sec, water absorption ratio of 65 sec and disintegration time of 27 sec. The best *in-vitro* drug release was found to be 97.17% at the end of 14 minutes.

Jay G Bhimani et al (2014) developed sublingual tablets of ropinirole is rapidly absorbed in humans and the tablets were prepared by direct compression procedure using different concentration of Crosspovidone and Crosscarmellose Sodium. Preformulation property of API was evaluated. Post-compression parameters such disintegration time, wetting time, water absorption ratio *in vitro* drug release and *ex vivo* permeability study of optimized formulation were determined. FTIR spectroscopy study revealed that there was no possible interaction between drug and polymers. The disintegration time of optimized formulation was up to 40 sec. The *in vitro* release of Ropinirole hydrochloride was up to 9 minutes. The percentage relative permeability of Ropinirole hydrochloride from optimized sublingual

tablets was found to be 90.51% after 30 minutes. Sublingual tablets Ropinirole hydrochloride of were successfully prepared with improved bioavailability.

Ruchita Jaiswani et al. (2014) Oral mucosal drug delivery via mucous membrane is considered to be a promising alternative to the oral route. Sublingual route is a useful gives rapid onset of action is desired with better patient compliance than orally ingested tablets. In terms of permeability, the sublingual area of the oral cavity (i.e. the floor of the mouth) is more permeable than the buccal (cheek) area, which in turn is more permeable than the palatal (roof of the mouth) area. The portion of drug absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolic process. Sublingual technology for patients need enhanced lifecycle management to convenient dosing for geriatric, pediatric and patient with dysphagia. This review highlights the sublingual dosage forms for the treatment of migraine, factors affecting the sublingual absorption, advantages, various *in vitro* and *in vivo* evaluation parameters and commercially available sublingual dosage forms.

Mujtaba Ali et al (2013) prepared sublingual tablets, containing the antiemetic drug ondansetron hydrochloride (OH) which suffers an extensive first-pass effect. OH is a bitter drug its taste was masked by complexing with Tulsion 335 using precipitation technique and formulations were prepared by direct compression method using a bioadhesive polymer. The optimized tablet formulation, containing OH- 5 mg (equivalent to 10.2 mg of DRC), Mannitol-71.8 mg, SMCC-11.5 mg, Cross-linked PVP-6 mg and Magnesium stearate-0.5 mg which gave a short DT of 23.45 ± 3.14 sec, maximum drug release

91.33 ± 3.11% and permeation through porcine sublingual mucosa 63.23 ± 2.01%. From the results, the inclusion of Cross-linked PVP, a bioadhesive polymer, in sublingual tablet formulations, prevented ondansetron from being swallowed, without hindering its release and absorption.

Trambadia, Dipen A et al (2013) developed sublingual tablets of metoprolol succinate is a potent cardio selective beta-1 adrenoreceptor blocker, mostly used in the treatment of acute disorders such as angina pectoris and hypertension. The main objectives of fast disintegrating sublingual tablet the comparative study between cross carmellose sodium and sodium starch glycolate was performed. The fast disintegrating sublingual tablets were prepared by different concentration of super disintegranting agents such as sodium starch glycolate (2%, 4%, 5%, and 6%) and cross carmellose sodium (2%, 4%, 5%, and 6%) by direct compression technique. The disintegration time of optimized formulation was up to 24 sec and in vitro drug release of Metoprolol succinate was up to 3 minutes. The optimized formulation containing 5% cross carmellose sodium which gives better swelling and wicking properties offers effective drug dissolution.

Shafayad Hossain Md et al. (2013) 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. The compressed core and coated tablets were evaluated for thickness, hardness, weight variation, friability, disintegration, dissolution, drug content

and stability. The powder blends for all formulations showed satisfactory bulk density, tapped density, compressibility index, hausner ratio, angle of repose and moisture content. All the core and coated tablets showed acceptable pharmaco-technical properties in terms of thickness, hardness, weight variation, friability, disintegration. Dissolution performances were varied depending on the composition of matrix tablet. Finally a formulation batch B05 consisting of Ticagrelor (34.61%), mannitol (61.15%), sodium starch glycolate (2.69%), hypromellose (HPMC-2910, 5cps) (0.77%), purified talc (0.38%), magnesium stearate (0.38%) and opadry grey (21k57558) (2%) showed maximum similarity with the reference product. Using this formulation a pharmaceutical will be able to meet regulatory compliance.

Naimish A *et al.* (2013) Schizophrenia and schizoaffective disorder are severe and chronic psychiatric illnesses for which treatment compliance is important in the prevention of relapse. Atypical antipsychotic drugs, such as risperidone, have been found to be effective in the treatment of a range of psychiatric disorders. Sublingual tablet of oral formulations of these drugs have been developed to improve their acceptability to patients and thus improve compliance. Improve solubility, bioavailability and to achieved rapid onset action was focus of present investigation.

Sundarshan K Singh et al (2012) formulated sublingual tablets of Lisinopril is the drug of choice in hypertension and have bioavailability of the drug is 25% of orally administered dose. The Objective of present study is to develop the sublingual tablet of Lisinopril and improve its bioavailability, in view to maximize therapeutic effect of the drug. The directly compressed tablet of Lisinopril was formulated using Mannitol, Micro Crystalline Cellulose

and Kyron T-314 as super disintegrant. Formulation (F1-F7) was evaluated for disintegration time and in vitro release study. Further the optimized sublingual formulation (F6) and marketed formulation was subjected to in-vivo comparative bioavailability study using white New Zealand rabbits. It was observed that concentration of Micro Crystalline Cellulose, Kyron T-314 has significant effect on the disintegration time of Lisinopril sublingual tablet formulations. The super disintegrant concentration 5% w/w (Kyron T-314) was found optimum in all tablet formulations. The bioavailability of optimized sublingual tablet of Lisinopril was improved by 1.44 times as compared to conventional oral marketed tablet of Lisinopril. The administration of sublingual tablet becoming easy and it will improve patient compliance to therapy for hypertension for pediatrics, geriatric and bed ridden patient

Nikunj J Aghera et al (2012) Sublingual tablets of Losartan Potassium were prepared to improve it's to avoid pre-systemic metabolism in the gastrointestinal tract and hepatic first pass elimination. The Sublingual tablets were prepared by direct compression procedure by using different concentration of starch 1500 and microcrystalline cellulose. Compatibility study between drug and polymer were performed by FTIR specroscopy and DSC. Preformulation study of API was evaluated. Postcompressional parameters such as disintegration time, wetting time, water absorption ratio, invitro drug release and invivo bioavailability of optimized formulation were determined. The disintegration time for optimized formulation was up to 48 sec and invitro drug release of losartan potassium was 15 min. the percentage relative bioavailability of Losartan Potassium from optimized sublingual tablets was found to be 144.7 %.

Kharshoum RM et al (2012) prepared a novel fast disintegrating Bisoprolol Hemifumarate (BH) tablet formulation for sublingual administration based on the use of 2- hydroxypropyl-βcyclodextrin (HP-βCD) which forms an inclusion complex with (BH) to improve the permeability of the drug to sublingual membrane, in addition to mask the taste of the drug through the inclusion complex (BH) using superdistintegrants like crosscarmellose sodium and crospovidone in concentration of (5%) and tablet were prepared by direct compression method using different mucoadhesive polymers such as chitosan and polyethylene glycol 6000 at different concentration (3% and 6%) for reduction the flushing action of saliva and to provide enough contact time for drug to be absorbed. The tablets were evaluated for the weight variation, hardness, friability, wetting time, disintegration time and dissolution study. The formulae B2 and B7 possessed the lowest disintegration time due to the presence of the high concentration of chitosan, which has some disintegration action, thus were subjected to a pharmacokinetic study using human volunteers. The bioavailability of B2 was significantly higher than that of the reference (Concor®) ($p > 0.05$). Thus, the present investigations suggest that (BH) sublingual tablets allowed the rapid tablet disintegration, improved bioavailability and effective in emergency treatment of anginal pain and hypertension.

Kharshoum RM et al (2011) formulated Ketotifen fumarate fast disintegrating sublingual tablets offers a fast relieve of asthma. To achieve this goal, superdisintegrants and diluents were evaluated for their effect on the disintegration behavior of KF tablets. Full factorial design (24) was applied for a screening study in which four factors were used at two levels (low and

high). The four factors, were the type of disintegrants either Ac-di-sol or Explotab, the concentration of each disintegrant (either 3% or 5% w/w), the binder either Avicel PH101 or PEG6000 and finally the diluent was either spray dried lactose or granular mannitol. Hydroxy propyle betacyclodextrin (2-HP-CD) was used for increasing the absorption of KF tablets formulae. Solid binary system of KF with betacyclodextrin (2-HP-CD) was prepared in molar ratios of 1:1 of drug to cyclodextrin. The formulation containing Ac-di-sol(5%w/w) , Avicel PH101(10%w/w) and granular mannitol as diluent was selected as best formulation that has the least disintegration time of 20 seconds and the highest cumulative dissolution percent of 80.28% after the first minute.

Bayrak Z et al (2011) prepared sublingual tablets of zolmitriptan for the treatment of migraine and the tablets were prepared by direct compression method using different mucoadhesive polymers such as hydroxypropyl methyl cellulose, chitosan and sodium carboxy methyl cellulose at a concentration range of 0.5-5% to reduce flushing action of saliva and provide enough time for drug to be absorbed. It was also concluded that microcrystalline cellulose, spray-dried lactose and sodium starch glycolate are the appropriate excipient and formulated in good proportions. In vivo studies indicated that formulation containing 5% chitosan has the maximum C(max) and AUC and minimum t(max) values ($p<0.05$) and sublingual tablet administration of zolmitriptan formulated with appropriate excipients and especially with chitosan seems promising alternative to traditional routes.

Sindu Abraham et al (2010) developed sublingual tablets of rabeprazole sodium, a class of proto pump inhibitors which is effective in the treatment of acid peptic disorders. The tablets were prepared by wet granulation method using superdisintegrats like cros povidone and cross carmellose sodium. An optimized formulation was prepared which provided a short wetting time of 27 seconds and in-vitro dispersion time of 32 seconds.

Rajat Sharma et al (2010) prepared fast dissolving sublingual tablet of glipizide for potential emergency treatment for diabetic coma. The superdisintegrant used in this study was crospovidone. The tablets were evaluated for weight variation, hardness, friability, wetting time, water absorption ratio, and disintegration time and dissolution study. The tablets were prepared by wet granulation procedure. Sublimation of naphthalene from tablets resulted in better tablets as compared to the tablets prepared from granules that were exposing to vacuum. The systematic formulation approach helped in understanding the effect of formulation processing variables.

Saadia A Tayel et al (2010) prepared sublingual tablets, containing the antiasthmatic drug ketotifen fumarate which suffers an extensive first-pass effect, using the fast-melt granulation technique. The powder mixtures containing the drug were agglomerated using a blend of polyethylene glycol 400 and 6000 as meltable hydrophilic binders. Granular mannitol or granular mannitol/sucrose mixture were used as fillers. A mechanical mixer was used to prepare the granules at 40°C. The method involved no water or organic solvents, which are used in conventional granulation, and hence no drying step was included, which saved time. Twelve formulations were prepared and characterized using official and non-official tests. Three formulations showed

the best results and were subjected to an ex vivo permeation study using excised chicken cheek pouches. The optimized formulation possessed the highest permeation coefficient due to the presence of the permeation enhancer (polyethylene glycol) in an amount which allowed maximum drug permeation, and was subjected to a pharmacokinetic study using rabbits as an animal model. Thus, fast-melt granulation allowed for rapid tablet disintegration and an enhanced permeation of the drug through the sublingual mucosa, resulting in increased bioavailabililty.

Sindhu Abraham *et al.* (2010) developed sublingual tablets of Rabeprazole Sodium, a class of Proton pump inhibitors which is effective in the treatment of acid peptic disorders. The tablets were prepared by wet granulation method based on a central composite design. The formulation variables included quantity of Crospovidone, (X1), and quantity of Croscarmellose Sodium (CCS), (X2), while the response variables determined were wetting time and *In vitro* dispersion time. A quadratic model was used to quantitatively evaluate the main effects and interaction. Surface response plots are presented, to graphically represent the effect of the independent variables on the wetting time and disintegration time. The hardness of all the formulations was in the range 3.0 – 4.0 kg/cm^2.

Kazerani H *et al.* (2009) This study aimed to evaluate the response rate, clinical efficacy and onset of action of sublingual captopril in patients diagnosed with hypertensive urgency. In this cross-sectional study (67 female and 34 male) patients with a diagnosis of hypertensive urgency (systolic pressure greater than or equal to 180 mmHg and/or diastolic pressure greater than or equal to 110 mmHg, and no findings of target organ damage) was

included. and blood pressure was measured during a follow-up period of 120 minutes. The Sublingual captopril (25 mg) was administered and blood pressure was measured during a follow-up period of 120 minutes, Sublingual captopril can be used as an successful, simply applicable and safe treatment and management of hypertensive need for 120 minutes for those who do not get multidrug antihypertensive regimens.

Noushin Bolourtchin et al (2008) developed sublingual tablets of captopril which is an effective drug in the treatment of hypertension. The tablets were prepared by direct compression method using different ingredients such as PVP, starch 1500, sodium starch glycolate. Tablets were evaluated for the physical properties including hardness, friability, wetting time, water absorption ratio, disintegration time and dissolution time.

David harries *et al.* (1992) The delivery of drugs via the mucous membranes lining the oral cavity with consideration of both systemic delivery and local therapy ,the structure and composition of mucousa at different site in the oral cavity, factor affecting mucosal permeability, penetration enhancement, selection of appropriate experimental systems for studying mucosal permeability ,and formulation factor relevant to the design of systems for oral mucosal delivery are discussed. The sublingual delivery gives raped absorption and good permeability this system is not suitable for sustained delivery systems. For this reason buccal mucosa is good for number of peptide drugs. It mainly low molecular weight, high potency. it is safe route for penetration enhancement and to delivery in systemic circulation.

John DN *et al.* (1992) The pharmacokinetics and pharmacodynamics of verapamil administered via the oral and sublingual routes were compared in a randomized, two way cross-over study involving six healthy male volunteers. Administered sublingually, a verapamil 40 mg crushed tablet produced a significantly higher peak plasma concentration, a greater rate of absorption, and greater bioavailability when compared with orally administered verapamil. In comparison with oral dosing, PR intervals were significantly (P less than 0.05) prolonged between 30 and 90 min after sublingual verapamil dosing. Correlations between log plasma verapamil concentration and percentage increase in PR interval were greater after sublingual compared with oral dosing in all volunteers.

CHAPTER IV

AIM OF THE WORK

AIM OF WORK

Difficulty in swallowing (dysphagia) is a common problem of all age groups, especially the elderly and pediatrics, because of physiological changes associated with these groups. Other categories that experience problems using conventional oral dosage forms include are the mentally ill, uncooperative and nauseated patients, those with condition of motion sickness, sudden episodes of allergic attack or coughing.

Sometimes it may be difficult to swallow conventional products due to unavailability of water. These problems led to the development of a novel type of solid dosage form called sublingual tablets, which disintegrate and dissolve rapidly in saliva without the need of drinking water. Upon ingestion, the saliva serves to rapidly dissolve the dosage form.

The saliva containing the dissolved or dispersed medicament is then swallowed and the drug is absorbed in the normal way. Some drugs are absorbed from the mouth, pharynx, and oesophagus as the saliva passes down into the stomach. In these cases, the bioavailability of drugs is significantly greater than those observed from conventional dosage forms.

So, the sublingual drug delivery systems have been introduced to overcome the drawback of low bioavailability problems associated with conventional oral dosage forms. Therapeutically active molecules for the treatment and prevention of new and existing diseases are currently being developed. Although pharmacological activity is the primary requirement for a molecule to be used as a therapeutic agent, it is equally important that the molecule reaches its site of action, and hence drug delivery technologies have assumed importance. Nevertheless, many existing and new molecules

provide challenges of poor pharmacokinetics leading to low bioavailability. Drug delivery systems such as sublingual dosage forms are used to overcome these challenges. Although the cost of these drug delivery technologies is considerably low and substantially less than the cost of developing a new molecule. Hence, a continued interest exists in developing novel drug delivery systems for the delivery of active agents. 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.

Oral administration of Ticagrelor is associated with bioavailability problem. Bioavailability of the drug is 36% of orally administered dose. Mucosa of a sublingual cavity is relatively permeable with rich blood supply, also sublingual drug delivery avoids pre systemic elimination of drug in GI Tract make this portal of drug administration quite attractive and feasible site for systemic delivery of drugs. So, the aim of present work was to develop and characterize sublingual tablet of Ticagrelor with improved bioavailability.

CHAPTER V

PLAN OF WORK

PLAN OF WORK

I. PREPARATION OF STANDARD CALIBRATION CURVE

a. Determination of λ-max for ticagrelor

b. Calibration of ticagrelor in phosphate buffer pH6.8

II. COMPATIBILITY STUDIES FOR DRUG AND EXCIPIENTS

a. Fourier transform Infra-Red Spectroscopic (FTIR) studies

b. Differential Scanning Colorimetry (DSC) studies

c. X-ray Diffraction (XRD) studies

III. FORMULATION AND EVALUATION OF SOLID DISPERSION

a. Formulation of solid dispersion

b. Estimation of percentage yield and drug content

c. Invitro dissolution studies

d. Selection of best formulations

IV. PEREFORMULATION EVALUATION OF POWDER BLEND

a. Angle of repose

b. Bulk density

c. Tapped density

d. Carr's index (I) or % compressibility index

e. Hausner's ratio

V. FORMULATION OF TICAGRELOR SUBLINGUAL TABLETS

a. By direct compression

VI. EVALUATION OF POST COMPRESSION PARAMETERS OF SUBLINGUAL TABLETS

a. General appearance

b. Tablet thickness and diameter

c. Hardness

d. Weight variation test

e. Friability

f. Uniformity of drug content

g. Water absorption ratio

h. Wetting time

i. *Invitro* drug release study

j. *Invitro* disintegration time

VII. EFFECT OF DIFFERENT SUPERDISINTEGRANT ON RELEASE PROFILE OF TICAGRELOR SUBLINGUAL TABLETS

VIII. COMPARISION OF DISSOLUTION DATA OF TICAGRELOR SUBLINGUAL

TABLETS CONTAINING DIFFERENT SUPERDISINTEGRANT

IX. SELECTION OF BEST FORMULATION

X. EVALUATION OF SELECTED FORMULATION

a. Differential scanning colorimetry (DSC) study

b. Fourier transform infra-red (FTIR) spectroscopic study

c. Powder X-ray Diffraction(PXRD) study

XI. DRUG RELEASE KINETIC MODEL

XII. STABILITY STUDIES

CHAPTER VI

MATERIALS AND EQUIPMENTS

MATERIALS AND SUPPLIERS

MATERIALS	MANUFATURERS / SUPPLIERS	USE IN FORMULATION
Ticagrelor	Drug Testing Laboratory, Chennai	Acive ingredient
PEG 6000	Madras pharma, chennai	Hydrophilic polymer
Sodium starch glycolate	Madras pharma, chennai	Superdisintegrant
Crosscarmellose sodium	Madras pharma, chennai	Superdisintegrant
Crosspovidone	Sai Mirrah innopharma	Superdisintegrant
Microcrystalline cellulose	Sai Mirrah innopharma	Diluent
Saccharin sodium	Madras phrama, chennai	Sweetening agent
Mannitol	Madras pharma,chennai	Diluent
Talc	Madras pharma, chennai	Glident
Magnesium stearate	Sai Mirrah innopharma	Lubricant

INSTRUMENTS /EQUIPMENTS AND SUPPLIERS

EQUIPMENTS / INSTRUMENTS	MANUFACTURERS / SUPPLIERS
Electronic Weighing Balance	A & D Company, Japan
UV Visible spectrophotometer	Shimadzu UV – 1800, Japan
Fourier Transform Infrared Spectroscopy	Shimadzu, Japan
Hot air oven	Induatrial headers, Chennai
Digital Vernier Calliper	Linker, Mumbai
Monsanto Hardness Tester	Erweka, Mumbai
Friability test apparatus	Indian equipment corporation
Disintegration apparatus	Rolex, India
Dissolution apparatus	Lab India Disso Apparatus
Stability Chamber	In labs Equipment(Madras) Pvt.Ltd
12-Station D/B Tooling Compression Machine	Fluid Pack, Ahmedabad

CHAPTER VII

DRUG PROFILE

DRUG PROFILE

TICAGRELOR

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.

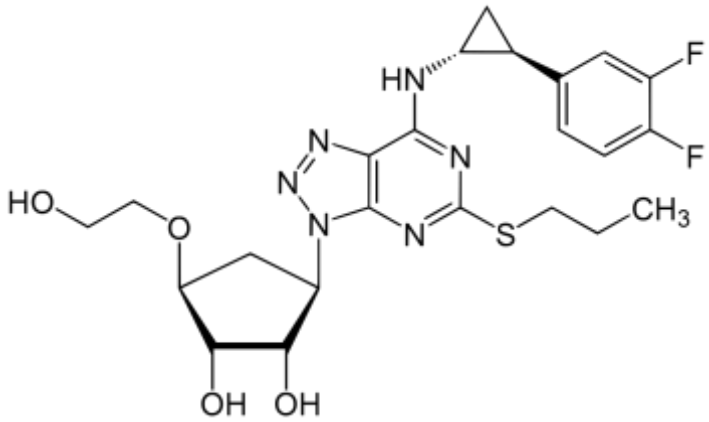
Therapeutic category

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.

CHEMICAL STRUCTURE



EMPIRICAL FORMULA

$C_{23}H_{28}F_2N_6O_4S$

MOLECULAR WEIGHT

522.6 g/mol

PHARMACOLOGIC CLASS

$P2Y_{12}$ receptor antagonist.

Adenosine Diphosphate (ADP) receptor inhibitor.

DESCRIPTION

- Physical State : Solid
- Colour : A white or off-white to pale pink
- Nature : Non hygroscopic, crystalline powder
- Melting Point : 138 – 140^0 C
- LogP : 2.31
- Bioavailability : 36%
- Solublility : Soluble in methanol, ethanol, DMSO, dimethyl formamide (DMF)
- Water solubility : 10 µg/ml (practically insoluble in water).
- Dose : 60 to 180 mg twice a day orally for one year
- Usual strength : 60mg; 90 mg.

PHARMACOLOGY

Mechanism of action

Ticagrelor, a member of the chemical class cyclopentyltriazolopyrimidines (CPTP), which is an oral, direct acting selective and reversibly binding P2Y12 receptor antagonist that prevents adenosine diphosphate (ADP)-mediated P2Y12 dependent platelet activation

and aggregation. Ticagrelor does not prevent ADP binding but when bound to the P2Y12 receptor prevents ADP-induced signal transduction. Since platelets participate in the initiation and/or evolution of thrombotic complications of atherosclerotic disease, inhibition of platelet function has been shown to reduce the risk of cardiovascular events such as death, myocardial infarction or stroke. Ticagrelor has no clinically significant direct effect on adenosine receptors (A1, A2A, A2B, A3) and is not metabolized to adenosine.

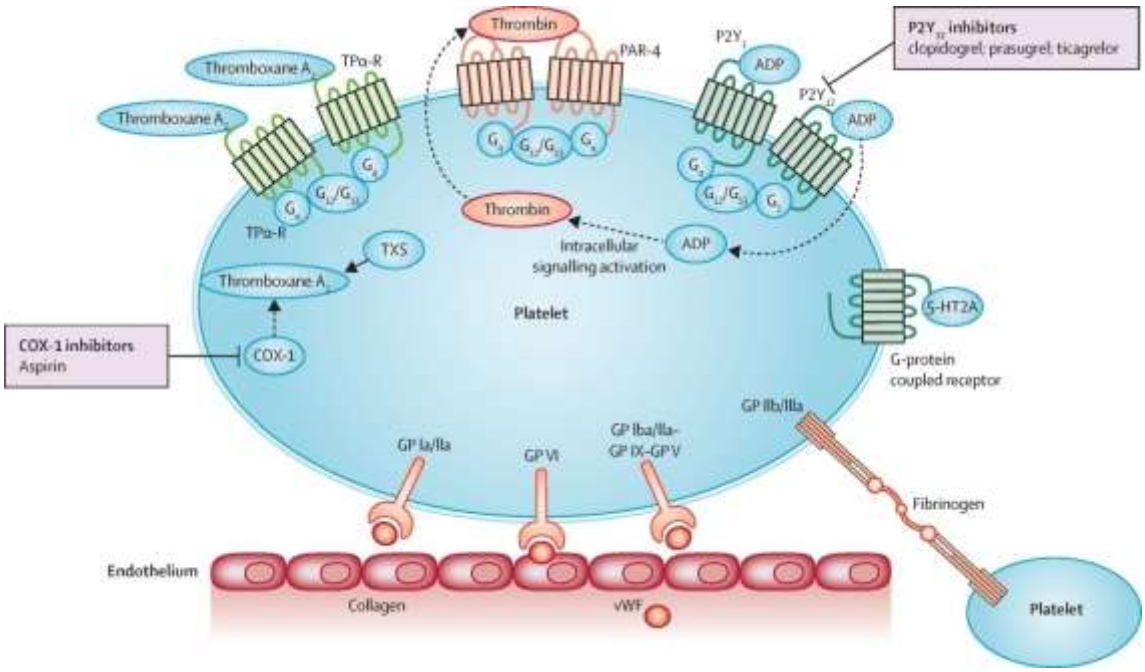


Figure. Mechanism of Action of P2Y$_{12}$ Inhibitors

PHARMACOKINETICS

Ticagrelor demonstrates linear pharmacokinetics. Exposure to ticagrelor and active metabolite AR-C124910XX are approximately dose proportional.

Absorption

Absorption of ticagrelor is rapid with a median tmax of approximately 1.5 hours. The formation of the major circulating metabolite AR-C124910XX (also active) from ticagrelor is rapid with a median tmax of approximately 2.5 hours. The Cmax and AUC of ticagrelor and the active metabolite increased in an approximately proportional manner with dose over the dose range studied (30-1260 mg).

The mean absolute bioavailability of ticagrelor was estimated to be 36%, (range 25.4% to 64.0%). Ingestion of a high-fat meal had no effect on ticagrelor Cmax or the AUC of the active metabolite, but resulted in a 21% increase in ticagrelor AUC and 22% decrease in the active metabolite Cmax. These small changes are considered of minimal clinical significance; therefore, Ticagrelor can be given with or without food.

