EFFECT OF SUPER DISINTEGRATING AGENTS ON IMANTINIB IN VITRO DRUG RELEASE STUDY USING KINETIC MODEL

Dissertation submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY

CHENNAI-32

In partial fulfilment of the requirement fo

the award of degree of

MASTER OF PHARMACY

IN

BRANCH- I PHARMACEUTICS

Submitted By

M.M.RAHAMATHULLAH

(Reg. No: 261910852)

Under the guidance of

Dr.N.PURUSHOTHAMAN,M.Pharm., Ph.D.,

Department of Pharmaceutics

PADMAVATHI COLLEGE OF PHARMACY

DHARMAPURI

OCTOBER-2021

DECLARATION

I hereby declare that the work incorporated in this thesis entitled "**EFFECT OF SUPER DISINTEGRATING AGENTS ON IMANTINIB IN VITRO DRUG RELEASE STUDY USING KINETIC MODEL"** has been carried out in Department of Pharmaceutics, Padmavathi College of Pharmacy, Periyanahalli, Dharmapuri – 635205. The work is original and has not been submitted in part or full for any other diploma or degree of any other university.

Place:

Date:

M.M.RAHAMATHULLAH

(261910852)

EVALUATION CERTIFICATE

This is to certify that the dissertation entitled "**EFFECT OF SUPER DISINTEGRATING AGENTS ON IMANTINIB IN VITRO DRUG RELEASE STUDY USING KINETIC MODEL"** a Bonafide research of **M.M.RAHAMATHULLAH & Reg.No.261910852** to **THE TAMILNADU Dr.M.G.R.MEDICAL UNIVERSITY** in partial fulfillment of requirement for the award of degree of **MASTER OF PHARMACY** is a Bonafide work carried out by me under the guidance of **Dr.M.PURUSHOTHAMAN, M.Pharm.,Ph.D.,** Professor cum Principal**,** Padmavathi college of Pharmacy, Dharmapuri -635205.

Internal Examiner **External Examiner**

Place:

Date:

GUIDE CERTIFICATE

This is to certify that the dissertation entitled "**EFFECT OF SUPER DISINTEGRATING AGENTS ON IMANTINIB IN VITRO DRUG RELEASE STUDY USING KINETIC MODEL"** Was carried out by **M.M.RAHAMATHULLAH (261910852)** (Department of Pharmaceutics)For the award of degree in MASTER OF PHARMACY (Pharmaceutics) **THE TAMILNADU Dr,M.G.R.MEDICAL UNIVERSITY, CHENNAI.**

Dr. M.PURUSHOTHAMAN, M.Pharm., Ph.D.,
Professor cum Principal
Padmavathi College of Pharmacy
Dharmapuri-635205.

Place:

Date:

ACKNOWLEDGEMENT

I greateful to thank to almighty for guiding me with his wisdom support throughout the project work.

I express my honorable thank to Chairman **Mr.M.G. Sekhar, BABL.,Ex-MLA., Ex- MP.,** for providing all the facilities and support during the period of my academic study.

I express my heartfelt thank to Vice Chairman **Mr. S. Venkeshwaran, B.E., MS(USA).,** for providing all the facilities and support during the period of my academic study.

I express my sincerely and humble thank to Secretary **Mr. M.Raja, M.Pharm., MBA.,** forproviding facilities essential for my project work.

It is with Immense pride and pleasure that I thank our Beloved **Principal, Prof. DR.M.Purushothaman, M.Pharm., Ph.D.,** Professor and Head of the Department of Pharmaceutics, Padmavathi College of Pharmacy, Periyanahalli, Dharmapuri for providing facilities, support and his guidance for work.

I now take this opportunity to express sincerely thank to our **Director, DR.D.C.Premanand, M.Pharm., Ph.D.,** Professor and Head of the Department of Pharmecutical Analysis for their valuable support, guideline and constant encouragement throughout the project work.

I take this opportunity with profound privilege and great pleasure in expressing my deep sense of gratitude to my respected guide **Prof. DR.M.Purushothaman, M.Pharm., Ph.D.,**Professor and Head of the Department of Pharmaceutics, Padmavathi College of Pharmacy, Periyanahalli, Dharmapuri for his gracious guidance, innovative ideas, constant inspiration, encouragement, suggestion and infinite help throughout my research work. I greatly thank his valuable support andendless consideration for the completion of the project work.