Ticagrelor as crushed tablets mixed in water, given orally or administered through nasogastric tube into the stomach, is bioequivalent to whole tablets (AUC and Cmax within 80-125% for ticagrelor and the active metabolite). Compared to whole tablets, the geometric least-squares (LS) mean concentrations of ticagrelor were higher at 0.5 hour and 1 hour following administration of crushed tablets suspended in water and dispersed tablets suspended in water administered via NGT, respectively. At two hours post-dose the geometric LS mean concentrations following administration of the crushed tablet suspended in water and the dispersed tablet suspended in water administered via NGT were similar to the geometric LS mean concentration following administration of the whole tablet.

Distribution

The steady state volume of distribution of ticagrelor is 87.5 L. Ticagrelor and the active metabolite is extensively bound to human plasma protein (>99.0%).

Metabolism

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 P2Y12 ADP-receptor. The systemic exposure to the active metabolite is approximately 30-40% of that obtained for ticagrelor.

Excretion

The primary route of ticagrelor elimination is via hepatic metabolism. When radiolabelled ticagrelor is administered, the mean recovery of radioactivity is approximately 84% (57.8% in faeces, 26.5% 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 active metabolite is mostly via biliary secretion. The mean t1/2 was approximately 6.9 hours (range 4.5-12.8 hours) for ticagrelor and 8.6 hours (range 6.5-12.8 hours) for the active metabolite.

Clearance of ticagrelor

The systemic clearance of ticagrelor is **14.2 L/h.**

ADVERSE EFFECTS

- Shortness of breath (dyspnea, 14%) and various types of bleeding, such as hematoma, nosebleed, gastrointestinal, subcutaneous or dermal bleedi ng
- Ventricular pauses of 3 seconds occur in 5 percent of people in the first week of treatment.
- Ticagrelor should be administered with caution or avoided in patients with advanced sinoauricular disease.
- Allergic skin reactions such as rash and itching have been observed in less than 1% of patients.

INDICATIONS

- Ticagrelor, in combination with aspirin, is indicated for the prevention of atherothrombotic events (cardiovascular death, myocardial infarction and stroke).
- In adult patients with acute coronary syndromes (unstable angina [UA], non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]) including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).

CONTRAINDICATIONS

- Active pathological bleeding,
- History of intracranial haemorrhage,
- Moderate to severe hepatic impairment,

- Co-administration of ticagrelor with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir) is contraindicated, as co-administration may lead to a substantial increase in exposure to ticagrelor.

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.(Example : rifampin, phenytoin, carbamazepine, phenobarbital)
- 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.


60 tablets
BRILINTA™
ticagrelor
90 mg
Film-coated tablets
AstraZeneca
Brilinta is a trade mark of the AstraZeneca group of companies.
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CHAPTER VIII

EXCIPIENTS PROFILE

EXCIPIENT PROFILE

MICROCRYSTALLINE CELLULOSE

Synonyms :

- Avicel PH
- Crystalline cellulose
- Cellet
- Emcocel
- Hellulosum microcristalinum

Chemical name:

- Cellulose

Empirical formula:

- $(C_6H_{10}O_5)_n$

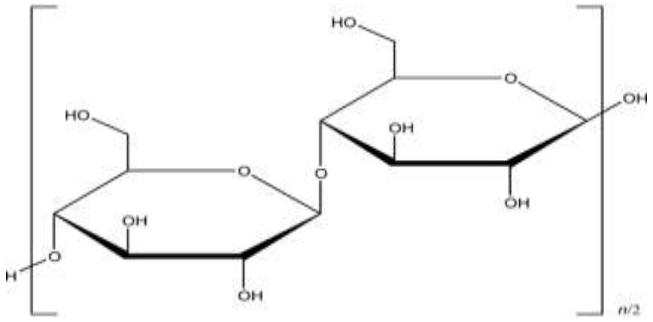
Molecular weight:

- 36000 gm/mol

Functional category:

- Adsorbent
- Suspending agent
- Tablet and capsule diluents
- Tablet disintegrant

Structural formula:



Application in pharmaceutical formulation or technology:

- Microcrystalline cellulose is widely used in pharmaceuticals primarily as binder / diluents in oral tablets and capsule formulation.
- Micerocrystalline cellulose is also used in cosmetics and food products.

Description :

- Microcrystalline cellulose is a white, odorless, tasteless, crystalline powder composed of polrous particles.

Melting Point:

- 260-270^{0}C

Solubility :

- Slightly soluble in 5% w/v NaOH solution, practically insoluble in water and most organic solvents.

Solubility and storage condition:

- Microcrystalline cellulose is stable though hygroscopic material.
- It should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

- Microcrystalline cellulose is incompatible with strong oxidizing agent.

Handling Precautions:

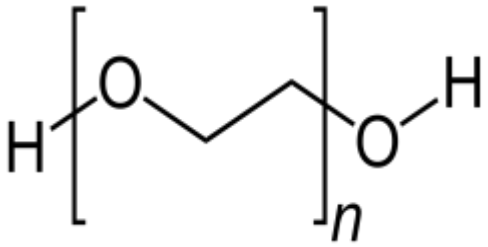
- Microcrystalline cellulose may be irritant to the eyes, Gloves, eye protection and dust mask are recommended.

  (Hand book of pharmaceutical Excipient by Raymond C Rowe.,5th Edition)

POLYETHYLENE GLYCOL 6000

- Polyethylene glycol 6000 (PEG) is a polyether compound. The structure of PEG is **HO-CH2-(CH2-O-CH2-)n-CH2-OH**
- PEG is also known as polyethylene oxide (PEO) or polyoxyethylene (POE), depending on its molecular weight.

Structure



Nonproprietary Names

- Carbowax, GoLYTELY
- GlycoLax, Fortrans
- TriLyte, Colyte
- Halflytely,
- Macrogol,
- MiraLAX

Synonyms

- PEG; Macrogol;
- Polyoxyethlene; Aquaffin;
- Nycoline alpha-hydro-omega-hydroxypoly(oxy-1,2-ethanediyl);
- polyethylene glycols; Poly Ethylene Oxide; Polyoxyethylene;
- Polyglycol; 1,2-ethanediol Ehoxylated;
- Polyoxyethylene ether;
- Polyoxyethylene; Poly(ethylene glycol);

Chemical Name and CAS Registry Number

- a-Hydro-o-hydroxypoly(oxy-1,2-ethanediyl) [25322-68-3]

Empirical Formula and Mol. Weight

- H(OCH2CH2)nOH [average 6000 g/mol]

Functional Category

- Lubricating agent,
- solubilizing agent,
- coating agent

DESCRIPTION:

- Boiling Point : Min. 250°C (1013 hPa)
- Melting Point : 55 to 62 °C
- Density : 1.13 g/cm³ (20°C)
- Appearance : White or almost white, waxy or paraffin-like
- Solubility : Soluble in water

Applications in Pharmaceutical Formulation or Technology

Chemical uses

- Polyethylene glycol has a low toxicity and is used in a variety of products. The polymer is used as a lubricating coating for various surfaces in aqueous and non-aqueous environments.
- Since PEG is a flexible, water-soluble polymer, it can be used to create very high osmotic pressures (on the order of tens of atmospheres).
- Polyethylene glycol is also commonly used as a polar stationary phase for gas chromatography, as well as a heat transfer fluid in electronic testers.
- In addition, PEG is used when working with green wood as a stabilizer, and to prevent shrinkage.
- PEG is often used (as an internal calibration compound) in mass spectrometry experiments, with its characteristic fragmentation pattern allowing accurate and reproducible tuning.
- PEG derivatives, such as narrow range ethoxylates, are used as surfactants.
- PEG has been used as the hydrophilic block of amphiphilic block copolymers used to create some polymersomes.

Industrial uses

- Nitrate ester-plasticized polyethylene glycol is used in Trident II ballistic missile solid rocket fuel.
- Dimethyl ethers of PEG are the key ingredient of Selexol, a solvent used by coalburning, integrated gasification combined cycle (IGCC)

power plants to remove carbon dioxideand hydrogen sulfide from the gas waste stream.

- PEG has been used as the gate insulator in an electric double-layer transistor to induce
- superconductivity in an insulator.
- PEG is also used as a polymer host for solid polymer electrolytes. Although not yet in commercial production, many groups around the globe are engaged in research on solid polymer electrolytes involving PEG, with the aim of improving their properties, and in permitting their use in batteries, electro-chromic display systems, and other products in the future.

Safety

- Polyethylene glycols are widely used in a variety of pharmaceutical formulations. Generally, they are regarded as nontoxic and nonirritant materials. Adverse reactions to polyethylene glycols have been reported, the greatest toxicity being with glycols of low molecular weight.
- However, the toxicity of glycols is relatively low.

Handling Precautions

- Observe normal precautions appropriate to the circumstances and quantity of material handled.
- Eye protection is recommended.

MANNITOL

Synonym:

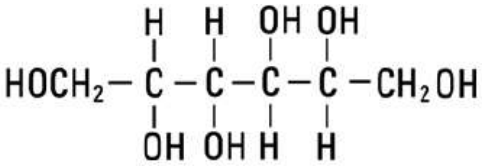
- Cordycepic acid
- Manna sugar
- D- mannite
- Mannogem
- Pearlitol

Chemical Name: Mannitol

Empirical Formula: $C_6H_{14}O_6$

Molecular Weight: 182.17

Structural Formula:



Functional Category:

- Diluents
- Sweetening agent
- Tonicity agent

Applications:

- It is used as a diluent in tablet formulations. (10-90% w/v)
- It is used in pharmaceutical formulations and food products.
- It is used in tablet applications include antacid preparation glyceryltrinitrite tablets and vitamin preparations. It is used as an excipient in the manufacture of chewable tablet formulation.
- It is also used in sweetness and mouth feel due to its negative heat of solution.

- In lyophilized preparations, mannitol (20-90%w/w) had been included as a carrier to produce a stiff, homogenous cake that improves the appearance of the lyophilized plug in vial.
- It is used in food application as a bulking agent.
- Mannitol administered parentally is used as an osmotic diuretic, it is used in diagnostic agent for kidney function, as an adjunct in the treatment of acute renal failure.

Description:

- Mannitol occurs as a white, odourless, crystalline powder or free flowing granule.
- It has a sweet taste, approximately as sweet glucose and half as sweet as sucrose and imparts a cooling sensation in the mouth.
- Mannitol was found to reduce the oral bio availability of cimetidine compared to sucrose.
- Mannitol is reducing sugar, impurities have been implicated in the oxidative degradation of a peptide in a lyophilized formation.

Handling precautions:

Mannitol is irritant to the eyes; eye protection is recommended.

CROSSPOVIDONE

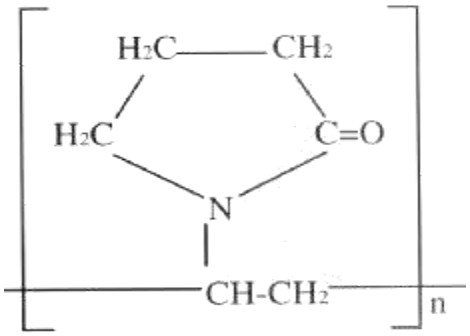
Synonym:

- Cross linked povidone
- Kollido
- 1-vinyl-2-pyrrolidone homopolymer
- Polyplasdone
- Polyvinylpolypyrrolidone

Chemical name :

- 1-Ethylene-2-pyrrolidinone homopolymer

Functional formula :



Empirical formula:

- $(C_6H_9NO)_n$

Molecular weight:

- >1000 000

Functional category:

- Tablet disintegrant.

Application in pharmaceutical formulation or technology:

- Tablet disintergrant and dissolution agent.
- Solubility enhancer for poorly soluble drug

Description:

- Crosspovidone is a white-creamy white
- Free flowing
- Practically tasteless
- Hygroscopic powder

Melting Point:

- $150^{O}C$

Stability and Storage condition:

- Crosspovidone is hygroscopic.
- It should be stored in an airtight container in a cool, dry place.

Incompatibilities:

- Crosspovidone is compatible with most organic and inorganic pharmaceutical ingredients.
- When exposed to a high water level.
- Crosspovidone may form molecular adduct with some materials.

Handling Precautions:

- Observe normal precaution appropriate to the circumstances and quantity of material handled.
- Eye protection gloves and a dust mask are recommended

(Hand book of Pharmaceutical Excipients by Raymond C Rowe 5^{th} Edition.)

TALC

Synonym:

- Altalc
- Hydrous magnesium calcium silicate
- Hydrous magnesium silicate

Chemical name:

- Talc
- Purified talc
- Talcum

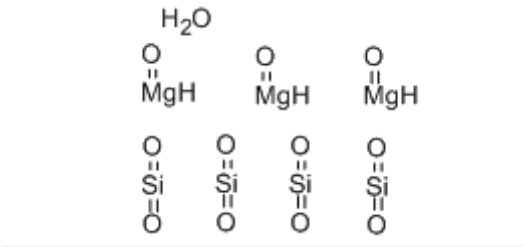
Empirical Formula:

- Talc is purified, hydrated, magnesium silicate.
- Mg6 ((Si2O5)4(OH) 4)
- It may contain small variable amounts of silicate and iron.

Molecular weight:

- 379.27

Structural Formula:



Functional Category

- Anticaking agent
- Glidant

- Diluent
- Lubricant

Application in pharmaceutical formulation or technology:

- Talc is widely used in solid dosage formulations.
- Lubricant and Glidant. (1.0-10.0)
- Diluents in tablet and capsule. (5.0-30)
- It is widely used as a dissolution retardant in the development of controlled-release products.
- Talc is novel powder coating for extended release pellets and as an adsorbent.
- It is used as a dusting powder. (concentration 90.0-99.0)
- It is used to clarify liquids and is used in cosmetics and food products.
- It is used in baby powder.

Description:

- Talc is very fine, white to grey-white, odourless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to touch and free from grittiness.

Melting Point:

- 800^{o}C

Solubility:

- Practically insoluble in organic solvent, water and in dilute acids & alkalis.

Stability and Storage condition:

- Talc is a stable material and may be sterilized by heating at 160^{o}C for not less than one hour.
- It may also be sterilized by exposure to ethylene oxide or gamma radiation.
- Talc should be stored in well closed container in a cool, dry place.

Incompatibilities:

- Incompatible with quaternary ammonium compounds.

Handling Precautions:

- Talc is irritant if inhaled and prolonged exposure may cause pneumoconiosis.
- In the UK, the occupational exposure limit for talc is long-term (8 hour TWA). Eye protection, gloves and respirator are recommended.

(Hand book of Pharmaceutical Excipients by Raymond C Rowe.,5th Edition)

MAGNESIUM STEARATE

Synonym:

- Magnesium octadecanoate
- Octadecanoic acid
- Magnesium salt
- Stearic acid
- Magnesium salt

Chemical Name:

- Octadecanoic acid magnesium salt (557-04-0)

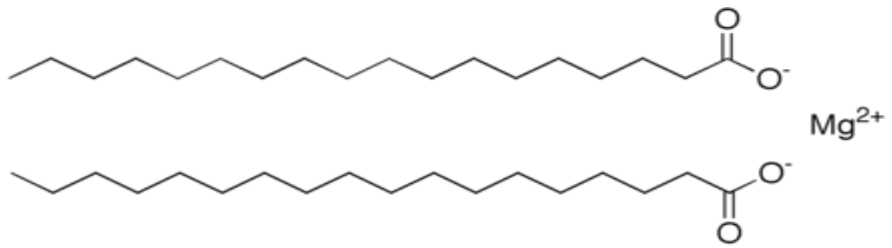
Empirical Formula:

- Magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists of variable proportions of magnesium stearate and magnesium palmitate.
- Magnesium stearate : C_{36} H_{20} MgO_4
- Magnesium palmitate : C_{32} H_{62} MgO_4

Molecular weight:

- 591.34

Structural Formula:



Functional Category:

- Tablet and capsule lubricant.

Application inpharmaceutical Formulation or Technology:

- It is widely used in cosmetics, foods and pharmaceutical formulations.
- It is used as a lubricant in capsule and tablet manufacture at concentrations 0.25% and 5.0% w/w.

Description :

- Magnesium Stearate is a very fine, light white, precipitated or milled, impalpable powder of low density, having a faint odour of stearic acid and a characteristic taste.
- The powder is greasy to touch and readily adheres to the skin

Melting Point:

- 117-150^{O}C

Solubility:

- Slightly soluble in warm benzene and warm ethanol.
- Practically insoluble in ethanol and water.

Stability and Storage condition:

- Magnesium stearate is stable and should be stored in well closed container in a cool, dry place

Incompatibilities:

- Incompatible with strong acids, alkalis and iron salts.
- Magnesium stearate cannot be used with aspirin, some vitamin and most alkaloidal salts.

Handling Precautions:

- Eye protection and gloves are recommended.
- Excessive inhalation of magnesium stearate dust may cause upper respiratory tract discomfort, coughing and choking.

  (Hand book of Pharmaceutical Excipients by Raymond C Rowe.,5thEdition).

CROSSCARMELLOSE SODIUM

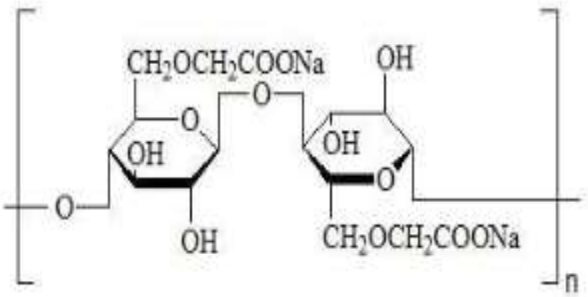
Synonyms:

- Ac-Di-Sol;
- carmellosum natricum conexum;
- crosslinked carboxymethylcellulose sodium;
- Explocel; modified cellulose gum;
- Nymcel ZSX; Pharmacel XL;
- Primellose; Solutab; Vivasol

Chemical name:

- Cellulose,
- carboxymethyl ether,
- sodium salt, crosslinked

Structure:



Chemical formula:

- $C_8H_{16}O_8$

Functional uses:

- Tablet and capsule disintegrant.

Description:

- Crosscarmellose sodium occurs as an odorless, white or grayish white powder.

Applications in Pharmaceutical Formulation or Technology:

- Crosscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets, and granules.
- In tablet formulations, crosscarmellose sodium may be used in both direct-compression and wet-granulation processes. When used in wet granulations, the crosscarmellose sodium should be added in both the wet and dry stages of the process (intra- and extragranularly) so that the wicking and swelling ability of the disintegrant is best utilized.
- Crosscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process

Stability and Storage Conditions:

- Crosscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with crosscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 30 8C for 14 months.
- Crosscarmellose sodium should be stored in a well-closed container in a cool, dry place

Incompatibilities:

- The efficacy of disintegrants, such as crosscarmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct-compression process that contain hygroscopic excipients such as sorbitol. Crosscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.

Safety:

- Crosscarmellose sodium is mainly used as a disintegrant in oral pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material.
- However, oral consumption of large amounts of crosscarmellose sodium may have a laxative effect, although the quantities used in solid dosage formulations are unlikely to cause such problems.

SODIUM STARCH GLYCOLATE

Nonproprietary Names

- BP: Sodium Starch Glycolate
- PhEur: Sodium Starch Glycolate
- USP-NF: Sodium Starch Glycolate

Synonyms

- Carboxymethyl starch,
- sodium salt;
- carboxymethylamylum natricum;
- Explosol;

- Explotab;
- Glycolys; Primojel;
- starch carboxymethyl ether,
- sodium salt; Tablo; Vivastar P.

Chemical Name

- Sodium carboxymethyl starch

Empirical Formula

- $C_2H_4O_3$ x Na x-Unspecified

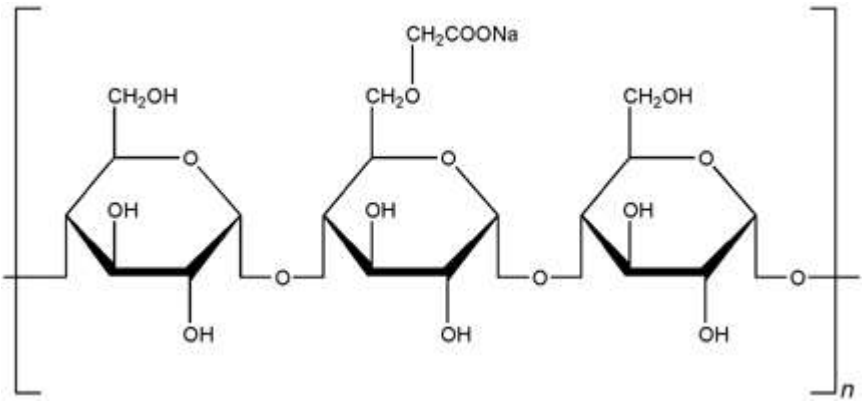
Fragment

- $C_2H_4O_3$ Component Na Unspecified

Molicular weight

- Sodium starch glycolate may be characterized by the degree of substitution and crosslinking. The molecular weight is typically 5 $x10^5$ – 1 x 10^6.

Structural Formula



Functional Category

- Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation or Technology

- Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations.
- It is commonly used in tablets prepared by either direct-compression or wet-granulation processes.
- The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient..
- Increasing the tablet compression pressure also appears to have no effect on disintegration time.
- Sodium starch glycolate has also been investigated for use as a suspending vehicle.

Description

- Sodium starch glycolate is a white or almost white free-flowing very hygroscopic.

Melting point

- Does not melt, but chars at approximately 200^0C

Solubility

- Practically insoluble in methylene chloride. It gives a translucent suspension in water.

Stability and Storage Conditions

- Tablets prepared with sodium starch glycolate have good storage properties.
- Sodium starch glycolate is stable although very hygroscopic, and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking.
- The physical properties of sodium starch glycolate remain unchanged for up to 3 years if it is stored at moderate temperatures and humidity.

Incompatibilities

- Sodium starch glycolate is incompatible with ascorbic acid.

Safety

- Sodium starch glycolate is widely used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. However, oral ingestion of large quantities may be harmful

Handling Precautions

- Observe normal precautions appropriate to the circumstances and quantity of material handled.
- Sodium starch glycolate may be irritant to the eyes; eye protection and gloves are recommended.
- A dust mask or respirator is recommended for processes that generate a large quantity of dust.

SACCHARIN SODIUM

Nonproprietary Names

- BP: Saccharin Sodium
- JP: Saccharin Sodium Hydrate
- PhEur: Saccharin Sodium
- USP: Saccharin Sodium

Synonyms

- 1,2-Benzisothiazolin-3-one 1,1-dioxide,
- sodium salt; Crystallose;
- E954; gendorf 450;
- saccharinum natricum;
- sodium o-benzosulfimide;
- soluble gluside; soluble saccharin;
- sucaryl sodium.

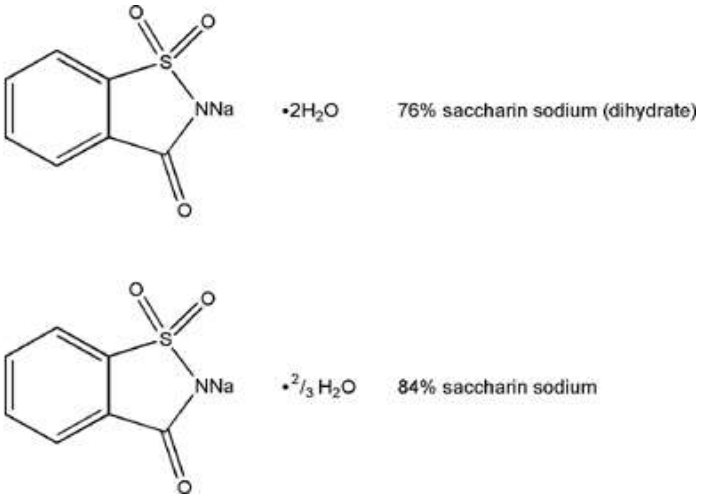
Chemical Name

- 1,2-Benzisothiazol-3(2 H)-one 1,1-dioxide

Empirical Formula and Molecular Weight

- $C_7 H_4 NNaO_3 S$ 205.16
- $C_7 H_4 NNaO_3 S. {}^1/_2 H2O$ (84%) 217.24
- $C_7 H_4 NNaO_3 S. 2H2O$ (76%) 241.19

Structural Formula



Functional Category

- Sweetening agent.

Applications in Pharmaceutical Formulation or Technology

- Saccharin sodium is an intense sweetening agent used in beverages, food products, table-top sweeteners, and pharmaceutical formulations such as tablets, powders, medicated confectionery, gels, suspensions, liquids, and mouthwashes.
- It is also used in vitamin preparations.
- Saccharin sodium is considerably more soluble in water than saccharin, and is more frequently used in pharmaceutical formulations.
- Its sweetening power is approximately 300–600 times that of sucrose. Saccharin sodium enhances flavor systems and may be used to mask some unpleasant taste characteristics.
- Injection of saccharin sodium has been used to measure the arm to-tongue circulation time.

Uses of saccharin sodium

- Dental paste/gel 0.12–0.3%
- IM/IV injections 0.9%
- Oral solution 0.075–0.6%
- Oral syrup 0.04–0.25%

Description

- Saccharin sodium occurs as a white, odorless or faintly aromatic, efflorescent, crystalline powder.
- It has an intensely sweet taste, with a metallic or bitter after taste that at normal levels of use can be detected by approximately 25% of the population. The aftertaste can be masked by blending saccharin sodium with other sweeteners. Saccharin sodium can contain variable amounts of water.

Melting point

- Decomposes upon heating.
- 228.8^0 C

Stability and Storage Conditions

- Saccharin sodium is stable under the normal range of conditions employed in formulations.
- Only when it is exposed to a high temperature 125^0C at a low pH (pH 2) for over 1 hour does significant decomposition occur. The 84% grade is the most stable form of saccharin sodium since the 76% form will dry further under ambient conditions.
- Solutions for injection can be sterilized by autoclave.

- Saccharin sodium should be stored in a well-closed container in a dry place.

Incompatibilities

- Saccharin sodium does not undergo Maillard browning.

Safety

- There has been considerable controversy concerning the safety of saccharin and saccharin sodium in recent years; however, it is now generally regarded as a safe, intense sweetener.
- The WHO has set a temporary acceptable daily intake of up to 2.5 mg/kg body-weight for saccharin, including its salts.
- In the UK, the Committee on Toxicity of Chemicals in Food, Consumer Products, and the Environment (COT) has set an acceptable daily intake for saccharin and its salts (expressed as saccharin sodium) at up to 5 mg/kg body-weight.

Handling Precautions

- Observe normal precautions appropriate to the circumstances and quantity of material handled.
- Eye protection and a dust mask are recommended.

CHAPTER IX

EXPERIMENTAL PROTOCOL

EXPERIMENTAL PROTOCOL

Colour and Appearance: ***(Indian Pharmacopoeia, 2018)***

The sample was observed visually.

Melting Point: ***(Indian Pharmacopoeia, 2018)***

Melting point of drug was determined by Melting point test apparatus.

Solubility: ***(Indian Pharmacopoeia, 2018)***

Solubility study was carried out as per the I.P.2018.In this maximum amount of solvent required to dissolve the solute was determined.

PREPARATION OF BUFFER SOLUTION ***(Indian Pharmacopoeia, 2014)***

Preparation of pH 6.8 phosphate buffer solution

Take 50 ml of 0.2M Potassium Dihydrogen phosphate in a200ml volumetric flask and add 22.4ml of 0.2M Sodium hydroxide solution, then the volume was made upto 200ml using distilled water.

Preparation of 0.2M potassium dihydrogen phosphate

27.218g of potassium dihydrogen phosphate was dissolved in distilled water and the volume was made up to 1000 using distilled water.

Preparation of 0.2M sodium hydroxide

8g of sodium hydroxide was dissolved in distilled water and made up to 1000ml with distilled water.

DETERMINATION OF MAXIMUM ABSORPTION (λ MAX)

The standard stock solution of ticagrelor having concentration 10µg/ml is prepared by dissolving 10mg of ticagrelor in 5ml methanol and diluted with phosphate buffer pH 6.8 up to 10 ml. The stock solution is further diluted

using phosphate buffer to produce 10µg/ml concentration. The resultant solution is scanned between wavelength of 200-400nm by UV spectrophotometer to get maximum absorption (λmax). ***(Ranjan Kumar et al.2016)***

PREPARATION OF STANDARD CALIBRATION CURVE FOR TICAGRELOR:

From the above stock solution, aliquots are taken into different volumetric flasks and volume are made up to 10 ml with phosphate buffer PH 6.8 solution, so as to get concentration of 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 µg/ml. The absorbance of these solution is measured at 295 nm by UV spectrophotometer. A calibration curve is plotted by taking concentration on X- axis and absorbance on Y-axis to obtain the standard curve.

DRUG- EXCIPIENTS COMPATIBILITY STUDIES

Fourier Transform infrared (FTIR) spectroscopy studies:

FT–IR spectra were recorded for ticagrelor pure drug and physical mixture using IR spectrophotometer. The samples were prepared in KBr dish and scanned over 400 to 4000 cm^{-1} ***(Rajendra B. Kakde et al. 2017)***

Differential scanning colorimetric (DSC) studies

Differential scanning calorimetry was used to characterize thermal properties of ticagrelor and other excipients. Shimadzu TA – 60WS thermal analyzer was used to obtain DSC measurements. Required amount of sample(about 2mg) were placed in flat bottomed aluminium pans(0.1mm thickness) and then crimped with an aluminium lid. Then the samples were placed into sample holder and allowed to heat from 25 to 300 ˚C at a fixed

heating rate (10 ˚C per minute) under a nitrogen flow (10cc/minute). The temperature calibration of the instrument was carried out using indium standard, the same heating rate and pan type used for the study. Heat flow and heat capacity signals were calibrated using powdered alumina (5mg, 100mesh) as a reference. ***(Nazare et al. 2017)***

FORMULATION AND EVALUATION OF SOLID DISPERSION:

a. Formulation of solid dispersion:

In this method is based on the hydrophilic polymer is heated and convert into a paste. The drug is then added to the above paste for a specified time. Then the mixture is dried and passed through a sieve if required. Four formulations (A1 to A4) of ticagrelor solid dispersion were prepared in different ratios of drug: carrier 1:1, 1:2, 1:3, and 1:4 and their drug content and percentage yield is estimated.

b. Estimation of percentage yield and drug content:

Percentage yield is calculated to know about percent of yield obtained or efficiency of method. Thus it helps in selection of appropriate method of production. It is found out by dividing the practical mass to the theoretical mass of the solid dispersion. The physical mixtures and solid dispersion equivalent to 10mg of ticagrelor are weighed accurately and dissolved in 10ml of ethanol. The solution is filtered, diluted suitably and drug content is analysed at λmax of 295nm by UV spectrophotometer.

***c. Invitro* dissolution studies:**

Invitro dissolution studies of pure drug ticagrelor, physical mixture and solid dispersion are performed by using dissolution test apparatus USP type-II at a paddle rotation speed of 50 in 900ml of phosphate buffer pH6.8 in distilled water and temperature is maintained at 37 ± 0.5^0 C. Samples equivalent to 10mg of ticagrelor is filled in hard gelatin capsule. Samples are collected at regular intervals of time (10, 20, 30, 40, 50, 60 minutes). The absorbance of samples are measured at 295nm after suitable dilution.

SELECTION OF BEST FORMULATION:

The selection of best formulation is done based on percentage yield, drug content and release rate of ticagrelor invitro dissolution studies.

EVALUATION OF SELECTED FORMULATION:

Powder X-ray diffraction (PXRD) studies:

Rigakuminiflex 600 X-ray diffractometer (Rigaku Co., Tokyo, Japan), operated at 600 watts (X-ray tube), with a fixed tube current (15 mA) and a fixed voltage(40 kV) was used to achieve the X-ray powder diffraction pattern. The X-ray beam(diffracted) was monochromated by a graphite monochromator and detection was carried out by a standard scintillation counter. Diffraction intensities were measured over a peak range of 5–80° (2θ)**.**Powder X-ray diffraction is a unique method in determination of of a compound. It is used in distinguishing between amorphous and crystallinity crystalline material. Crystal is composed of periodic arrangement of atoms whereas amorphous atoms do not possess that periodicity. When there is periodic arrangement of atoms, the x-ray will be scattered only in certain

direction. This will cause high intensity peaks. In amorphous phase, x-rays will be scattered in many direction leading to large bump distributed in a wide range instead of high intensity narrower peak. ***(Nazare et al. 2017)***

Fourier transform infrared (FTIR) spectroscopic studies:

FT–IR spectra were recorded for ticagrelor pure drug and solid dispersion using IR-spectrophotometer. The samples were prepared in KBr dish and scanned over 400 to 4000 cm^{1}. The shift in characteristic bands reveal a modification in the drug environment. ***(Rajendra B.Kakde et al. 2017)***

PRECOMPRESSION EVALUATION OF POWDER BLEND:

a. Angle of repose:

For the angle of repose of the material was poured through a funnel to form a cone. The tip of the funnel should be held closed to the growing cone and slowly raised as the pile grows, to minimize the impact of falling particles. Stop pouring the material when the pile reached a predetermined height or the base a predetermined width. Rather than attempt to measure the angle of the resulting cone directly, divided the height by half the width of the base of the cone. The inverse tangent of this ratio is the angle of repose. It is defined as maximum angle possible between surface of the pile of powder and the horizontal plane.

Formula for angle of repose:

$\tan \theta = h/r$

$\theta = \tan^{-1} h/r$

h = height of pile,

r = radius of pile

b. Bulk density:

Bulk density of was determined by taking a known mass of powder in a 50 ml graduated measuring cylinder which is attached to the bulk density apparatus. The bulk density was calculated by following equation,

$$\textbf{Bulk density} = \frac{\boldsymbol{Weight\ of\ Powder}}{\boldsymbol{Bulk\ volume\ of\ Powder}}$$

c. Tapped density

Tapped density was determined by tapping method using measuring cylinder containing weighed amount of powder. The cylinder was dropped 3 times from a height of 1 inch at an interval of 2 sec. tapped density was calculated by following equation.

$$\textbf{Tapped density} = \frac{\boldsymbol{Mass\ of\ Powder}}{\boldsymbol{Tapped\ volume\ of\ Powder}}$$

$$\textbf{Dt} = \frac{\boldsymbol{M}}{\boldsymbol{Vt}}$$

d. Carrs compressibility index

This is an important property in maintaining uniform weight. It is calculated by using following formula.

$$\textbf{\%compressibility index} = \frac{\boldsymbol{Tapped\ density - Bulk\ density}}{\boldsymbol{Tpped\ density}} \textbf{ X 100}$$

e. Hausner's ratio:

A similar index to indicate the flow properties can be defined by hausner's ratio. Hausner's ratio can be calculated by using following formula:

$$\textbf{Hausner's ratio} = \frac{\boldsymbol{Tapped\ Density}}{\boldsymbol{Bulk\ Density}}$$

$$\textbf{H} = \frac{\boldsymbol{Dt}}{\boldsymbol{Db}}$$

Flow Property	Angle of Repose(Ɵ)	Compressibility Index (%)	Hauser's Ratio
Excellent	25-30	<10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very poor	56-65	32-37	1.46-1.59
Very very poor	>65	>38	>1.60

f. Drug content

Weight of the powder material equivalent to 100 mg of Ticagrelor is dissolved in methanol and transferred into 100 ml volumetric flask. Then 30 ml of phosphate buffer pH 6.8 is added slowly, mixed properly and the volume is made up to 100 ml with phosphate buffer pH 6.8. The above solution is filtered and 10 ml of filtrate is taken into 100 ml volumetric flask and made up to final volume with phosphate buffer pH 6.8 and the drug content is estimated by measuring the absorbance at λ max 295 nm using a UV spectrophotometer.

FORMULATION OF TICAGRELOR SUBLINGUAL TABLETS

1. Formulation development

Sublingual tablets containing 6 mg of model drug were prepared with a total tablet weight of 200mg. Considering the preformulation studies and the literature survey conducted the excipients were selected and an attempt to

produce sublingual tablets with ideal mouth feel maintaining the basic tablet properties was made.

2. Selection of superdisintegrants:

Short disintegration time with good dispersability is the most important characteristics of a sublingual or mouth dispersible tablets. The necessity of a Sublingual tablet is to disintegrate within seconds, in limited amount of the water available in the form of saliva. Different superdisintegrants crosscarmellose sodium, crosspovidone, Sodium starch glycol late in the concentration range of 1.5% to 7.5% were used which act as disintegrates used at various concentrations and a comparative study was carried out.

3. Selection of diluents

Since direct compression method was followed the choice of directly compressible diluents was important. Microcrystalline cellulose was selected as the filler or diluents owing to its multiple functionality as binder, disintegrant, compressibility and flowability. Of the various grades available the granular form Avicel PH102 was selected as it had been already reported to provide lower crushing strengths and shorter disintegration times. Mannitol was selected to produce a cooling and pleasant mouth feel, it was reported that mannitol above the concentration of 33% gives good mouth feel, thus mannitol in all the batches was fixed at a concentration of 60%. Besides mannitol also possesses sweetening properties and reduces the gritty mouth feel effect due to microcrystalline cellulose. It also has good compressibility properties and solubility in water.

4. Selection of additional ingredients

The flow property of the pure drug was found to be moderate (Hauser's ratio ~ 1.4) thus to still improve the flow of the blend magnesium stearate (0.75%) as lubricant were incorporated also magnesium stearate decreases the hardness of tablets without affecting the disintegration time. Saccharin sodium was used in the concentration of 0.5% as the sweetener.

5. Formula

Sublingual tablets of model drug was formulated using mannitol, Avicel pH102 (microcrystalline cellulose) as diluents. Sublingual tablet was prepared by direct compression technique as it's a cost effective method. Crosspovidone, Crosscarmellose sodium, Sodium starch glycolate used as a superdisintegrant. Sacchari sodium as sweetening agent. Magnesium stearate (0.75%) as lubricant and talc (0.75) used as a glident.

6. Formulation of different batches

The main aim of the present study was to formulate different batches using three various superdisintegrants and other ingredients in varying concentrations. So different batches of formulations was planned accordingly. According to that F1, F2, F3, F4, F5 (with Sodium starch glycolate 1.5%, 3%, 4.5%, 6%, 7.5%), F6, F7, F8, F9, F10(with Crosscarmellose 1.5%, 3%, 4.5%, 6%, 7.5%)and F11, F12, F13, F14, F15(with crosspovidone 1.5%, 3%, 4.5%, 6%, 7.5%).The slight bitter taste of the drug was masked using aspartame (2.5% to 6%) as the sweetening agent.

Method of formulation

1. Direct compression method.

The solid dispersion containing ticagrelor is thoroughly mixed with the superdisintegrants, and then other excipients are added to the mixer and passed through the sieve (#:60). Collect the powder mixer, blend with magnesium stearate (pre sieved), and subject the blend for tablet compression.

Representation of Direct Compression Technique for design of Sublingual Tablets

The drug and the excipients were passed through sieve no: 60 except lubricant. The blend was further lubricated with Magnesium stearate (#:60) and the powder blend is subjected to drying for removal of moisture content and was compressed by direct compression method by using 12 station B/D tolling compression machine. Round punches measuring 8.7mm diameter were used for compression. Tablet of 200mg was prepared by adjusting hardness and volume screw of compression machine properly.**(kalyankar *et al.,* 2015).**

POST COMPRESSIONAL EVALUATION OF TICAGRELOR SUBLINGUAL TABLETS

a. General appearance

The general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance. Include in are tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

b. Tablet thickness & diameter

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness and diameter can be measured using a simple procedure. 5 tablets were taken and their thickness and diameter was measured using digital Vernier calliper***.(Pati Vaishali et al.2015)***

c. Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Monsanto Hardness tester. ***(Pati Vaishali et al.2015)***

d. Drug Content

Randomly ten tablets are selected from formulation, finely powdered and powder equivalent mg of drug is accurately weighed and transferred to 100 ml volumetric flasks containing solution of desired pH. The flask is shaken to mix the contents thoroughly. The volume is made up to the mark with solution and filtered. One ml of the filtrate is suitably diluted and drug content is estimated using a double beam UV-visible spectrophotometer. This procedure is repeated thrice and the average value is calculated. ***(Pati Vaishali et al.2015)***

e. Uniformity of weight

I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a

digital weighing balance. The average weight of one tablet was determined from the collective weight. ***(Pati Vaishali et al.2015)***

IP Limit For Weight Variation (Indian Pharmacopoeia)

Average weight of tablet	Percentage deviation allowed
80mg or less	±10
60mg but < 250 mg	±7.5
250 mg or more	±5

f. Friability test

The friability of tablets is determined using Roche friabilator. Twenty tablets are randomly selected from each formulation and initial weight of 20 tablets are calculated and then transferred into friabilator. The friabilator is operated at 25 rpm for 4 minutes (100 revolutions). The tablets are dedusted and weighed again (final weight). The percentage friability is calculated by the following equation,

$$\mathbf{F} = \frac{\boldsymbol{Initial\ weight - Final\ weight}}{\boldsymbol{Final\ weight}} \text{ x } \mathbf{100}$$

Compress tablet that lose less than 0.1 to 0.8% of the tablet weight are consider acceptable.

g. Wetting time (WT)

A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small petri dish (ID = 6.5 cm) containing 6 ml of Sorenson's buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch and the standard deviation were also determined.

The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet is then recorded using a stopwatch. ***(Ruchita Jaiswani et al. 2014)***

h. Water absorption ratio

A piece of tissue paper folded twice is placed in a small Petri dish Containing 6 ml of water. A tablet is put on the tissue paper and allowed to completely wet. The wetted tablet is then weighted. Water absorption ratio, R was determined using following equation. ***(Ruchita Jaiswani et al. 2014)***

$$\mathbf{R} = \frac{Wa - Wb}{Wa} \times 100$$

Where,

Wa = Weight of tablet after water absorption

Wb = Weight of tablet before water absorption.

i. Disintegration test

A relatively simple method with rigorous conditions is developed. Each individual tablet is dropped into 10-ml glass test tube (1.5-cm diameter) containing 2ml distilled water, and the time required for complete tablet disintegration is observed visually and recorded using a stopwatch. The visual inspection is enhanced by gently rotating the test tube at a 45^0 angle, without agitation, to distribute any tablet particles that might mask any remaining no disintegrated portion of the tablets. In the USP disintegration test for sublingual tablets, the disintegration apparatus for oral tablets is used without the covering plastic disks, and 2 minutes is specified as the acceptable limit for tablet disintegration. ***(Ruchita Jaiswani et al. 2014)***

j. In-vitro dissolution studies

Dissolution study was carried out in USP II paddle type apparatus using 500 mL of phosphate buffer (pH 6.8) as a dissolution medium at 50 rpm. Temperature of the dissolution Medium was maintained at 37±0.5ºC. Samples of 5ml were withdrawn at every 5 minute Interval, filtered (through 0.45µ) and replaced with 5ml of fresh dissolution medium. The Samples were suitably diluted and estimated spectrophotometrically at 295 nm by using Shimadzu-1700 UV-Visible Spectrophotometer. The dissolution experiments were conducted in triplicate. Dissolution rate was studied for all designed formulations and dissolution parameters were calculated acceptable time limit for tablet disintegration. ***(Ruchita Jaiswani et al. 2014)***

Parameter	**Specifications**
Apparatus	USP II Paddle
Dissolution medium	300ml phosphate buffer pH6.8
Rotation speed	50 rpm
Temperature	37±0.5^{0}C
Withdrawn sample	5ml
Sampling interval	5 min
Absorbance measured	295nm

EFFECT OF DIFFERENT SUPERDISINTEGRANT ON RELEASE PROFILE OF TICAGRELOR SUBLINGUAL TABLETS

SELECTION OF BEST FORMULATION

The selection of best formulation is done based on rate of ticagrelor release from the Invitro dissolution release studies.

EVALUATION OF SELECTED FORMULATION

Fourier Transform infrared (FTIR) spectroscopy studies:

FT–IR spectra were recorded for ticagrelor pure drug and physical mixture using IR spectrophotometer. The samples were prepared in KBr dish and scanned over 400 to 4000 cm^{-1}

Differential scanning colorimetric (DSC) studies

Differential scanning calorimetry was used to characterize thermal properties of ticagrelor, ticagrelor with PEG-6000 and other excipients. The DSC thermograms were recorded using TA-60 thermal analyzer (Schimadzu). The samples were hermetically sealed in aluminium pans and heated at a constant rate of 20^{o}/min over temperature range of 50 to 200^{0} C. Inert atmosphere was maintained by purging nitrogen gas at flow rate of 50 ml/min.

Powder X-ray diffraction (PXRD) studies

Powder X-ray diffraction is a unique method in determination of crystallinity of a compound. It is used in distinguishing between amorphous and crystalline material. Crystal is composed of periodic arrangement of atoms whereas amorphous atoms do not possess that periodicity. When there is periodic arrangement of atoms, the x-ray will be scattered only in certain direction. This will cause high intensity peaks. In amorphous phase, x-

rays will be scattered in many direction leading to large bump distributed in a wide range instead of high intensity narrower peak.

EVALUATION OF INVITRO RELEASE KINETICS

To study the invitro release kinetics of the sublingual tablets, data obtained from invitro dissolution study were plotted in various kinetics models.

1. Zero order release rate kinetics

The zero order order release kinetics can be obtained by plotting cumulative % drug released Vs time (hours).

$$C=K_0 t$$

Where K_0 = Zero order constant in conc/time

T= time in hours

2. First order release rate kinetics

The graph was plotted as log% cumulative drug remaining Vs time in hours.

$$LogC=logC_0 – Kt/2.303$$

C_0=Initial drug concentration

K= First order constant

t = Time in hours

3. Higuchi kinetics

The graph was plotted with % cumulative drug released Vs squre root of time.

$$Q = K t^{1/2}$$

Where K= constant reflecting design variable system

t= time in hours

The drug release rate is inversely proportional to the square root of time.

4. Hixson and Crowell erosion equation

To evaluate the drug release with changes in the surface area and the diameter of particles, the data were plotted using the Hixson and crowell erosion equation. The graph was plotted by cube root of % drug remaining Vs Time in hours.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} X t$$

Q_t = Amount of drug released at time t

Q_0 = Initial amount of drug

K_{HC} = Rate constant for Hixson crowell equation

5. Korsmeyer – peppas equation

To evaluate the mechanism of drug release, it was further plotted in peppas equation as log cumulative % of drug released Vs log time.

$$M_t / M_\alpha = K t^n$$

Where, M_t / M_α = Fraction of drug release at time t

t = release time

K= Kinetics constant

N=Diffutional exponent indicative of the mechanism of drug release

If slope values is 0.5 or less, the release mechanism is “Fickian diffusion” and if 0.5<n<1 it follows “Non Fickian diffusion” (anomalous transport). The drug release follows zero order drug release and Non-Fickian case II transport if the values is 1. For the values of n higher than 1, the

mechanism of drug released is regarded as non-fickian case II transport. The model is used to analyse the release of pharmaceutical polymeric dosage forms when the release mechanism is not known or more than one type of release is involved.

Effect of 'n' value for drug transport mechanism

Release exponent (n)	Drug transport mechanism
n = 0.5	Fickian Diffusion
0.5<n<1	Non-Fickian Diffusion
n = 1	Case II transport
n > 1	Super case II transport

STABILITY STUDIES

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted. ICH specifies the length of study and storage conditions.

Long-Term Testing: 25^0 C ± 2^0 C / 60% RH ± 5% for 12 Months

Accelerated Testing: 40^0 C ± 2^0 C /75% RH± 5% for 6 Months

Stability studies were carried out at 40^0 C ± 20^0 C /75% RH ± 5% for all the formulations for a period of 1 month.

The selected formulations were closely packed in aluminium foils and then stored at 40^0 C ± 2^0 C /75% RH ± 5% in stability chamber for 1 month and evaluated for their physical appearance, drug content and *in-vitro* drug release studies at intervals of 15 days.

CHAPTER X

RESULTS AND DISCUSSION

TABLES & FIGURES

RESULTS AND DISCUSSION

PREPARATION OF STANDARD CALIBRATION CURVE

Determination of maximum absorption (λmax) of Ticagrelor

The absorption maximum (λmax) of the Ticagrelor was estimated by scanning the drug solution (10µg/ml) between 200-400 nm regions on UV spectrophotometer. The obtained spectrum showed that the absorption maximum (λmax) was 295nm for the Ticagrelor. FIG.1

Preparation of satandard calibration curve for Ticagrelor

The Standard Calibration curves of Ticagrelor were prepared using phosphate buffer pH6.8. The absorbance were measured at λmax of 295nm. The correlation coefficient was found to be 0.9987. Ticagrelor obeys the beer's law within the concentration range of (2-20µg/ml). Calibration plot of Ticagrelor in phosphate buffer pH6.8 was shown in FIG.2 and Table-1.

DRUG EXCIPIENTS COMPATIBILITY STUDIES

Fourier Transform Infrared (FTIR) Spectroscopic studies:

FT-IR spectrum of the pure drug, and physical mixtures were recorded. Pure Ticagrelor spectra showed sharp characteristic peaks at 3383.14 cm^{-1}(O-H Str),3292.49cm^{-1}(N-H Str), 1624.06 cm^{-1}(C=C Str) 1585.49 cm^{-1}(C=N Str)1517.98 cm^{-1} (N=N Str),1274.95 cm^{-1} (C-F Str). And the above characteristic peaks appear in the IR spectrum of pure drug and physical mixtures indicating that there were no modification or interaction between drug, carrier and diluents. **(FIG.3, FIG.43)**

Differential Scanning Calorimetric (DSC) Studies:

DSC thermogram of the best formulation was recorded. Pure Ticagrelor exhibits a sharp endothermic peak at 142.5^{0}C **(FIG. 13).** An endothermic peak corresponding to the melting point of pure drug was prominent in the physical mixtures **(FIG. 44)**, which suggested clearly that there was no interaction between the drug and the diluents and the drug existed in its unchanged form.

FORMULATION AND EVALUATION OF SOLID DISPERSION

a. Formulation of Soild Dispersion

In the present study, four formulations of Ticagrelor were prepared by using carrier PEG-6000 in the ratio of 1:1, 1:2, 1:3 and 1:4 by melting method. The prepared solid dispersions were found to be uniform and homogeneous in appearance **(Table 2).**

b. Estimation of Percentage Yield:

The percentage yield of all the formulations was determined by weighing the practical yield. Percentage yield is calculated for all the formulations. The percentage yield of solid dispersion ranged from 86.94% to 96.22%. The percentage yield of the solid dispersion A4 was found to be high (96.22%) when compared to the other formulations. This indicates that there is no considerable loss in the yield during the mixing process. **(Table 3)**

c. Determination of Drug Content:

The drug content in all the formulations was estimated Spectrophotometrically at 295nm (Shimadzu UV1800, Japan). The drug content of the prepared solid dispersion was found to be in the range of

96.57% to 98.09% indicating the uniform distribution of drug in the formulation**. (Table 3)**

d*. In vitro* Dissolution Studies:

The cumulative percentage drug release profile data obtained for all solid dispersion formulations are tabulated in **Table 4.** The cumulative percentage of drug release of pure drug (Ticagrelor) at the end of one hour was found to be 21.93%.

In melting method, PEG-6000 was used as a carrier. The release profiles of formulation in the ratios of 1:1, 1:2, 1:3, and 1:4 were found to be 60.52%(A1), 67.78%(A2), 83.33%(A3), and 91.92 %(A4) after 1 hour **(FIG. 5) and Table 4**. From the results, it was observed that A4 (1:4 ratio) exhibits maximum drug release of 91.92% and it was rated as the best formulation melting method using PEG-6000.

Selection of Best Formulation:

The best formulation was selected based on the results obtained from the drug *invitro* release studies. *In vitro* dissolution studies revealed that there is marked increase in the dissolution rate of Ticagrelor solid dispersion when compared to pure drug. The A4 formulation (melting method) containing drug and PEG-6000 (1:4 ratio of Drug: carrier) showed higher dissolution rate of 91.92% after 1hour, so it was considered as the overall best formulation.

The order of drug release profile is Pure drug < Solid dispersion.