I also extend our thank to **Vice Principal, Dr.V.Palanivel, M.Pharm., Ph.D.,** Professor and Head of the Department of Pharmacology, Padmavathi College of Pharmacy, Periyanahalli, Dharmapuri for support and his guidance of work.

I also extend my thank to our Department of Pharmaceutics all staff members for their co-operation.

I would like to thank our lab assistant **Mrs.M.Kaviya, BBA.,** and library staff **Mr.C.Prabakaran, MLIS.,** for providing all facilities required for this successful completion ofmy thesis work.

I would like to sincerely thank to my friends for the timely help and co-operation.

I would like to give sincerely thank to my seniors for their moral support to carry out my project work.

I would like to express my heartfelt thank to my parents, brothers and sisters for their moralsupport to successful carry out my project work.

THANK YOU ALL

1. INTRODUCTION

Oral route has been one of the most popular routes of drug delivery due to its ease of administration, patient compliance, least sterility constraints and flexible design of dosage forms. For many decades' treatment of an acute disease or chronic illness has mostly accomplished by delivery of drugs to patients using conventional drug delivery system. Even today these conventional drug delivery systems are the primary pharmaceutical products commonly seen in the prescription. Conventional oral drug products are formulated to release the active principle immediately after oral administration to obtain rapid and complete systemic drug absorption.

Drug absorption is defined as the process of movement of unchanged drug from the site of administration to systemic circulation[1].

Systemic drug absorption from a drug product consists of a succession of rate process for solid oral, immediate release drug products.

The rate process includes

- Dissolution of the drug in aqueous environments.
- Absorption across cell membranes into systemic circulation.

For drugs that have very poor aqueous solubility, the rate at which the drug dissolves (dissolution) is often the slowest step and therefore exhibits a rate limiting effect on drug bioavailability. In contrast, for a drug that has a high aqueous solubility the dissolution rate is rapid the rate at which the drug crosses or permeates cell membrane is the slowest or rate limiting step[2].

Together with the permeability, the solubility behavior of a drug is a key determinant of its oral bioavailability. They have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. Examples such as griseofulvin, digoxin, phenytoin, sulphathiazole & chloramphenicol come immediately to mind. With the recent advent of high through put screening of potential therapeutic agents, the number of poorly soluble drug candidates has risen sharply and the formulation of poorly soluble compounds for oral delivery now presents

one of the most frequent and great challenge to pharmaceutical scientists in pharmaceutical industry.

Consideration of the modified Noyes - Whitney equation provides some hints as to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral availability.

$$\frac{dc}{dt} = \frac{AD\,(C_s - C)}{h}$$

Where, dc/dt = rate of dissolution

A = surface area available for dissolution

D = diffusion coefficient of the compound

C_s = solubility of the compound in the dissolution medium

C = concentration of drug in the medium at time t

h = thickness of the diffusion boundary layer adjacent to surface of the dissolving compound

The main possibilities for improving dissolution according to this analysis are to increase the surface area available for dissolution by decreasing the particle size of the solid compound and/or by optimizing the wetting characteristics of the compound to decrease the boundary layer thickness, to ensure sink conditions for dissolution and, last but definitely not least, to improve the apparent solubility of the drug under physiologically relevant conditions.

1.1 Various approaches to improve the solubility or to increase the available surface area for dissolution include[3]:

I. Physical modifications

a) Particle size

i) Micronization

ii) Nano suspension

b) Modifications of the crystal habit

i) Polymorphs

ii) Pseudo polymorphs

c) Complexation / solubilization

i) Use of surfactants.

ii) Use of cyclodextrins

II. Chemical modifications

Covalent polymer drug conjugates.

a) Particle size

i. Micronization:

The effective surface area of the drug is increased enormously by a reduction in the particle size. Particle size and particle size distribution studies are important for drugs that have low water solubility. Griseofulvin, nitrofurantoin, and many steroids are drugs with low aqueous solubility; reduction of the particle size decreased by milling to a micronized form has improved the oral absorption of the drugs, smaller particle size results in an increase in the total surface area of the particles, enhances water penetration into the particles and increases the dissolution rate[4].

b) Modification of the crystal habit:

The crystal form of drug is important variable in the present pharmaceutical processing. Therefore, they may exhibit different physico-chemical properties such as dissolution rate, powder flow and compressibility which is of pharmaceutical interest can differ for different habits of the same drug. In paracetamol, hexamethyl melamine and nitrofurantoin there is a modification of crystal habit which is useful to increase the oral absorption of drugs[5].