The drug dissolution was increased in solid dispersion formulation. It happens because of the enhanced wettability, hydrophilic nature of the carriers and possibility of reduced crystallinity of the drug and conversion of amorphous form of the drug**.**

This study was planned to continue with best resultant product with crosspovidone, SSG and CCS as superdisintegrants and with different diluents and excipients to formulate sublingual tablets. The formula as on **Table-5.1, 5.2.**

PREFORMULATION STUDY FOR SUBLINGUAL TABLETS:

a. Angle of Repose:

The angle of repose was used to determine the flow properties of powder blend. The angle of repose of the formulations ranged from 26˚.56' to 35˚.24'. The results of angle of repose for all the formulations were shown in **Table 6** and **FIG. 15**.

b. Bulk density:

The bulk density is used as an index of the ability of the powder to flow. The bulk density of the formulations was in the range of 0.60 – 0.69 g/ml. The results of bulk density for all the formulations were shown in **Table 6** and **FIG. 16**.

c. Tapped Density:

The tapped density was used to access the free flowing properties of powder blend. The tapped density of all formulations were in the range of 0.67-0.78 g/ml. The results of tapped density for all the formulations were shown in **Table 6** and **FIG.17**.

d. Carr's Compressibility Index:

The Carr's compressibility index was used to determine the free flowing properties of powder blend. The compressibility index of all the formulations ranged from 9.71 -13.96%. The results of compressibility for all formulations were shown in **Table 6** and **FIG. 18**.

e. Hausner's Ratio:

The Hausner's ratio was an indirect index of ease of powder flow. The Hausner's ratio of all the formulations ranged from 1.11 – 1.18. This indicates better flow property of blend. The results of Hausner's ratio for all the formulations were shown in **Table 6** and **FIG.19**.

FORMULATION OF TICAGRELOR FAST DISINTEGRATING SUBLINGUALTABLETS:

The sublingual tablets of Ticagrelor was prepared by direct compression method using solid dispersion with different ratio (1.5%- 7.5%) of superdisintegrant (Crosspovidone, SSG and CCS) and with diluents (Mannitol) and microcrystalline cellulose. The compositions of the different formulation were given in **Table-5.1, 5.2.** Fifteen Formulations (F1 to F15) were prepared as per formula designed. All the tablets were white color and round in shape having 8 mm diameter.

POST COMPRESSION EVALUATION:

The prepared tablets were evaluated on various parameters such as thickness and diameter, hardness, weight variation, friability, uniformity content, wetting time, water absorption ratio, *In-vitro* disintegration time and *In-vitro* dissolution test. The results were summarized in **Table 7, 8, and 9**.

a. General Appearance:

The tablets were white coloured and round shaped. All tablets were elegant in appearance.

b. Thickness and Diameter:

The thickness and diameter of the formulations were used to determine the uniformity of size and shape of the tablets. From the results it was found that the thickness of the tablet in all formulation was 3.8 – 4 mm and the diameter of the tablet in all formulation was 8mm.The results indicated that all the formulations had uniform size and shape. The results were shown in **Table 7**.

c. Hardness:

The hardness of the tablets was used to determine the resistance capacity of the tablets to chipping, abrasion or breakage under conditions of storage, transportation and handling before usage. The hardness of the tablets of all the formulations was found to be in the range of 2.8 – 4.0 kg/cm^2. The result indicated that all the tablets had a good mechanical strength. The results of the hardness for all the formulations were shown in **Table 7.**

d. Weight Variation Test:

The weight variation test was used to ensure the uniformity of the tablet in all formulations. The weight of all the tablets from each formulation was in the range from 199.9 mg to 202.2 mg. It was found all the tablets passed weight variation test, as the percentage weight variation was within the acceptable limits of 7.5%. The results were shown in **Table 7**.

e. Friability test:

Friability test was measured to ensure the mechanical strength of tablet. The results showed that the friability of all the formulation ranged from

0.51% to 0.65%. Friability of all the formulation was lesser than 1 % which indicated the tablets had a good mechanical resistance. The results were shown in **Table 7.**

f. Uniformity of drug Content:

The uniformity content test was used to determine the uniform amount of active ingredient present in all formulations. The drug content in the content uniformity of all the formulations was found to be in the range of 97.3 % - 98.9 %. The results indicated all the formulations were within the acceptable limits as per USP limits. The results were shown in **Table 7**.

g*. In-vitro* drug release Studies:

The dissolution profile range in 30 minutes was 51.1 % to 98.2 % (table 12). The maximum dissolution drug release rate was observed in combination of crospovidone (7.5%) with diluent **(FIG. 25, 26, 27)**. The order of the dissolution rate with various superdisintegrants was found to be Crospovidone> SSG > CCS.

h. Disintegration Time:

The *in-vitro* disintegration time was determined by 10ml class test tube apparatus. The results were shown in **Table 8.** Formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12, F13, F14, and F15 showed the disintegration time obtained from 62.1 to 71.9 seconds respectively. It was observed that Formulation F10 containing Crospovidone (7.5%) and mannitol as diluent disintegrated rapidly in a short time (55.8 seconds). The results of disintegration of all the tablets were found to be lesser than 75 seconds. So all the formulation satisfied the criteria of fast dissolving sublingual tablets.

i. Water Absorption Ratio:

The water absorption ratio test was used to ensure the capacity of the superdisintegrant and the diluent to absorb the water. The results of water absorption ratio of all the formulation were shown in **Table 8.**

Formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12, F13, F14 and F15 showed the water absorption ratio 43.2%, 44.2%, 45.5%, 47%, 47.2%, 51.4%, 52.5%, 54.1%, 54.6%, 55.8%, 43.8%, 44.7%, 44.8%, 45.3%, and 45.9% respectively. The results showed that as concentration of superdisintegrant increased water absorption ratio was also increased. Formulation F10 containing crosspovidone (7.5%) as superdisintegrant showed highest water absorption ratio (55.8 %) when compared to other formulations. The reason for high water absorption ratio for F10 formulation combined with the superdisintegrant action. Crosspovidone quickly wicks water in to the tablet to generate volume expansion. Crosspovidone uses combination of swelling and wicking.

j.Wetting Time:

Wetting time of the tablet was used to assess the capacity of the tablets to disintegrate by swelling in water. All the formulations showed quick wetting, this may be due to ability to swelling and also capacity of absorption of water. The results of wetting time of all the formulations were shown in **Table 8**.

The formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12, F13, F14 and F15 showed the wetting time, 68.1, 66.7, 61.6, 57.6, 55.8, 66.6, 62.3, 58.8, 56.3, 54.3, 71.9, 70.9, 65.9, 61.2, 57.5 seconds respectively. The results indicated that the concentration of superdisintegrant influenced

the wetting time. Formulation F10 containing crospovidone (7.5%) showed lesser wetting time than other formulations.

This may be due to fact that superdisintegrant –Crospovidone performed its action by the combination of wicking and swelling action. Formulation F10 showed shorter wetting time.

EFFECT OF DIFFERENT SUPERDISINTEGRANT ON RELEASE PROFILEOF TICAGRELOR SUBLINGUAL TABLETS:

To study the effect of different superdisintegrant on release rate of ticagrelor sublingual tablets, fifteen formulations (F1 to F15) were prepared by using CCS, Crosspovidone, SSG as superdisintegrant in various concentration (1.5%, 3%, 4.5%, 6%, 7.5%) with mannitol as diluents respectively. The formulated tablets were subjected to various quality tests and the release rates were shown in **FIG. 25, 26 and 27**. The dissolution data was presented in the **Table 9**. The invitro kinetics was presented in the **Table 11.1, 11.2**. The dissolution rate followed first order kinetics as the graph between log cumulative % drug unreleased Vs time were found linear.

SELECTION OF BEST FORMULATION:

Among Fifteen formulations, the best was selected on the basis of lowest disintegration time, rapid drug release profile, higher water absorption ratio, short wetting time. Formulation F10 showed lowest disintegration time of 55.8 seconds, faster drug release rate of 98.2 %in 30 minutes, comparatively high water absorption ratio of 55.8 %, short wetting time of 54.3 seconds and minimum chemicals composition. In these parameter would drive the F10 formulation as a best comparatively.

EVALUATION OF BEST FORMULATION

Differential scanning calorimetric (DSC) Studies:

Any possible drug polymer interaction can be studied by thermal analysis. The DSC thermogram of Ticagrelor exhibited an endothermic peak corresponding to its melting point. The thermogram of the final best formulation of ticagrelor with other excipients show the existence of drug endothermic peak within the range which indicated the absence of interaction between the drug and other excipients. The DSC thermogram of pure drug and the final best formulation is presented in **FIG. 13 and 44**.

Fourier transform infrared (FTIR) spectroscopic Studies:

Infrared spectra of the ticagrelor sublingual tablets showed major peaks at 3383.14 cm^{-1}(O-H Str), 3292.49cm^{-1}(N-H Str), 1624.06 cm^{-1}(C=C Str) 1585.49 cm^{-1}(C=N Str), 1517.98 cm^{-1}(N=N Str) 1274.95 cm^{-1} (C-F Str) indicated that there was no interaction between the drug and the final formulation throughout the preparation of sublingual tablets. The result was shown in **FIG. 3, 43.**

Powder X-ray Diffraction Sudies:

The diffractogram of Ticagrelor shows so many numbers of peaks, it indicates that the drug substance is crystalline in nature. From the diffractogram of solid dispersion of sublingual formulation, it was clearly evident that the intensity (heights) of peaks has been reduced significantly. This indicates that the percentage of crystallinity was reduced by solid dispersion. The enhancement in the rate of drug release from solid dispersion sublingual formulation is ascribed to the marked reduction in the crystallinity of Ticagrelor. **FIG. 14, FIG. 45.**

DRUG RELEASE KINETIC MODEL

The drug release profiles of Ticagrelor sublingual tablets were fitted to various kinetic models such as Zero order, First order, Higuchi, Korsmeyer Peppas and Hixson-Crowell. In order to describe the kinetics of the release process of drug in all formulations, equations such as zero-order and first-order rate equations were used. Zero order rate equation describes the system where the release rate is independent of the concentrations of the dissolved species. While the first- order equation describes the release from systems where dissolution rate is dependent on the concentration of the dissolving species. It is evident from **Table 11.1 and 11.2** that the drug release process is not zero order in nature. This indicates that the dissolution rate of the drug is not independent of the amount of drug available for dissolution and diffusion from the matrix. The dissolution data of all formulations when fitted in accordance with the first order equation it is evident that a linear relationship was obtained with 'r' (correlation coefficient) value close to unity and higher than 'r' obtained from zero order equation for all formulation (table), showing that the release is an apparent first order process. This indicates that the amount of drug released is dependent on the matrix.The obtained from *invitro* dissolution studies were fitted to zero –order, first-order and Korsmeyer Peppas equation. The first-order plots were found to be fairly linear as indicated by their high regression values. To confirm the exact mechanism of drug release, the data were fitted according to Korsmeyer Peppas equation:

$$\mathbf{Mt/m\infty = kt^n}$$

where mt/m∞ is fraction of drug released, k is kinetic constant, t is release

time and *n* is the diffusional exponent for drug release. Peppas stated that the above equation could adequately describe the release of solutes from slabs, spheres, cylinders and discs, regardless of the release mechanism. The value of '*n*' gives an indication of the release mechanism; when *n* =1, the release rate is independent of time (zero-order) (case II transport), *n* = 0.5 for Fickian diffusion and when 0.5 < *n* <1.0, diffusion and non-Fickian transport are implicated. Lastly, when *n* > 1.0 super case II transport is apparent. '*n*' is the slope value of log mt/m∞ versus log time curve**.** Slope values (*n* > 1.0) suggest that the release of ticagrelor from sublingual tablets followed Supercase-II transport suggesting that more than one mechanism may be involved in the release kinetics. The results were shown in **table 11.1and 11.2.**

STABILITY STUDIES:

The optimized formulation F10 was evaluated for *in-vitro* drug release studies after keeping the tablets at accelerated stability conditions (40^0 C/75%RH) for 1 months. It is evaluated initially,15 days and 1 month. In 15 days time interval, the tablets were analysed for hardness, drug content, uniformity of weight, invitro disintegration time, % drug release. *In-vitro* drug release studies were performed in phosphate buffer pH 6.8 by using USP dissolution test apparatus-Type II, Rotating Paddle method. The results indicated that there was no significant change in i*n-vitro* drug release studies. The data for *in-vitro* release profile was shown in Table No-13.

TABLE-1: CALIBRATION OF TICAGRELOR IN PHOSPHATE BUFFER PH6.8

S.No	Concentration (µg/ml)	Absorbance (nm)
1	2	0.076 ± 0.011
2	4	0.119 ± 0.011
3	6	0.165 ± 0.009
4	8	0.214 ± 0.023
5	10	0.263 ± 0.025
6	12	0.307 ± 0.029
7	14	0.356 ± 0.037
8	16	0.358 ± 0.056
9	18	0.444 ± 0.057
10	20	0.492 ± 0.069

N=3* **REGRESSION VALUE = 0.9986 ± 0.0006**

TABLE-2: COMPOSITION OF SOLID DISPERSION

S.No	Formulation code	Method	Ratio	Composition
1	M1	Melting	1:1	Drug:PEG-6000
2	M2	Melting	1:2	Drug:PEG-6000
3	M3	Melting	1:3	Drug:PEG-6000
4	M4	Melting	1:4	Drug:PEG-6000

TABLE-3: PERCENTAGE OF YEILD AND DRUG CONTENT OF TICAGRELOR SOLID DISPERSION

S.No	Formulation Code	Method	Ratio	Percentage of yield ± SD	Drug content ± SD
1	A1	Melting	1 : 1	86.94 ± 0.34	96.57
2	A2	Melting	1 : 2	89.05 ± 0.34	96.95
3	A3	Melting	1 : 3	90.61 ± 0.41	97.71
4	A4	Melting	1 : 4	96.22 ± 0.63	98.09

TABLE-4: CUMULATIVE PERCENTAGE DRUG RELEASE OFTICAGRELOR SOLID DISPERSION USING PEG-6000 CARRIER BY MELTING METHOD

Time (min)	Percentage drug release ± SD				
	A1 1:1	A2 1:2	A3 1:3	A4 1:4	Pure drug
10	22.14±1.89	25.15±1.26	25.23±1.04	28.89±1.73	06.31±1.44
20	31.43±1.07	34.83±1.71	44.60±0.37	48.76±0.66	11.63±1.22
30	38.53±1.87	40.54±0.82	70.92±1.07	65.85±1.30	14.42±0.28
40	44.18±1.53	47.43±1.30	74.23±1.59	74.01±1.08	17.45±0.88
50	56.13±1.20	57.20±1.55	78.23±1.23	85.75±1.32	19.49±0.47
60	60.52±0.83	67.78±1.09	83.33±1.30	91.92±1.26	21.93±0.76

N=3*

TABLE-5.1: TICAGRELOR SUBLINGUAL TABLET FORMULATIONS

Ingredients (mg)	Formulation code						
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
Solid dispersion equivalent to 6mg ticagrelor	30	30	30	30	30	30	30
Crosscarmellose sodium	3	6	9	12	15	-	-
Crosspovidone	-	-	-	-	-	3	6
SSG	-	-	-	-	-	-	-
MCC 102	43	40	37	34	31	43	40
Mannitol	120	120	120	120	120	120	120
Saccharin sodium	1	1	1	1	1	1	1
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5

TABLE-5.2: TICAGRELOR SUBLINGUAL TABLET FORMULATIONS

Ingredients (mg)	Formulation code							
	F8	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**
Solid dispersion equivalent to 6mg ticagrelor	30	30	30	30	30	30	30	30
Crosscarmellose sodium	-	-	-	-	-	-	-	-
Crosspovidone	9	12	15	-	-	-	-	-
SSG	-	-	-	3	6	9	12	15
MCC 102	37	34	31	43	40	37	34	31
Mannitol	120	120	120	120	120	120	120	120
Saccharin sodium	1	1	1	1	1	1	1	1
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

TABLE-6: PRECOMPRESSION EVALUATION SUBLINGUAL FORMULATIONS

Formulation code	Angle of repose (Θ)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's ratio	Carr's index (%)
F1	34.73 ± 1.96	0.66 ± 0.038	0.73± 0.025	1.14 ± 0.098	12.38
F2	34.17 ± 1.02	0.61 ± 0.030	0.69± 0.024	1.13 ± 0.031	12.06
F3	33.71 ± 1.96	0.66 ± 0.073	0.75 ± 0.076	1.14 ± 0.025	12.81
F4	33.79 ± 1.85	0.69 ± 0.021	0.78 ± 0.028	1.13 ± 0.005	11.62
F5	30.95 ± 0.22	0.64 ± 0.020	0.72 ± 0.025	1.11 ± 0.004	10.69
F6	34.24 ± 1.88	0.63 ± 0.019	0.70 ± 0.034	1.11 ± 0.002	09.71
F7	34.83 ± 1.04	0.60 ± 0.010	0.67 ± 0.023	1.12 ± 0.070	10.84
F8	32.54 ± 1.30	0.60 ± 0.031	0.68 ± 0.024	1.13 ± 0.004	10.67
F9	31.39 ± 0.59	0.61 ± 0.010	0.68 ± 0.024	1.12 ± 0.072	10.93
F10	26.56 ± 0.62	0.63 ± 0.033	0.72 ± 0.025	1.13 ± 0.029	12.22
F11	35.24 ± 0.76	0.63 ± 0.037	0.72 ± 0.024	1.14 ± 0.037	12.32
F12	35.74 ± 0.55	0.63 ± 0.018	0.73 ± 0.025	1.18 ± 0.062	13.79
F13	33.98 ± 1.25	0.60 ± 0.036	0.71 ± 0.024	1.18 ± 0.066	15.35
F14	30.88 ± 0.90	0.63 ± 0.041	0.71 ± 0.065	1.12 ± 0.043	11.20
F15	30.01 ± 0.62	0.61 ± 0.017	0.70 ± 0.047	1.16 ± 0.004	13.96

N=3*

TABLE-7: POST COMPRESSION EVALUATION OF TICAGRELOR SUBLINGUAL TABLETS

Formulation code	Hardness (kg/cm^2) ± SD	Thickness (mm) ± SD	Friability ± SD (%)	Weight variation (mg) ± SD	Drug content (%) ± SD
F1	3.4± 0.15	3.9 ± 0.05	0.5 ± 0.05	201.3 ± 0.75	98.38 ± 0.34
F2	3.4 ± 0.05	3.9 ± 0.05	0.5 ± 0.04	201.3 ± 1.23	98.17 ± 0.60
F3	3.2 ± 0.05	3.9 ± 0.11	0.5 ± 0.04	200.4 ± 0.80	98.37 ± 0.69
F4	3.3 ± 0.23	3.8 ± 0.05	0.5 ± 0.05	200.5 ± 1.56	97.77 ± 0.35
F5	3.2 ± 0.15	3.7 ± 0.05	0.6 ± 0.03	199.9 ± 1.01	97.97 ± 0.35
F6	4.0 ± 0.20	3.8 ± 0.05	0.5 ± 0.02	201.0 ± 0.60	98.58 ± 0.69
F7	3.0 ± 0.11	3.7 ± 0.11	0.5 ± 0.01	201.6 ± 0.49	97.97 ± 0.69
F8	2.8 ± 0.05	3.8 ± 0.05	0.6 ± 0.01	201.0 ± 0.76	98.18 ± 0.00
F9	3.1 ± 0.23	3.8 ± 0.17	0.6 ± 0.01	201.3 ± 0.51	98.17 ± 1.05
F10	3.7 ± 0.40	4.0 ± 0.05	0.4 ± 0.06	201.3 ± 0.15	98.98 ± 0.35
F11	3.5 ± 0.10	3.9 ± 0.17	0.6 ± 0.02	201.9 ± 0.40	98.38 ± 0.92
F12	3.2 ± 0.25	4.0 ± 0.05	0.5 ± 0.01	201.2 ± 0.46	98.78 ± 0.60
F13	3.3 ± 0.05	3.8 ± 0.10	0.5 ± 0.06	202.3 ± 0.45	97.97 ± 0.92
F14	3.2 ± 0.10	4.0 ± 0.10	0.5 ± 0.02	200.3 ± 0.20	97.57 ± 0.61
F15	3.1 ± 0.05	3.9 ± 0.10	0.6 ± 0.02	202.4 ± 0.55	97.36 ± 0.35

N=3*

TABLE-8: POST COMPRESSION EVALUATION OF TICAGRELOR SUBLINGUAL TABLETS

Formulation code	Wetting time (sec)	Water absorption ratio (%)	Disintegration time (sec)
F1	68.1 ± 0.27	43.2 ± 0.44	66.8 ± 0.80
F2	66.7 ± 0.41	44.2 ± 0.54	65.9 ± 0.55
F3	61.6 ± 0.51	45.5 ± 0.59	64.5 ± 0.50
F4	57.6 ± 0.44	47.04 ± 0.26	63.1 ± 0.56
F5	55.8 ± 0.67	47.2 ± 0.52	61.9 ± 0.90
F6	66.6 ± 0.96	51.4 ± 0.75	64 ± 0.07
F7	62.3 ± 0.60	52.5 ± 0.22	62.9 ± 0.17
F8	58.8 ± 0.25	54.1 ± 0.32	62.1 ± 0.65
F9	56.3 ± 0.57	54.6 ± 0.12	60.7 ± 0.36
F10	54.3 ± 0.28	55.8 ± 0.40	55.8 ± 0.80
F11	71.9 ± 0.22	43.8 ± 0.20	71.9 ± 0.90
F12	70.9 ± 0.55	44.7 ± 0.35	70.3 ± 0.55
F13	65.9 ±0.40	44.8 ± 0.19	68.4 ± 0.36
F14	61.2 ± 0.23	45.3 ± 0.22	66.1 ± 1.00
F15	57.5 ± 0.50	45.9 ± 0.20	62.5 ± 0.86

N=3*

TABLE-9: INVITRO RELEASE PROFILE OF TICAGRELOR SUBLINGUAL TABLETS

Formulation code	Time					
	5 min	10 min	15 min	20 min	25 min	30 min
F1	52.4±0.66	74.2±0.66	79.9±0.66	83.1±0.43	86.1±0.87	88.9±0.66
F2	57.2±1.09	74.1±0.66	78.1±1.64	83.2±3.08	88.2±1.52	91.8±1.99
F3	56.6±1.09	76.5±0.43	81.5±2.19	86.1±0.87	89.31.32±	92.4±0.66
F4	58.2±0.88	78.3±0.87	84.2±0.66	87.9±0.43	91.2±0.25	94.7±0.50
F5	59.2±0.66	79.2±0.87	85.1±0.66	88.9±0.67	92.4±0.66	95.6±0.90
F6	53.7±0.66	75.2±0.87	80.9±0.75	84.4±0.87	87.0±0.87	90.0±0.43
F7	59.4±0.50	79.2±0.87	86.1±0.87	89.2±0.87	92.5±0.25	94.1±1.64
F8	60.1±0.66	80.0±0.87	86.0±0.66	89.7±0.67	93.4±0.66	96.4±0.90
F9	61.0±0.67	81.0±1.09	87.0±0.43	90.9±0.43	94.7±0.66	97.7±0.67
F10	61.4±1.09	79.3±1.09	85.7±1.15	90.5±0.87	94.5±0.67	98.2±0.67
F11	51.1±0.67	72.8±0.67	78.7±1.15	81.8±0.00	83.9±0.43	87.4±0.43
F12	52.0±0.66	73.5±0.86	79.2±0.86	82.2±0.43	84.8±0.43	88.0±0.67
F13	52.8±0.90	75.4±1.09	80.2±1.09	83.4±0.90	86.6±0.43	89.2±0.87
F14	54.3±2.42	71.6±1.32	75.2±1.15	84.2±1.52	87.6±1.32	90.9±1.30
F15	58.4±0.90	78.3±0.87	85.1±1.09	88.2±0.90	91.5±0.66	93.7±0.67

N=3*

TABLE-10.COMPARISION OF INVITRO RELEASE OF PURE DRUG, CONVENTIONAL TABLET, TICAGRELOR SUBLINGUAL TABLETS

TIME	PURE DRUG	CONVENTINAL TABLET	SUBLINGUAL TABLETS
5	06.11±0.79	13.32±0.91	61.4±1.09
10	11.17±0.69	24.21±0.78	79.3±1.09
15	14.96±0.35	37.42±0.56	85.7±1.15
20	17.48±0.06	45.78±0.91	90.5±0.87
25	19.43±0.05	53.97±0.88	94.5±0.67
30	21.95±0.16	61.20±0.76	98.2±0.67

TABLE-11.1: INVITRO RELEASE KINETICS DATA OF TICAGRELOR SUBLINGUAL TABLETS

Formulation code	Zero order		First order		Higuchi		Korsmeyer peppas		Hixon crowell	
	r^2	$K^0(h^{-1})$	r^2	$K_1(h^{-1})$	r^2	$K_H(h^{-1/2})$	r^2	n	r^2	$K_{HC}(h^{-1/3})$
F1	0.702	2.456	0.894	-0.029	0.920	10.44	0.825	1.260	0.831	-0.071
F2	0.704	2.475	0.962	-0.036	0.924	11.15	0.816	1.251	0.875	-0.079
F3	0.693	2.515	0.926	-0.038	0.919	11.38	0.819	1.263	0.884	-0.076
F4	0.690	2.569	0.952	-0.043	0.916	12.06	0.818	1.272	0.879	-0.085
F5	0.688	2.591	0.961	-0.031	0.917	11.79	0.817	1.273	0.897	-0.091
F6	0.693	2.471	0.927	-0.040	0.918	10.81	0.823	1.261	0.832	-0.073
F7	0.675	2.562	0.949	-0.047	0.908	12.43	0.820	1.260	0.837	-0.082
F8	0.686	2.612	0.966	-0.053	0.914	12.30	0.817	1.276	0.891	-0.068

N=3*

TABLE-11.2: INVITRO RELEASE KINETICS OFTICAGRELOR SUBLINGUAL TABLETS

Formulation code	Zero order		First order		Higuchi		Korsmeyer peppas		Hixon crowell	
	R^2	$K^0(h^{-1})$	R^2	$K_1(h^{-1})$	R^2	$K_H(h^{-1/2})$	R^2	n	R^2	$K_{HC}(h^{-1/3})$
F9	0.686	2.647	0.977	-0.053	0.915	12.45	0.819	1.263	0.902	-0.095
F10	0.699	2.657	0.955	-0.055	0.922	12.12	0.814	1.277	0.936	-0.102
F11	0.697	2.407	0.889	-0.027	0.920	10.16	0.818	1.251	0.829	-0.068
F12	0.695	2.418	0.919	-0.028	0.918	10.42	0.820	1.273	0.825	-0.069
F13	0.675	2.425	0.923	-0.031	0.916	10.72	0.823	1.258	0.874	-0.077
F14	0.733	2.514	0.974	-0.035	0.941	09.06	0.827	1.259	0.947	-0.088
F15	0.681	2.552	0.981	-0.042	0.912	12.06	0.816	1.270	0.921	-0.099

TABLE-12: STABILITY STUDY FOR BEST FORMULATION

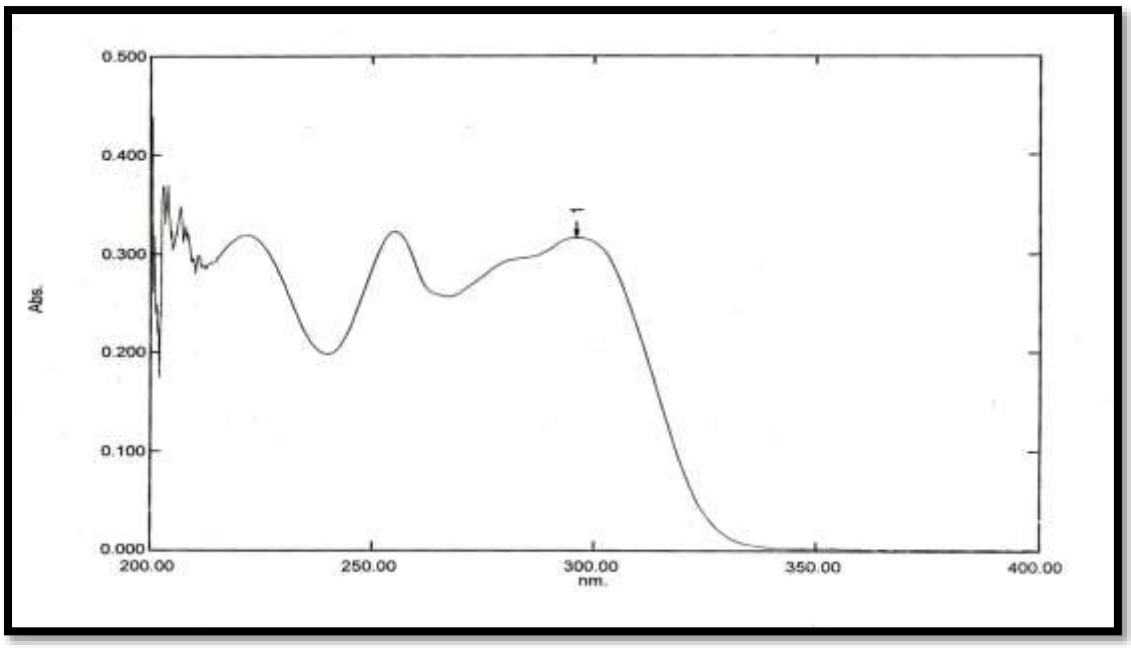
TEMPERATURE	DAYS	DRUG CONTENT (%)	HARDNESS IN Kg/cm^2	DISINTEGRATION TIME IN SEC	DRUG RELEASE
25^0C	15	98.78±0.35	3.81±0.05	40.26±1.41	97.97±0.35
	30	98.58±0.34	3.85±0.01	52.03±0.73	97.77±0.35
40^0C/75% RH	15	97.97±0.35	3.88±0.01	44.30±0.81	97.36±0.35
	30	97.77±0.34	4.06±0.11	47.30±0.95	97.16±0.35

N=3*

TABLE-13: INVITRO DRUG RELEASE OF STABILITY STUDIES FOR THE BEST FORMULATION (F10)

TIME IN MINUTES	CONTROL	25^0C (Room Temperature)		40^0C / 75% RH	
		15th day	30th day	15th day	30th day
5	61.44±1.09	61.30±0.98	62.60±1.09	60.43±0.79	60.67±0.88
10	79.35±1.09	80.51±0.78	79.20±1.03	78.33±0.78	78.17±0.97
15	85.73±1.15	87.04±0.87	85.30±0.98	84.86±0.94	84.63±1.09
20	90.52±0.87	89.65±0.89	90.52±0.88	91.39±0.38	88.31±1.09
25	94.58±0.66	94.44±0.86	95.31±0.86	94.00±0.75	94.03±0.59
30	98.21±0.66	97.48±1.03	97.79±0.95	97.35±0.57	97.31±0.83

FIG.1: DETERMINATION OF λ MAX FOR TICAGRELOR



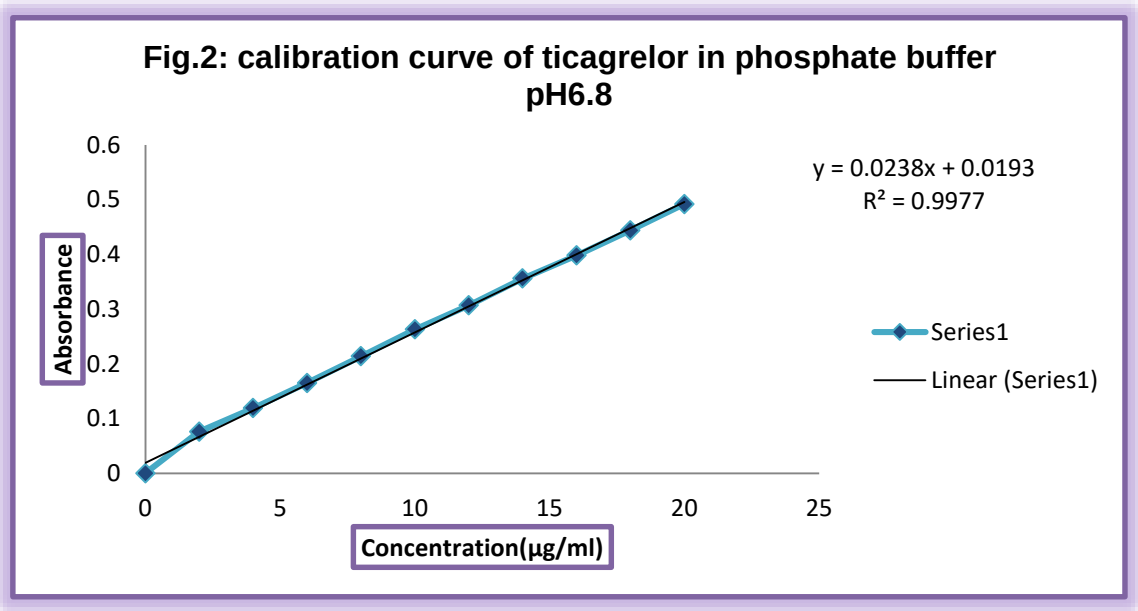


FIG.3: FT-IR SPECTRUM OF TICAGRELOR PURE DRUG

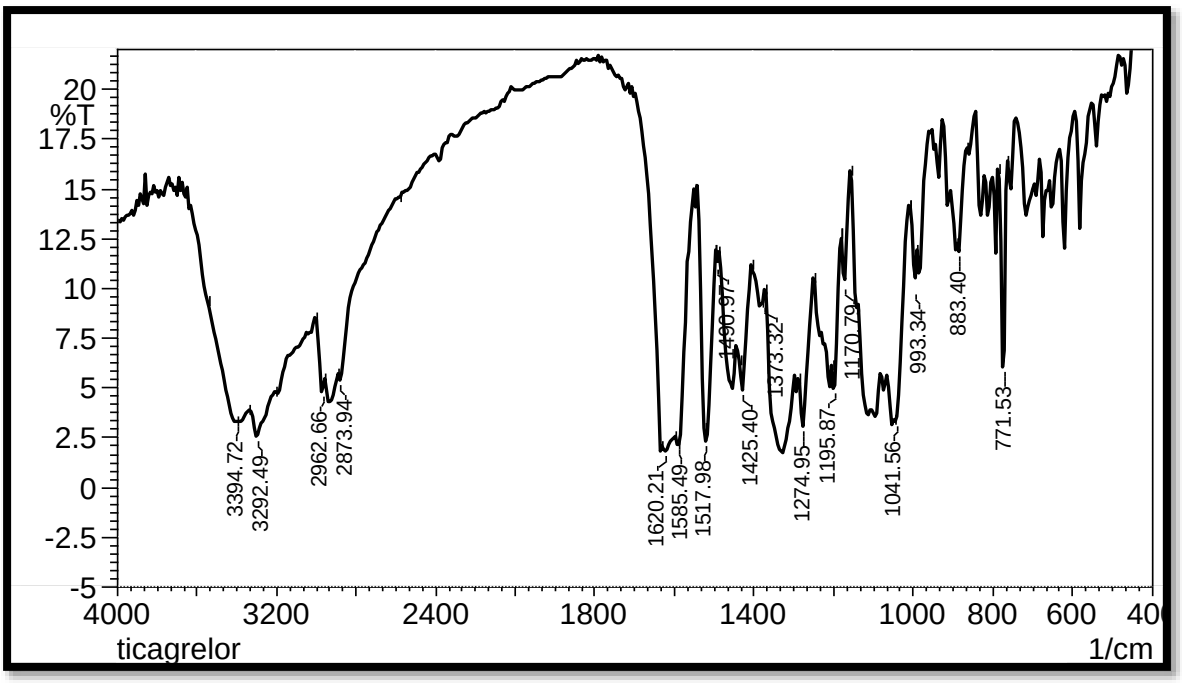


FIG.4: FT-IR SPECTRUM OF SODIUM STARCH GLYCOLATE

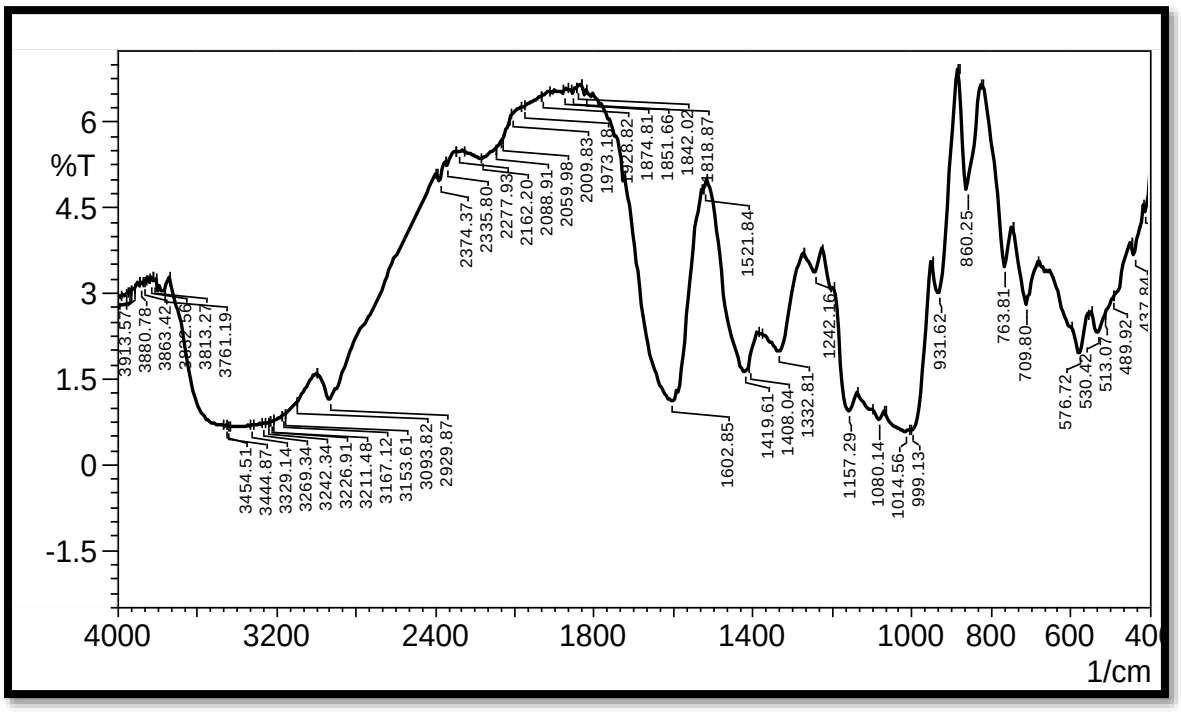


FIG.5: FTIR SPECTRUM OF SSG+TICAGRELOR

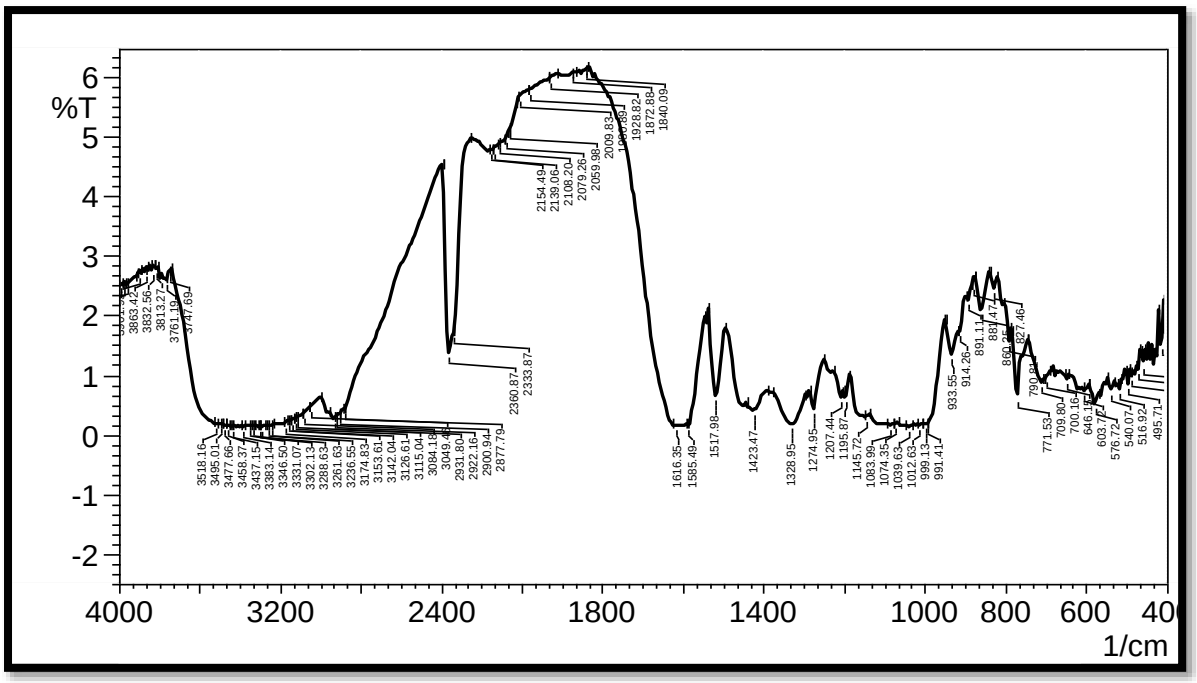


FIG.6: FT-IR SPECTRUM OF CROSSCARMELLOSE SODIUM

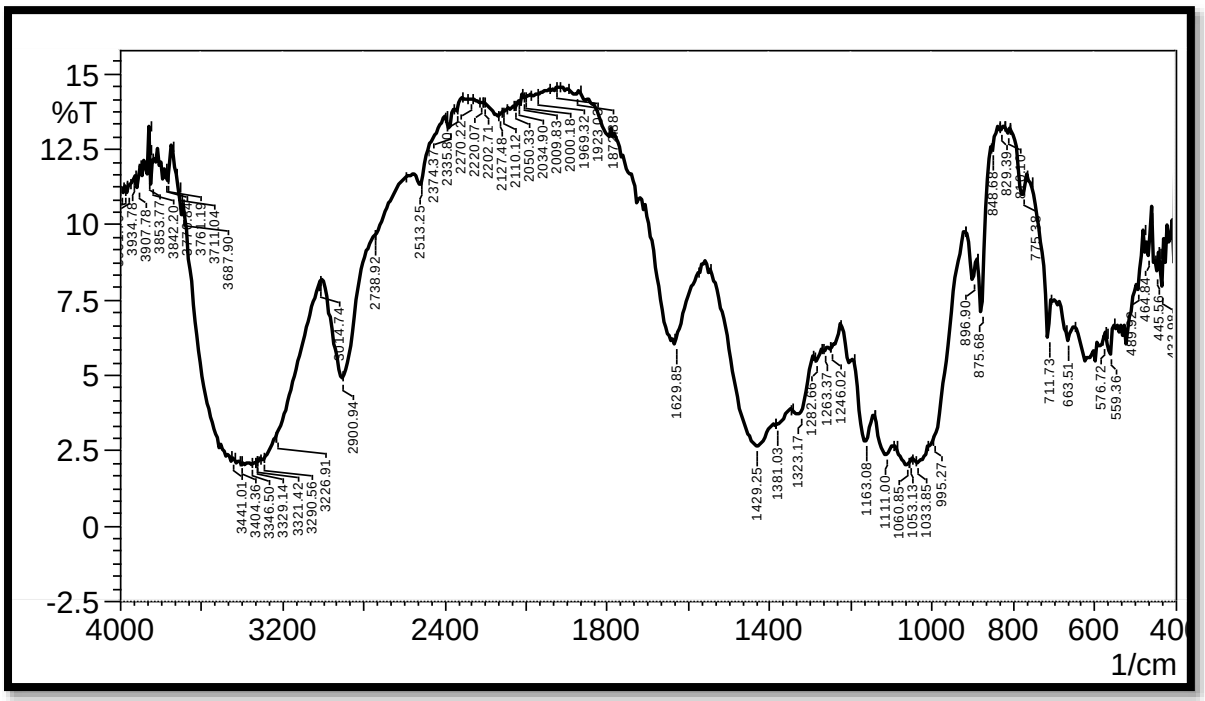


FIGURE.7: FT-IR SPECTRUM OF CCS+TICAGRELOR

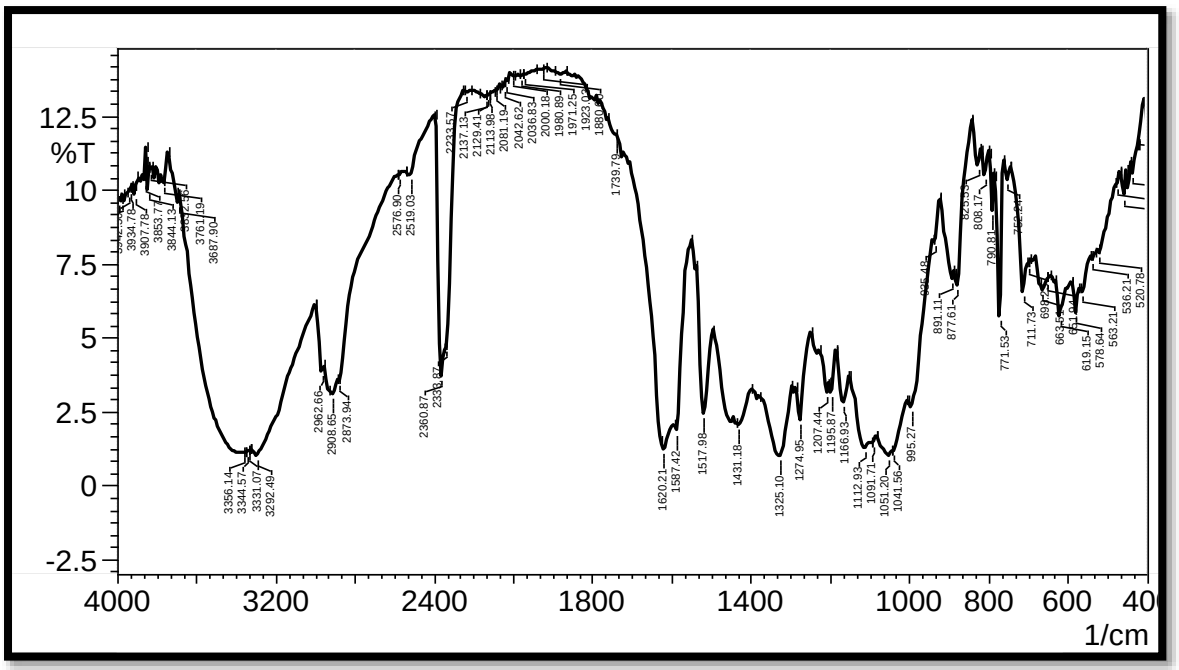


FIGURE.8: FT-IR SPECTRUM OF CROSSPOVIDONE

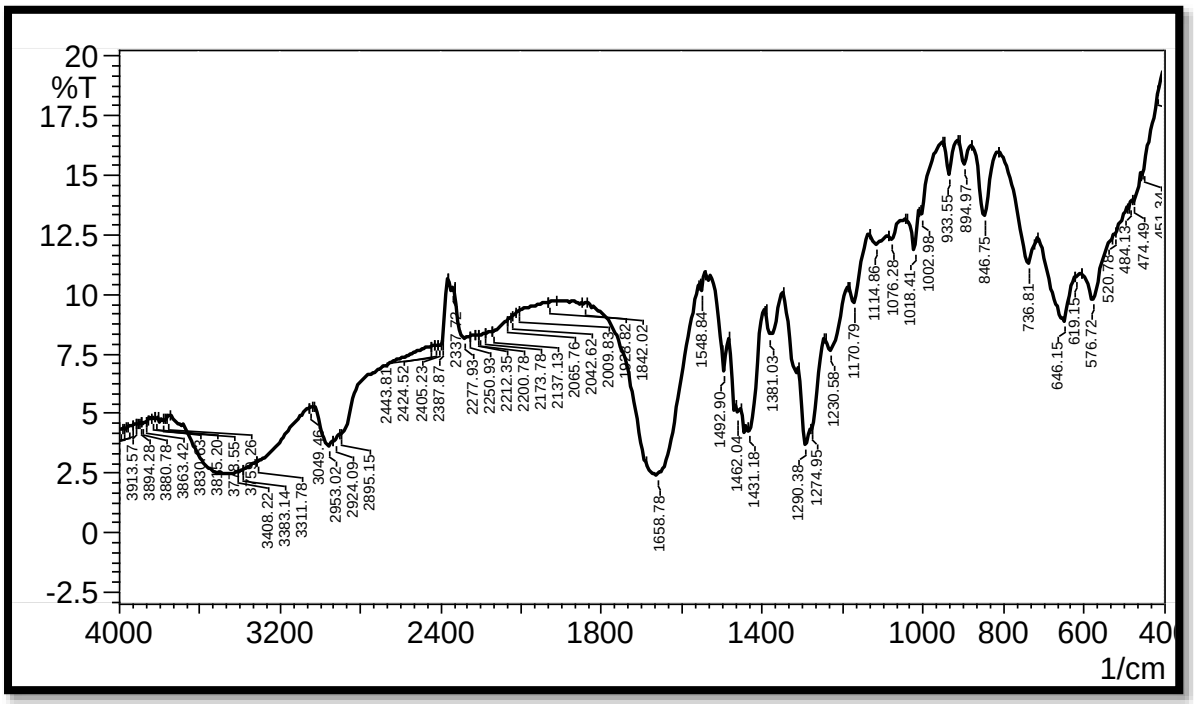


FIGURE.9: FT-IR SPECTRUM OF CROSSPOVIDONE + TICAGRELOR

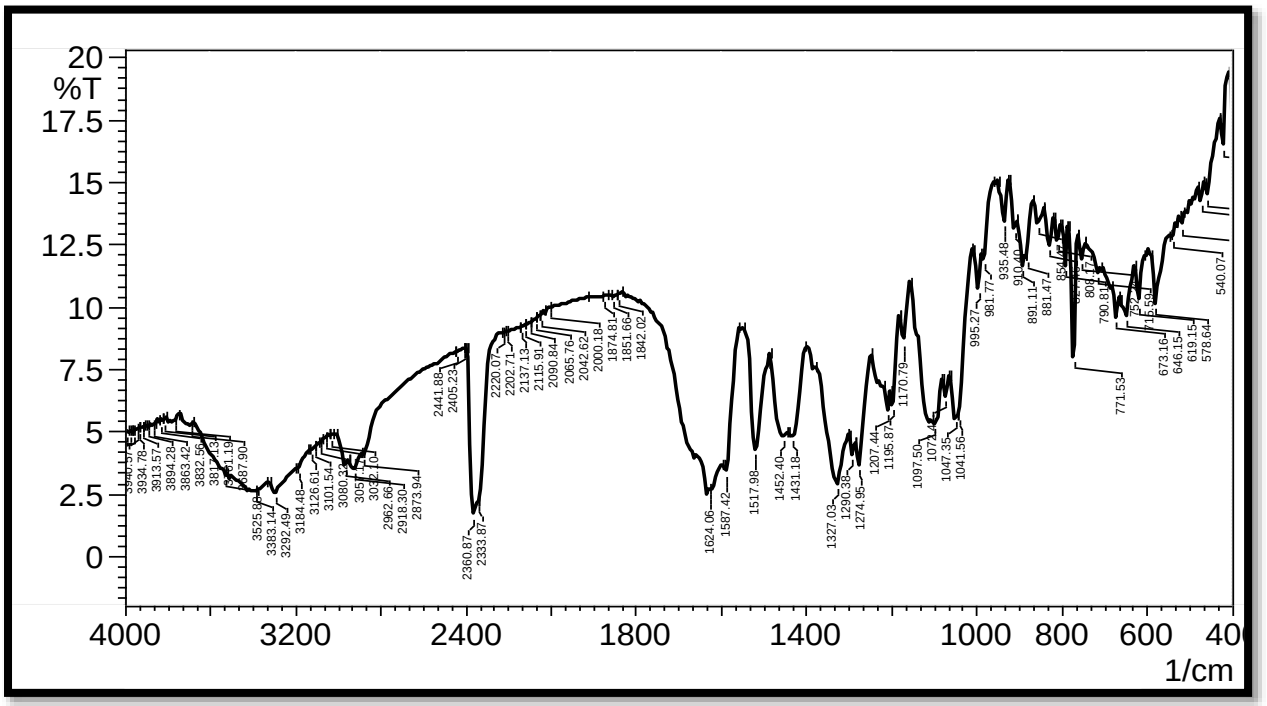


FIGURE.10: FT-IR SPECTRUM OF MICROCRYSTALLINE CELLULOSE

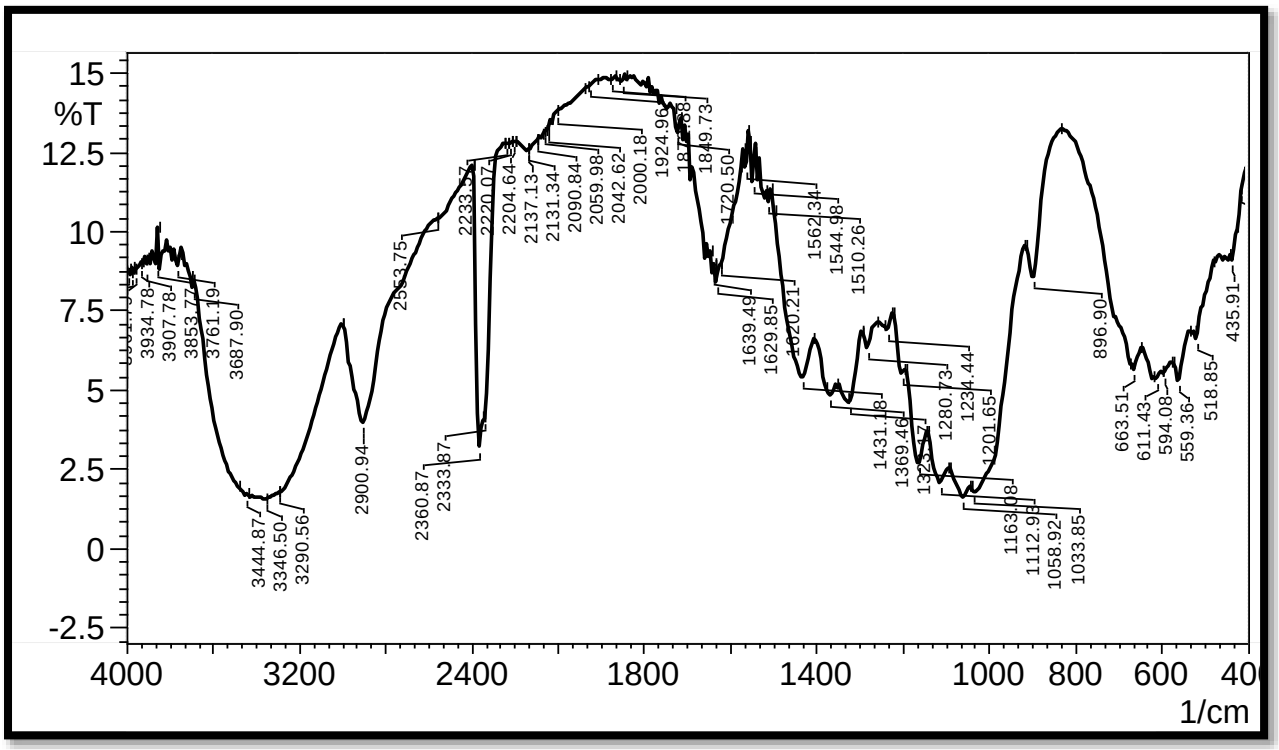


FIGURE.11: FT-IR SPECTRUM OF MCC 102 + TICAGRELOR

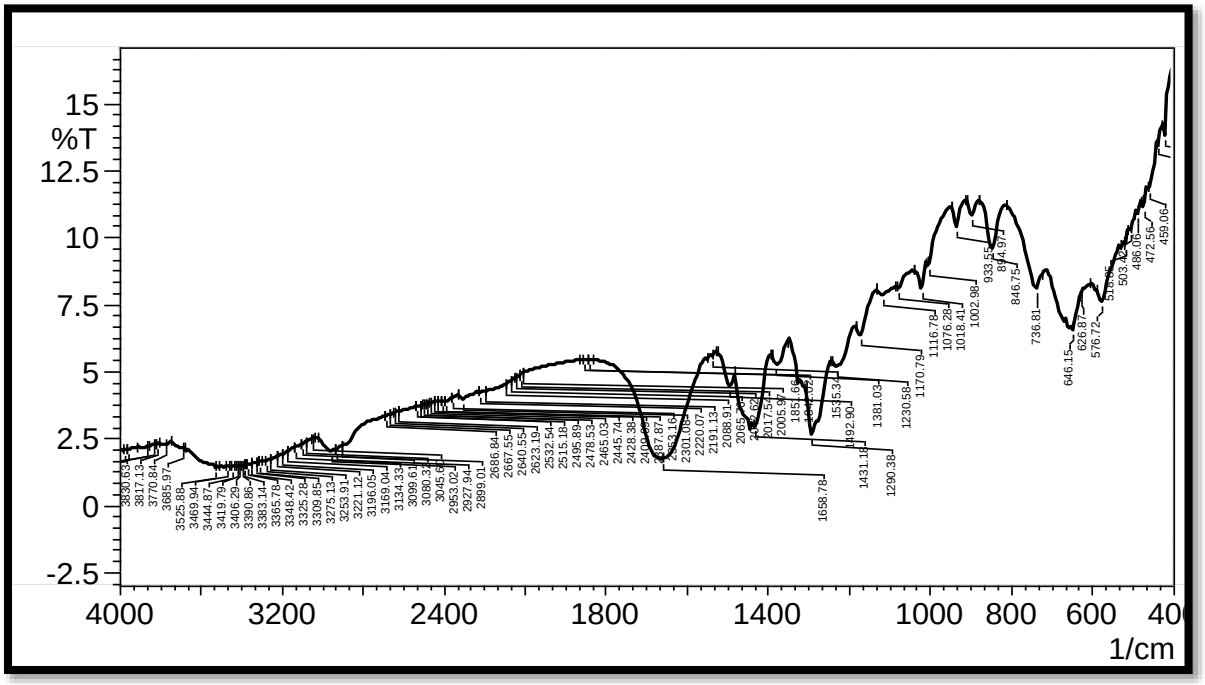


FIGURE.12:FT-IR SPECTRUM OF TICAGRELOR SOLID DISPERSION

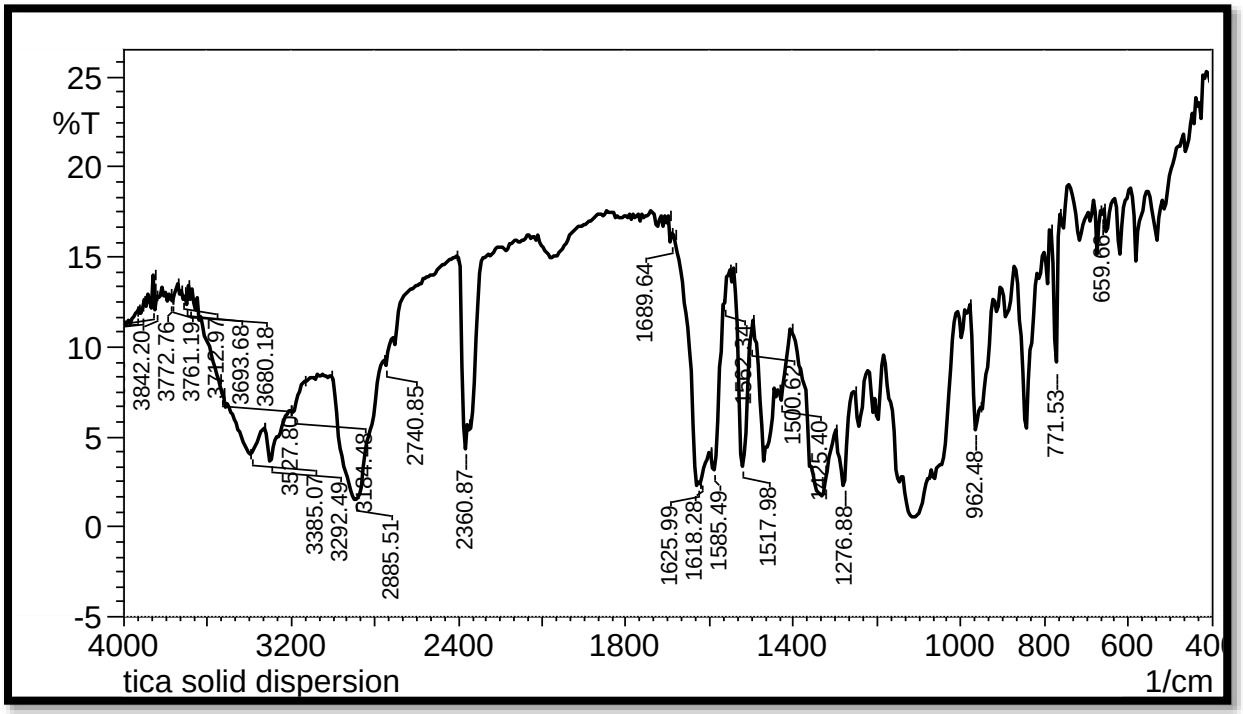


FIGURE.13: DSC THERMOGRAM OF TICAGRELOR PURE DRUG

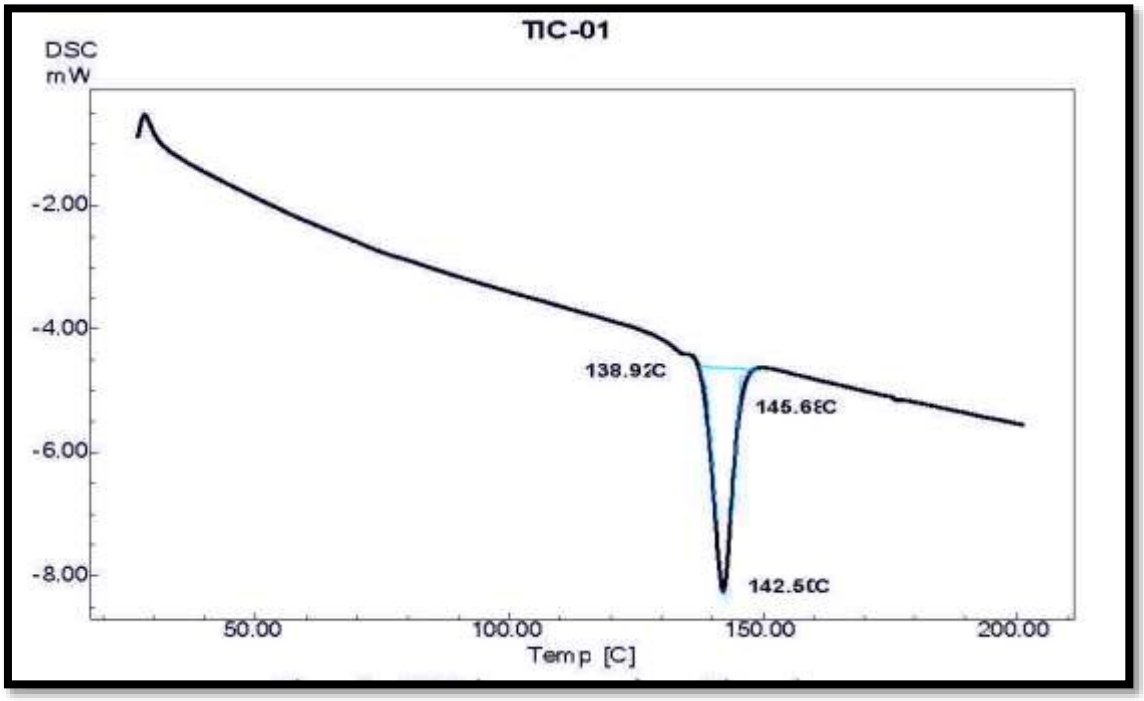


FIGURE.14: PXRD PATTERN OF TICAGRELOR PURE DRUG

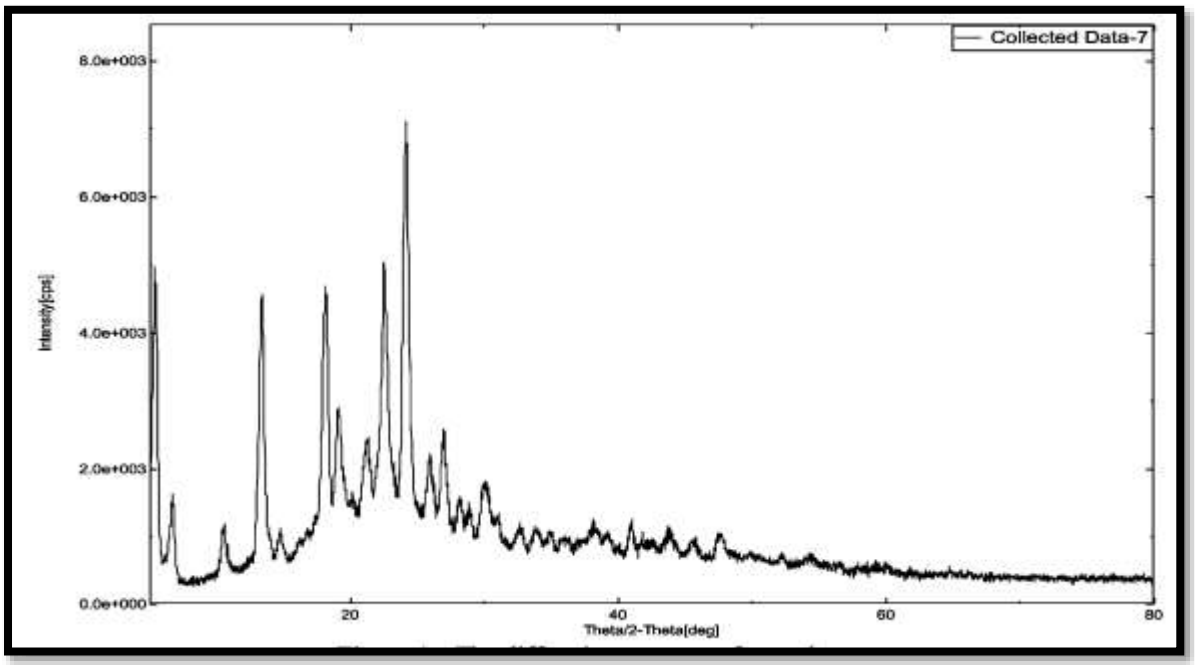


FIG.15: ANGLE OF REPOSE OF TICAGRELOR SUBLINGUAL TABLETS

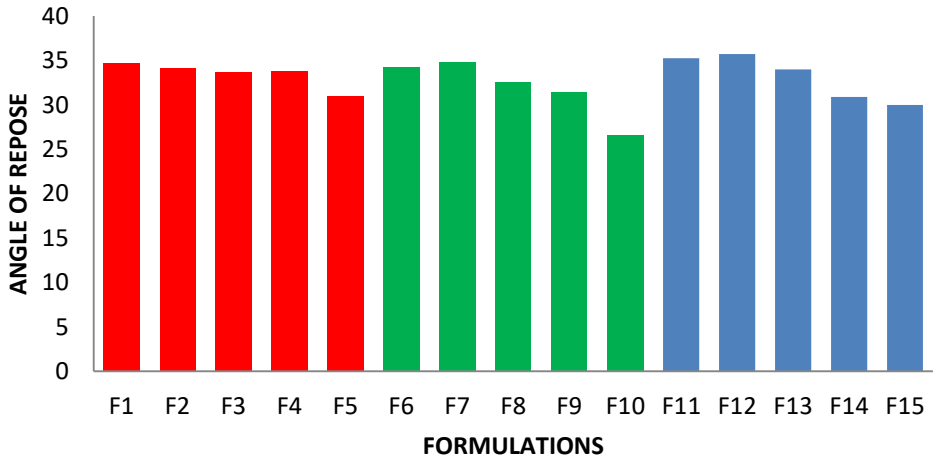


FIG.16: BULK DENSITY OF TICAGRELOR SUBLINGUAL TABLETS

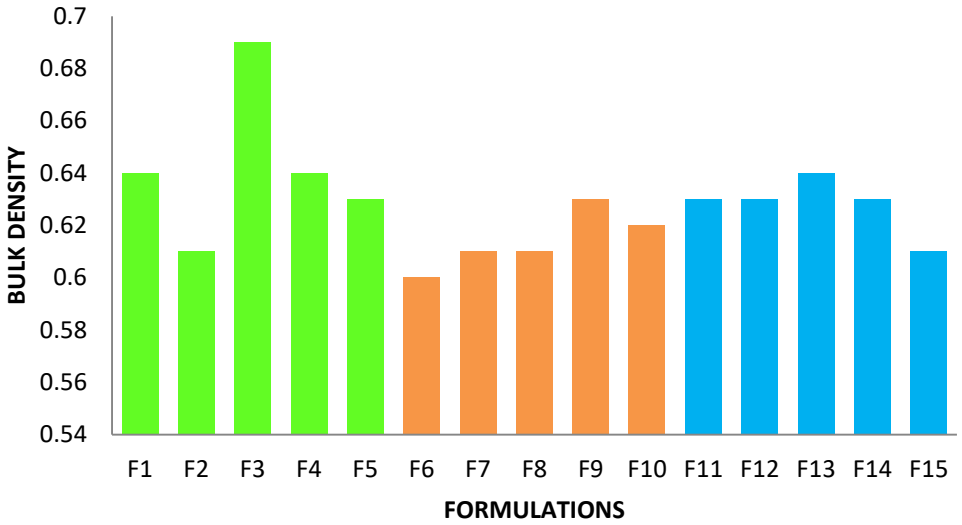


FIG.17: TAPPED DENSITY OF TICAGRELOR SUBLINGUAL TABLETS

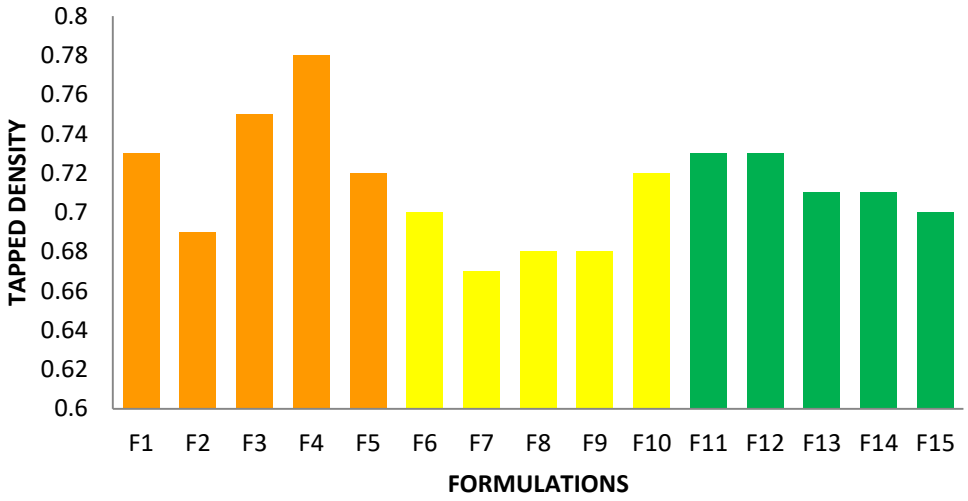


FIG.18: CARR'S INDEX OF TICAGRELOR SUBLINGUAL TABLETS

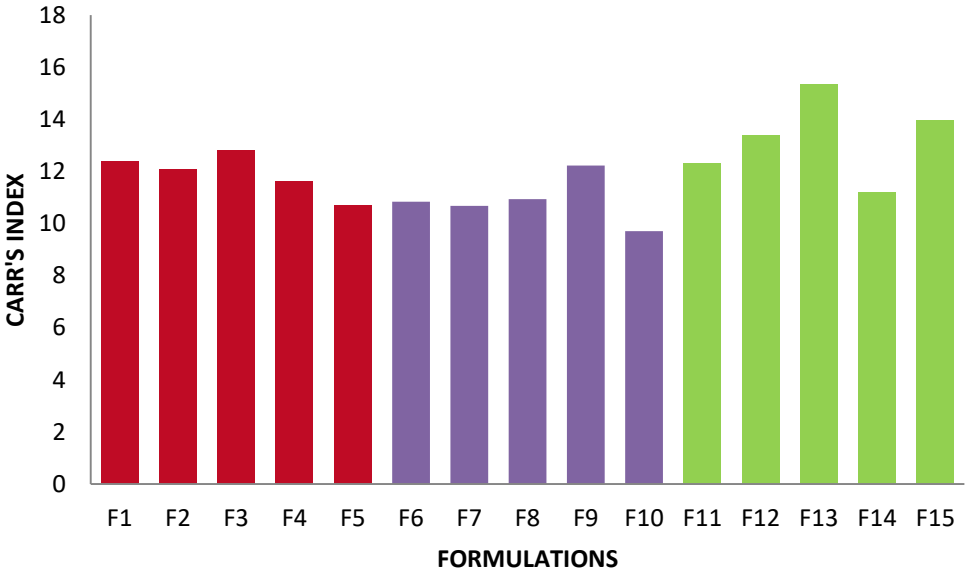


FIG.19: HAUSNER'S RATIO OF TICAGRELOR SUBLINGUAL TABLETS

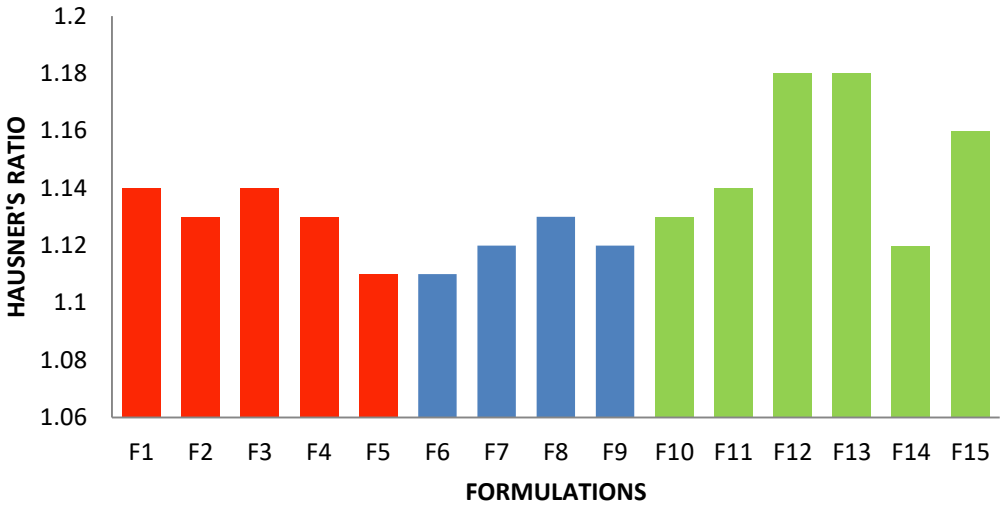
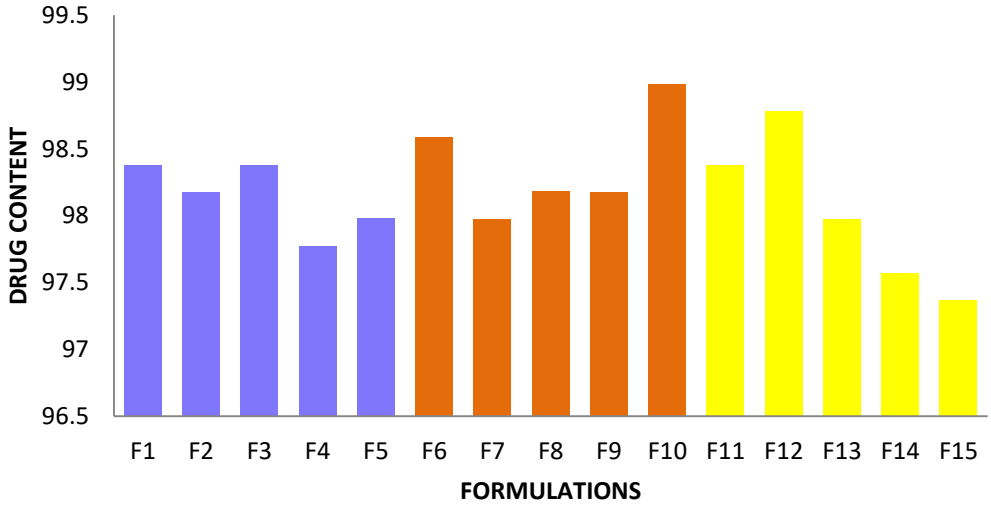


FIG.20: GRUG CONTENT OF TICAGRELOR SUBLINGUAL TABLETS



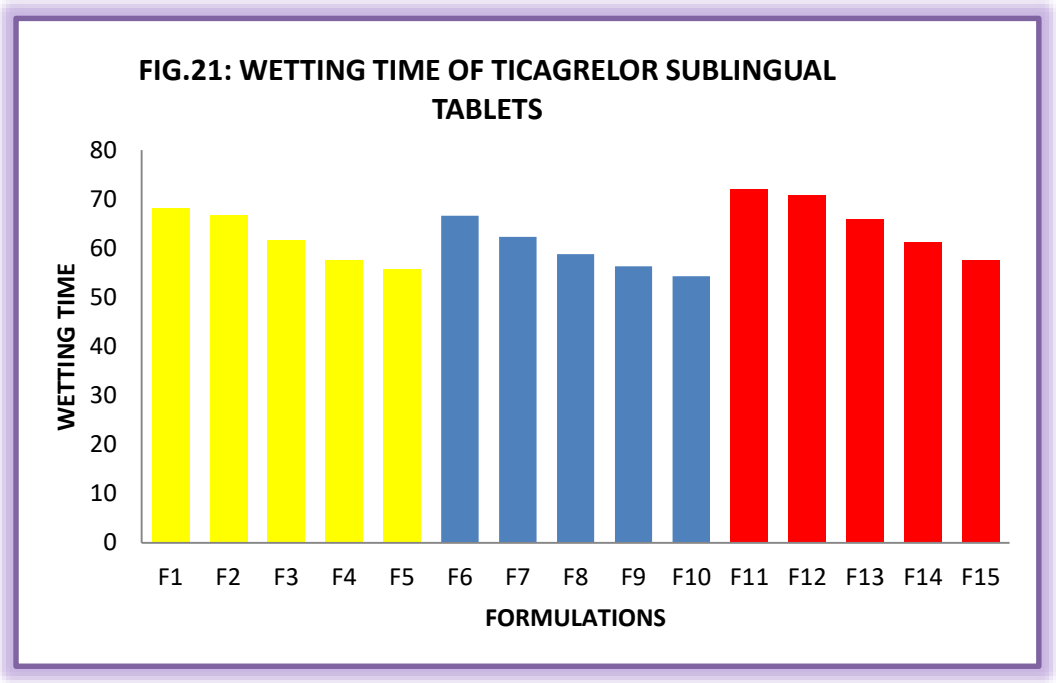


FIG.21: WETTING TIME OF TICAGRELOR SUBLINGUAL TABLETS
WETTING TIME
80
70
60
50
40
30
20
10
0
F1 F2 F3 F4 F5 F6 F7 F8 F9 F10 F11 F12 F13 F14 F15
FORMULATIONS

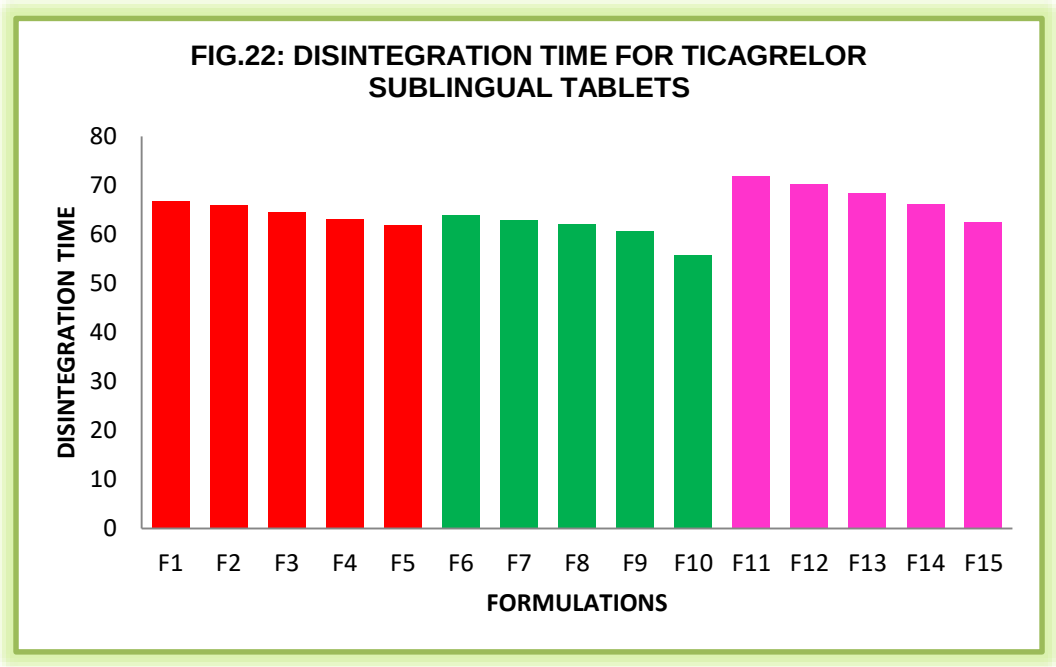


FIG.22: DISINTEGRATION TIME FOR TICAGRELOR SUBLINGUAL TABLETS
DISINTEGRATION TIME
80
70
60
50
40
30
20
10
0
F1 F2 F3 F4 F5 F6 F7 F8 F9 F10 F11 F12 F13 F14 F15
FORMULATIONS

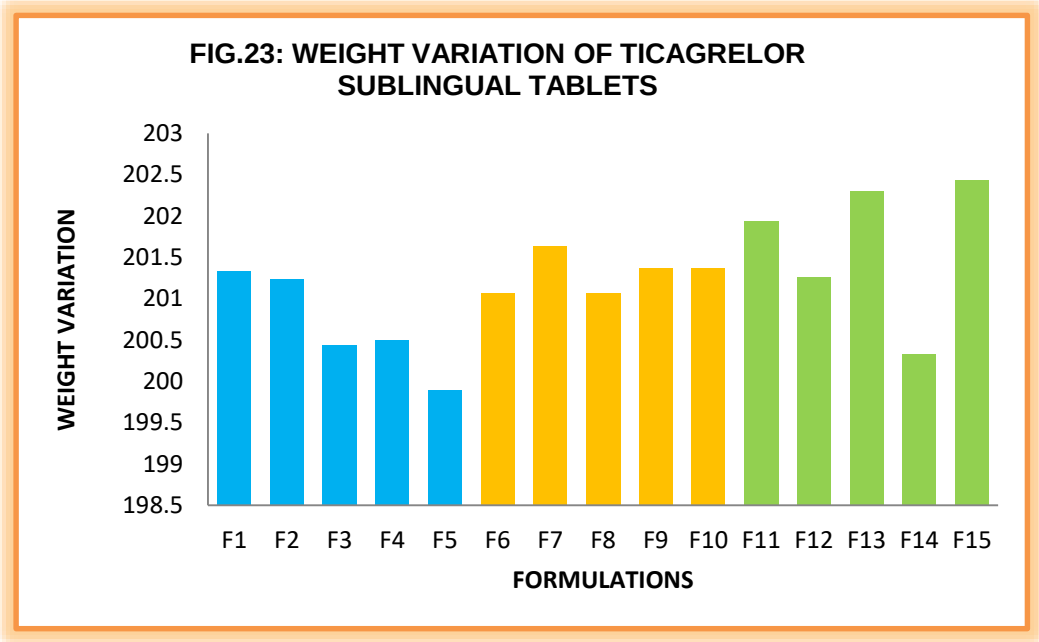


FIG.23: WEIGHT VARIATION OF TICAGRELOR SUBLINGUAL TABLETS
WEIGHT VARIATION
203
202.5
202
201.5
201
200.5
200
199.5
199
198.5
F1 F2 F3 F4 F5 F6 F7 F8 F9 F10 F11 F12 F13 F14 F15
FORMULATIONS

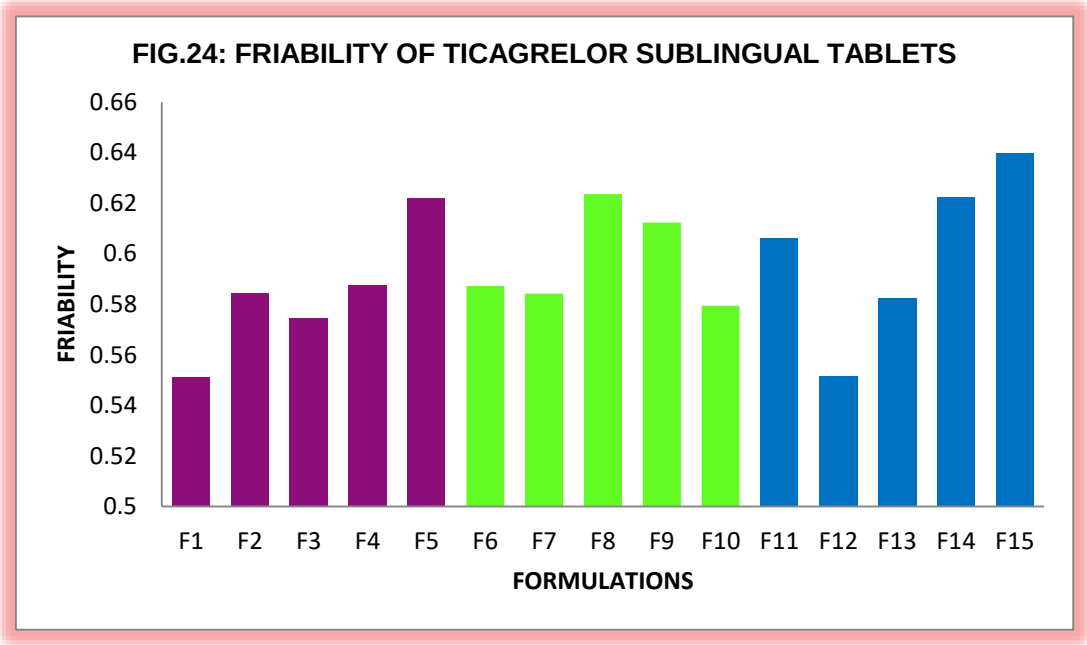


FIG.24: FRIABILITY OF TICAGRELOR SUBLINGUAL TABLETS
FRIABILITY
0.66
0.64
0.62
0.6
0.58
0.56
0.54
0.52
0.5
F1 F2 F3 F4 F5 F6 F7 F8 F9 F10 F11 F12 F13 F14 F15
FORMULATIONS

FIG.25: INVITRO RELEASE PROFILE OF TICAGRELOR SUBLINGUAL TABLETS

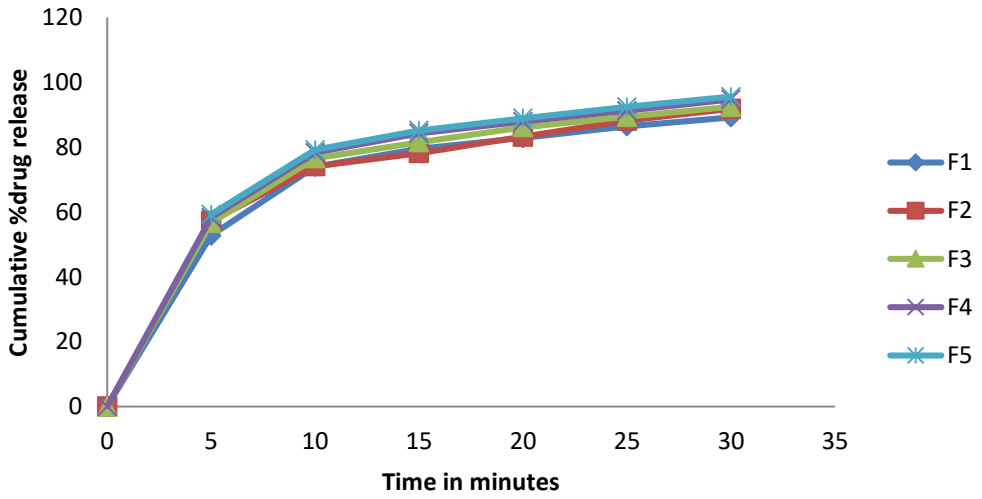


FIG.26: INVITRO RELEASE PROFILE OF TICAGRELOR SUBLINGUAL TABLETS

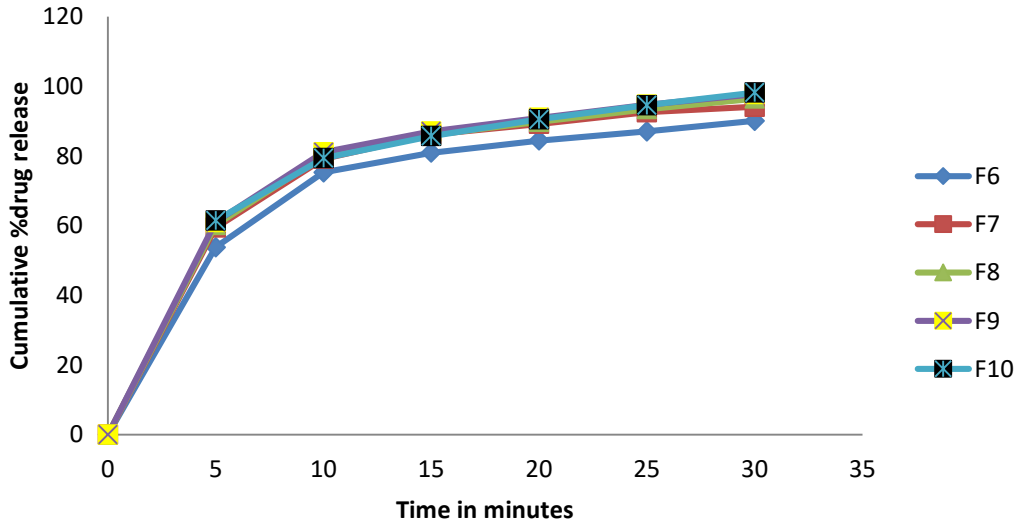


FIG.27: INVITRO RELEASE PROFILE OF TICAGRELOR SUBLINGUAL TABLETS

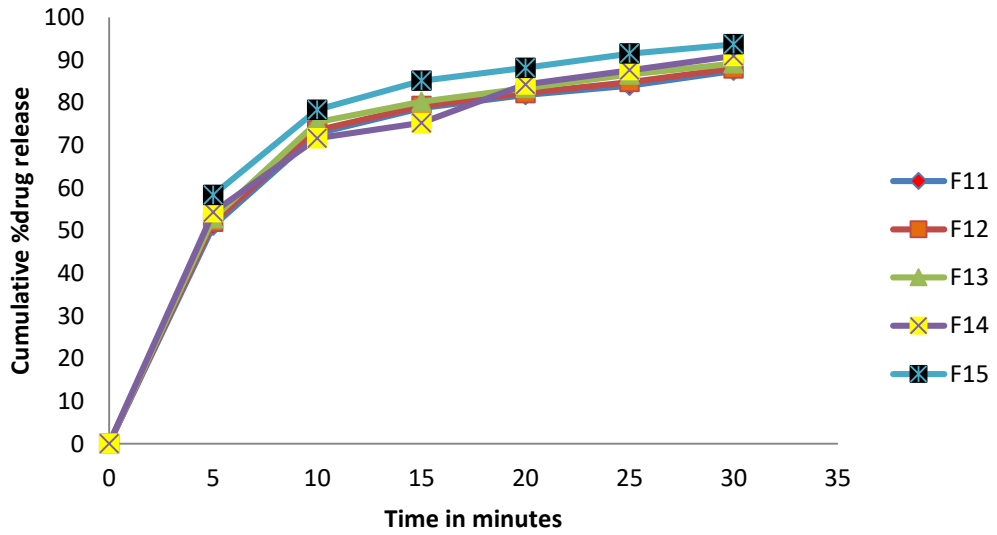


FIG.28: COMPARISION OF INVITRO ZERO ORDER RELEASE KINETICS OF FORMULATION CONTAINING CCS

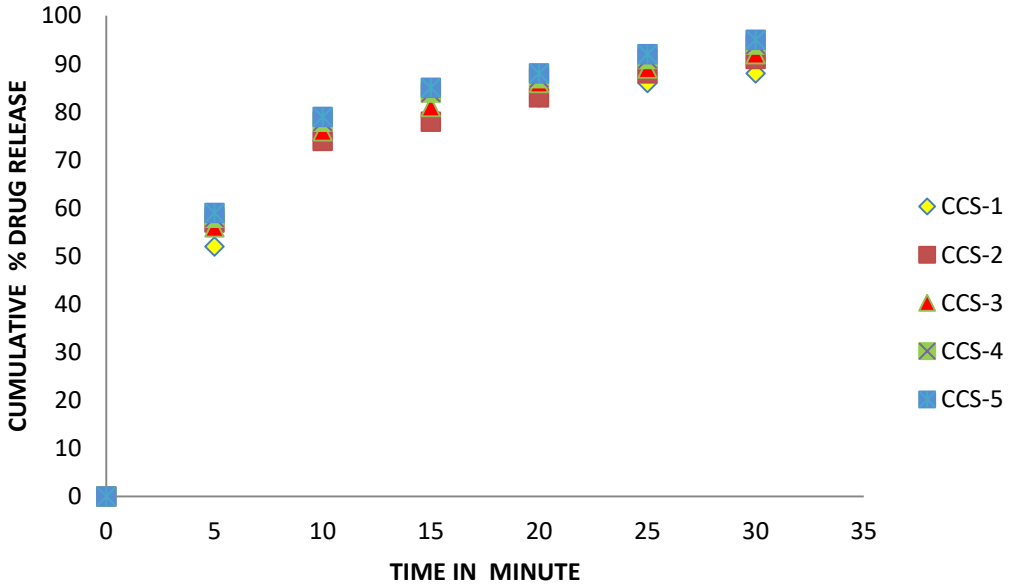


FIG.29 COMPARISION OF INVITRO ZERO ORDER RELEASE KINETICS OF TICAGRELOR SUBLINGUAL TABLETS CONTAINING CROSSPOVIDONE

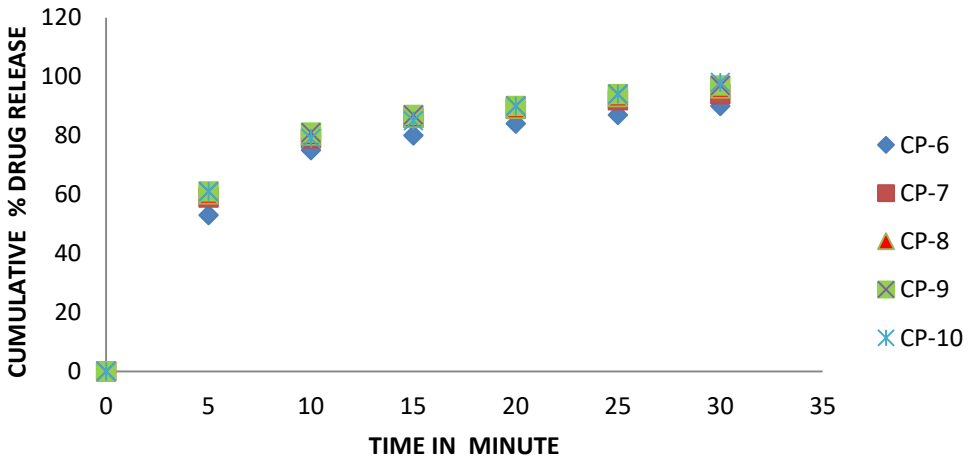


FIG.30: COMPARISION OF INVITRO ZERO ORDER RELEASE KINETICS OF TICAGRELOR SUBLINGUAL TABLETS CONTAINING SSG

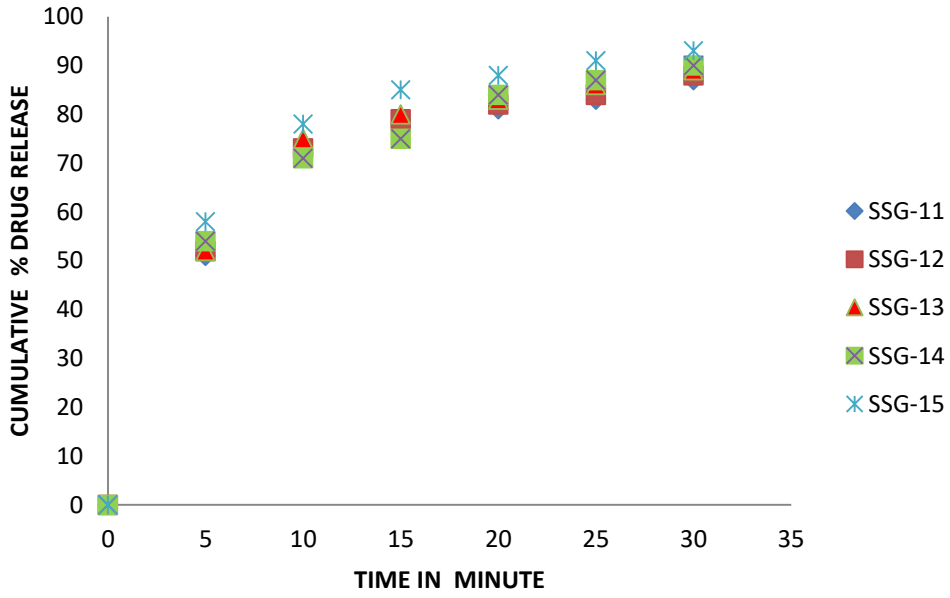


FIG. 31:FIRST ORDER PLOTS OF TICAGRELOR SUBLINGUAL TABLETS CONTAINING CROSSCARMELLOSE SODIUM

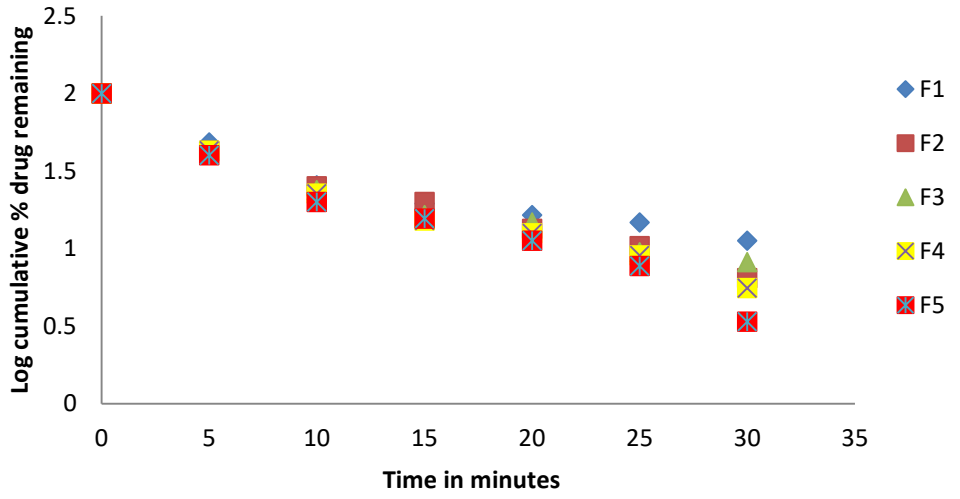


FIG.32: FIRST ORDER PLOTS OF TICAGRELOR SUBLINGUAL TABLETS CONTAINING CROSSPOVIDONE

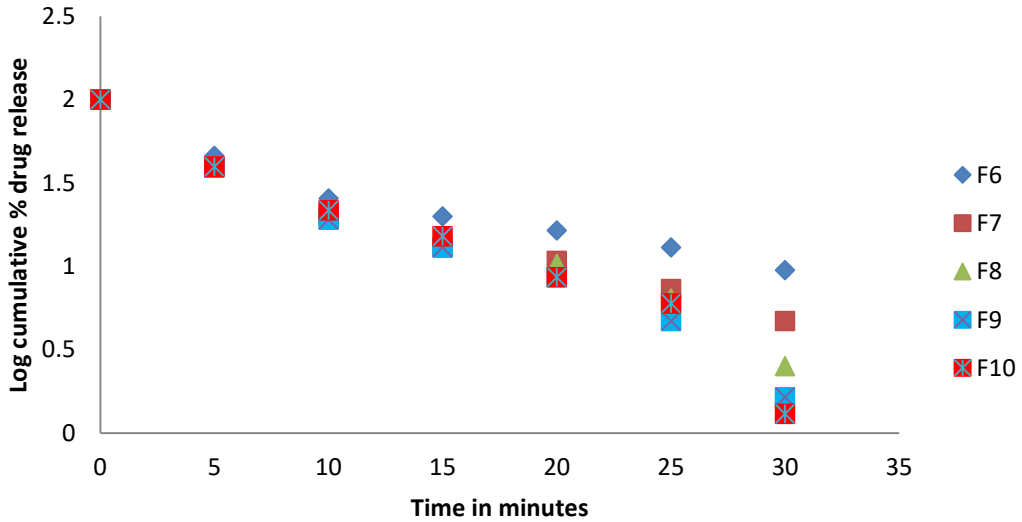


FIG. 33:FIRST ORDER PLOTS OF TICAGRELOR SUBLINGUAL TABLETS CONTAINING SODIUM STARCH GLYCOLATE

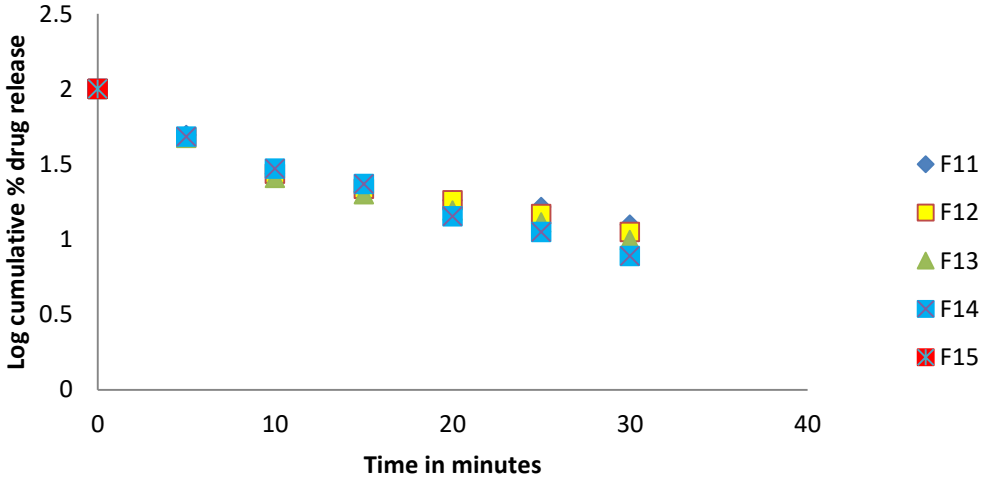


FIG.34: COMPARISION OF INVITRO HIGUCHI MODEL RELEASE KINETICS OF FORMULATION CONTAINING CCS

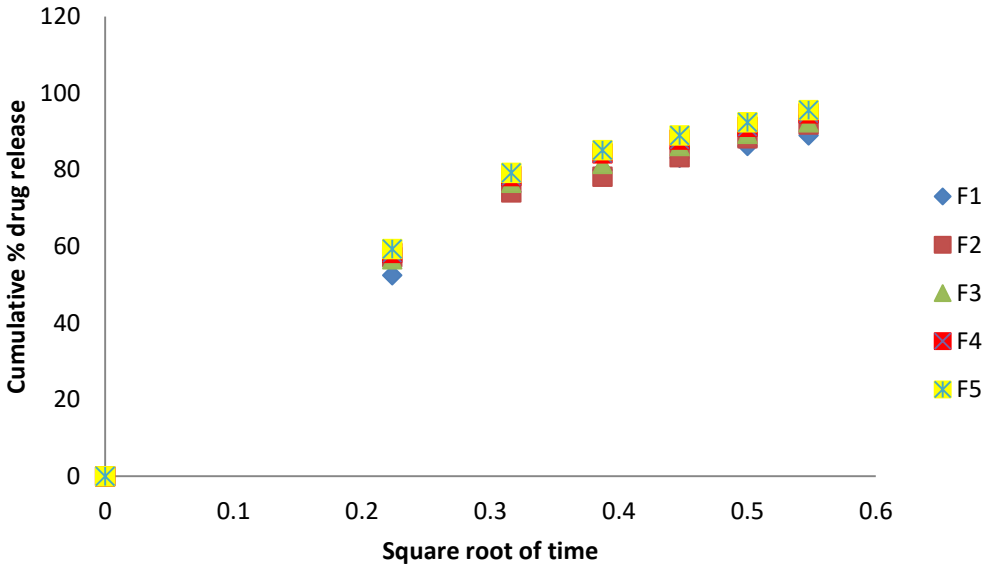


FIG.35: COMPARISION OF INVITRO HIGUCHI MODEL RELEASE KINETICS OF FORMULATION CONTAINING CROSSPOVIDONE

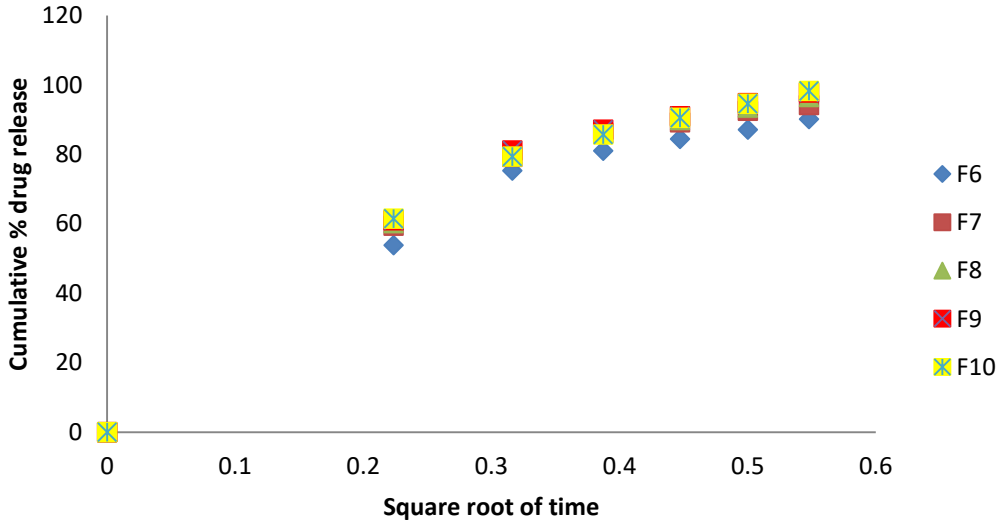


FIG.36: COMPARISION OF INVITRO HIGUCHI MODEL RELEASE KINETICS OF FORMULATION CONTAINING SSG

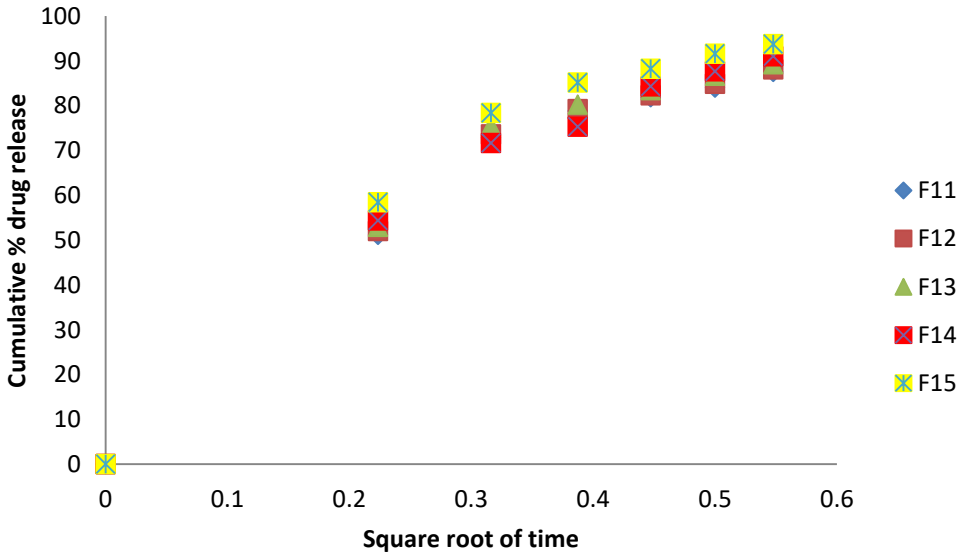


FIG.37: COMPARISION OF INVITRO KORSMEYER-PEPPAS MODEL RELEASE KINETICS OF FORMULATION CONTAINING CCS

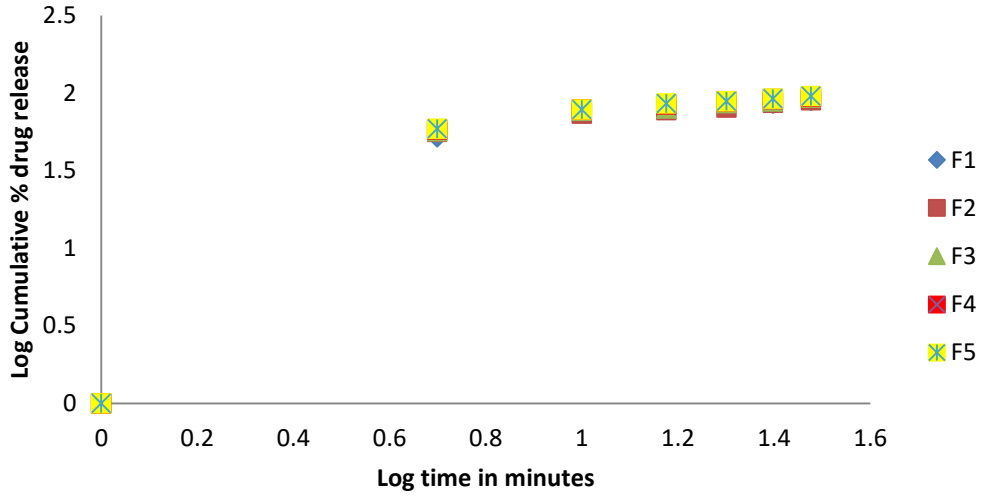


FIG.38: COMPARISION OF INVITRO KORSMEYER - PEPPAS MODEL RELEASE KINETICS OF FORMULATION CONTAINING CROSSPOVIDONE

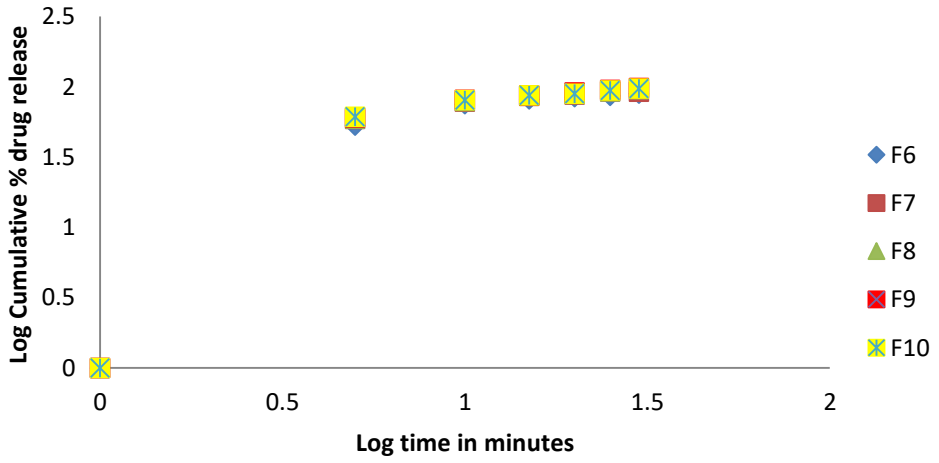


FIG. 39:COMPARISION OF INVITRO KORSMEYER - PEPPAS MODEL RELEASE KINETICS OF FORMULATION CONTAINING SSG

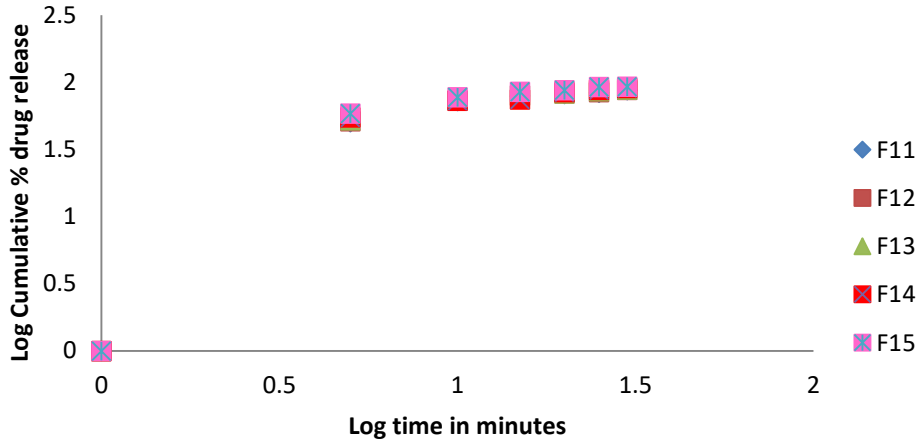


FIG.40: COMPARISON OF INVITRO HIXON CROWELL RELEASE KINETICS OF TICAGRELOR SUBLINGUAL TABLETS CONTAINING CCS

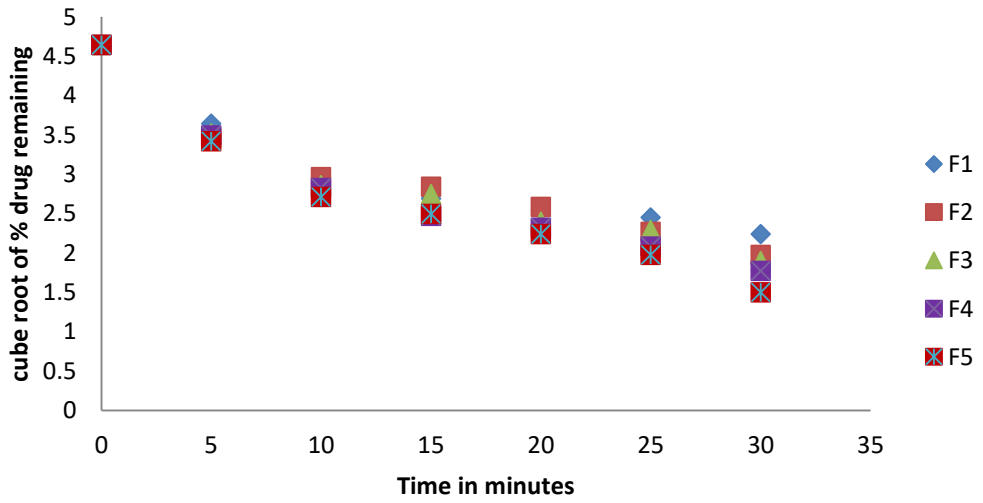


FIG.41: COMPARISON OF INVITRO HIXON CROWELL RELEASE KINETICS OF TICAGRELOR SUBLINGUAL TABLETS CONTAINING CROSSPOVIDONE

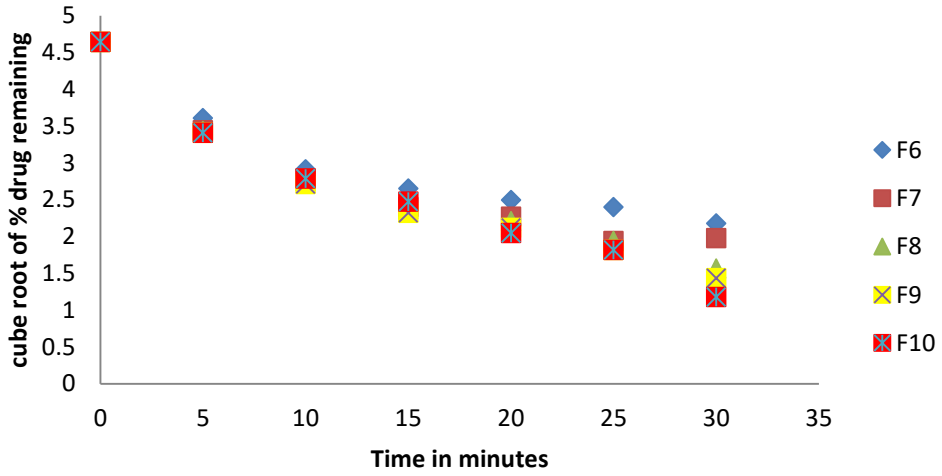


FIG. 42: COMPARISON OF INVITRO HIXON CROWELL RELEASE KINETICS OF TICAGRELOR SUBLINGUAL TABLETS CONTAINING SSG

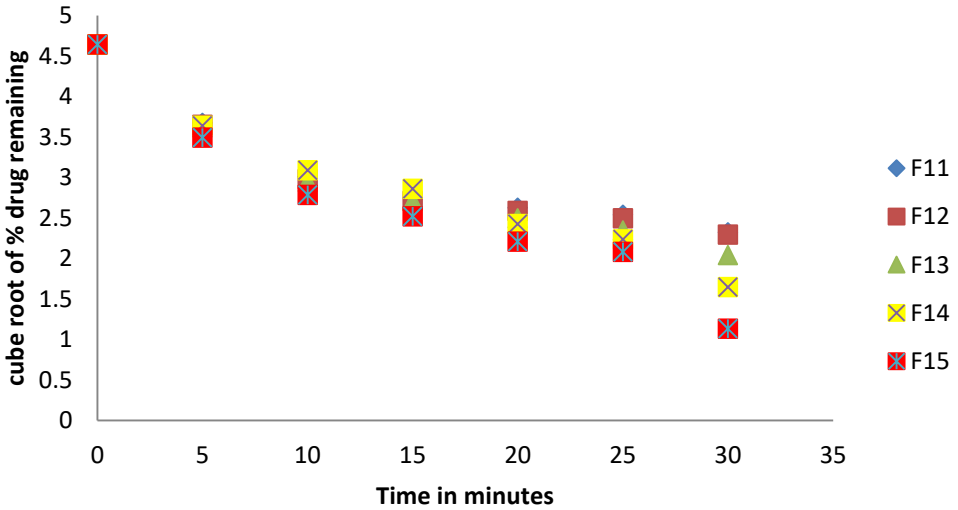


FIGURE.43: FTIR SPECTRUM OF TICAGRELOR SUBLINGUAL BEST FORMULATION (F10)

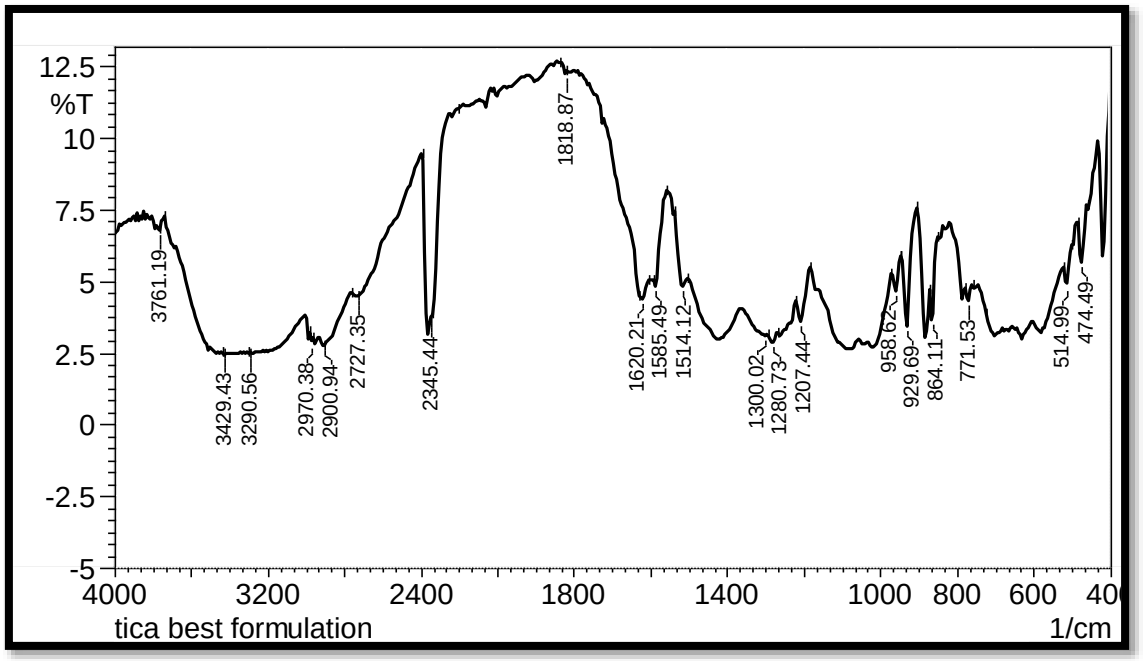


FIGURE.44: DSC THERMOGRAM FOR TICAGRELOR SUBLINGUAL BEST FORMULATION

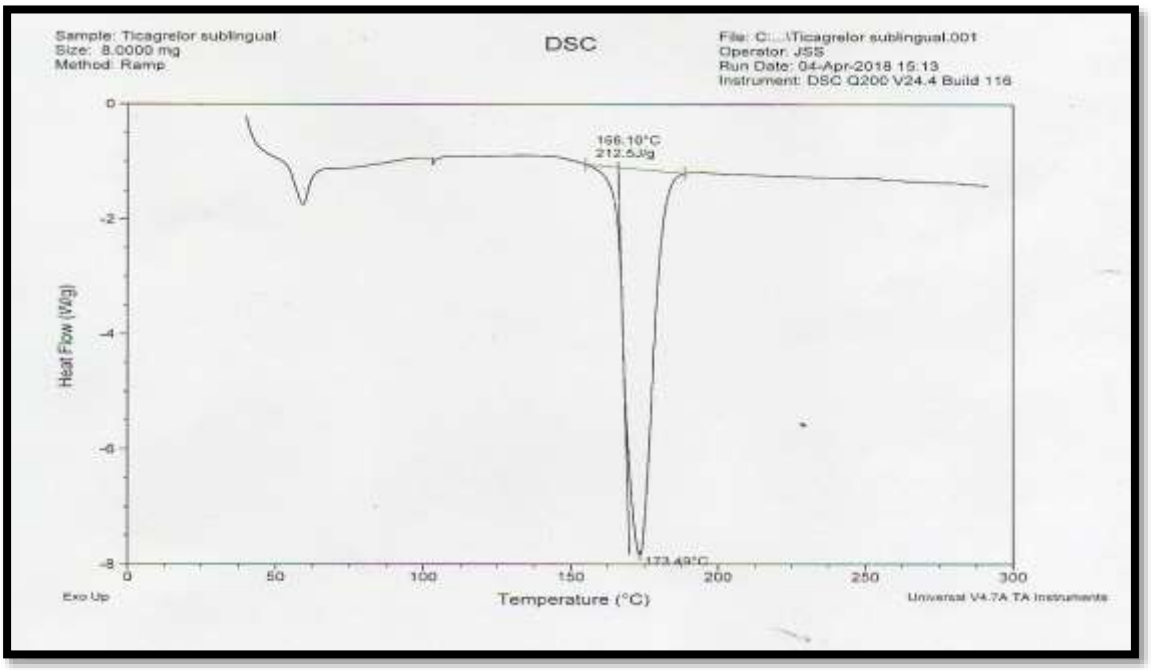


FIGURE.45: PXRD PATTERN OF TICAGRELOR SUBLINGUAL BEST FORMULATION (F10)

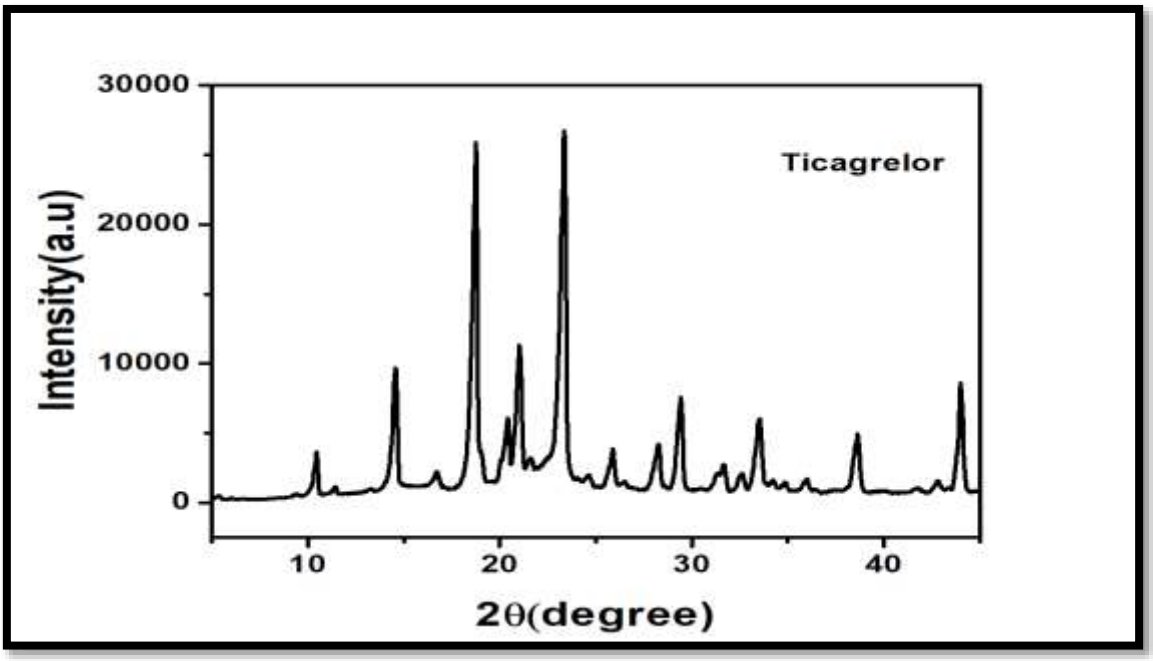
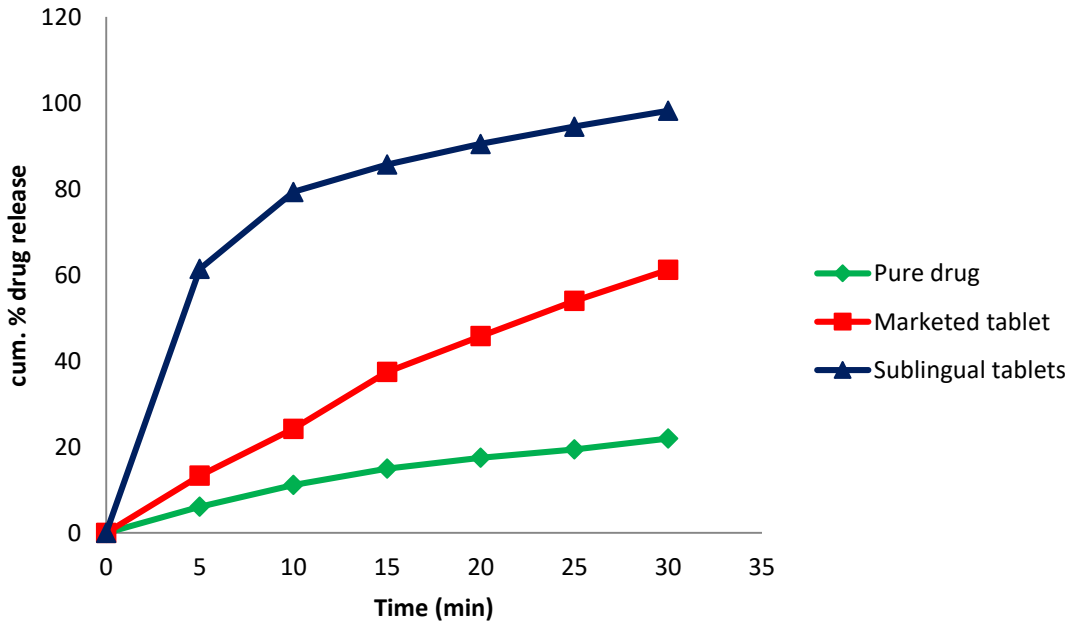


FIG.46: COMPARISION OF INVITRO DRUG RELEASE



CHAPTER XI

SUMMARY AND CONCLUSION

SUMMARY AND CONCLUSION

SUMMARY

The aim of the present study was to develop oral sublingual tablets of ticagrelor to give quick onset of action by rapidly disintegrating in a few seconds without the need of water with better patient compliance. In such cases, bioavailability of drug is significantly greater and adverse event is reduced than those observed from conventional tablet dosage form.

The work done is summarized as follows:

- Ticagrelor is very slightly soluble in water; so the study plan was done, to improve the solubility of ticagrelor by solid dispersion, and then was to formulate sublingual tablets.
- Solid dispersion was prepared by melting method using water soluble carrier polyethylene glycol 6000 showed better *in vitro* release studies in phosphate buffer pH6.8 using USP Type II apparatus.
- The results revealed that the increase in the carrier concentration increased the dissolution rate (1:4 ratios).
- The *in vitro* release studies revealed that the solid dispersion formulations showed a faster drug release when compared to the physical mixture and pure drug.
- By performing Drug - Excipients compatibility studies by IR spectrophotometry, no interaction drug-excipients was confirmed. Oral disintegrating tablets were formulated by direct compression method and suitable analytical method based on UV-Visible spectrophotometer was developed for the model drug

- Standard calibration curve prepared to determine the drug content in the prepared tablets and UV analysis was performed to determine the drug during *in vitro* release studies.
- Prior to compression, the blend of drug and excipients were evaluated for flow properties such as Angle of repose, loose bulk density, Tapped density, % Compressibility, and Hausner's ratio. All the formulations showed good flow properties.
- Sublingual tablets were prepared by direct compression technique using 12-Station D/B Tooling Compression Machine, equipped with concave round punch of 8 mm diameter.
- Post compression evaluation of prepared sublingual tablets were carried out with the help of different pharmacopoeial tests.
- The shape and colour of all the formulations were found to be circular and white in colour.
- The thickness was found to be uniform in specific formulations. The hardness, weight variation, diameter are also within the permitted limits.
- The friability of all the tablets was found to be < 1%, which indicates the good mechanical resistance.
- The wetting time of sublingual tablets containing crosspovidone (7.5%) was found to be 54 seconds.

CONCLUSION

The study conclusively demonstrated significant results for ticagrelor sublingual tablets. The sublingual tablets of ticagrelor was more palatable, and it is mostly helpful to the patients for the treatment of acute coronary

syndrome, cardiac angina. The sublingual tablets of ticagrelor can be successfully prepared by direct compression method using selected superdisintegrants with Crosscarmellose sodium 1.5%, 3%, 4.5%, 6%, 7.5%, Crosspovidone 1.5%, 3%, 4.5%, 6%, 7.5% and Sodium starch glycolate 1.5%, 3%, 4.5%, 6%, 7.5% for the better patient compliance and effective therapy the relative efficiency to improve the disintegration and dissolution rate of tablets were found. The disintegration time of F10 with 7.5% Crosspovidone formulation to be as 55.8 seconds respectively and is almost better than other formulations. Invitro dissolution studies were performed for all formulations. The formulation F10 showed 98.21% release within the 30 minutes. Crosspovidone shows good result as compare to other superdisintegrants.

Crosspovidone > crosscarmellose sodium > sodium starch glycolate

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