i) Polymorphism:

It refers to the arrangement of a drug in various crystal forms or polymorphs. Polymorphs have same chemical structure but different physical properties such as solubility, density, hardness and compression characteristics. As a rule, for a drug that which exists in multiple polymorphic forms, the polymorph with the highest oral crystalline is the most stable form i.e., with the least amount of free energy, and consequently posses the highest melting point and the least solubility. Amorphous or metastable forms of drugs possessing high free energy can be forcibly created by controlling the crystallization process. They offer the advantage of

high solubility. For example, E-form of chloramphenicol suspension is more soluble and better absorbed. So, polymorphism is a way to increase the solubility of poorly soluble drugs[6].

ii) Pseudo polymorphism:

Solubility of a poorly soluble drug is increased by Pseudo-polymorphism. The crystalline form of a drug can either be a polymorph or molecular adduct or both. The stoichiometric type of adducts where the solvent molecules are incorporated in the crystal lattice of the solid are called as the solvates and the trapped solvent as solvent of crystallization. The solvates can exist in different crystalline forms called as pseudo polymorphs. This phenomenon is known as Pseudo polymorphism. When the solvent in associated with the drug is water, the solvate is known as a hydrate. Hydrates are most common solvate forms of drugs.

Anhydrous form of a drug has greater aqueous solubility than the hydrates. For example, anhydrous form of theophylline and ampicillin have higher aqueous solubilities, dissolve at a faster rate show better bioavailability in comparison to their monohydrate and trihydrate forms respectively[7].

c) Complexation/ Solubilization

These are approaches to increase the solubility of the drug. Solubilizing excipients in the form of pH adjusters, co-solvent and surfactants can significantly improve the solubility and dissolution of poorly water soluble drugs. pH adjustment depends on the pKa of the drugs generally regarded as safe buffering agents are used as necessary. pH ranges from 2 to 11 are generally acceptable for oral products, where as it is desirable to formulate as close to the physiological pH as possible for parental products.

In the co-solvent approach, a poorly soluble drug is mixed with a water miscible organic solvent, in which the drug has high solubility before addition to an aqueous medium. The solubility of a non-polar drug has generally been observed to increase in a log-linear fashion with the addition of co-solvent. The concepts of dielectric constant, solubility parameter and hydrogen bonding have been used to explain the phenomenon of co-solvency. The most commonly used co-solvents are ethanol, propylene glycol, glycine and low molecular weight polyethylene glycols.

Inclusion complexes:

Lipophilic drug-cyclodextrin complexes, commonly known as inclusion complexes, can be formed simply by adding the drugs and excipients together resulting in enhanced solubilisation. The drug molecule resides insides the structure and is protected from unfavorable environments. Cyclodextrins don't increase the permeability of drugs in fact; formulation with cyclodextrins can reduce permeability.

Hydrophilic cyclodextrins are non toxic in normal doses while lipophilic ones may be toxic. Hence methyl, hydroxylpropyl, sulfoalkyated and sulfated derivatives of natural cyclodextrins that posses improved aqueous solubility are preferred for pharmaceutical use.

Novel nanotechnologies for solubilisation include:

i.) Nanocrystal technology uses a proprietary wet milling (also known as pearl milling) technique where the drug nanocrystal particles are sterically stabilized against agglomeration by surface adsorption of stabilizers. Polyvinyl pyrolidone, casein, glycerol polyethylene glycol and polyvinyl alcohol are examples of steric stabilizers to inhibit crystal growth[8].

ii.) Spray freezing into liquid technique involves the atomization of drug is incorporated in a fluid medium directly into cryogenic liquids such as liquid nitrogen. The frozen particles are lyophilized to obtain highly porous and dry free flowing particles.

1.2 Fast Disintegrating Tablets

The novel technology of fast-disintegrating dosage forms is known as fast dissolve, rapid dissolve, rapid melt and quick disintegrating tablets. However, the function and concept of all these dosage forms are similar.

Definition of Fast Disintegrating Tablets:

A solid dosage form that dissolves or disintegrates quickly in the oral cavity, resulting in solution or suspension without the need for the administration of water, is known as an fast-disintegrating dosage form.[9]

Difficulty in swallowing (dysphagia) is common among all age groups, especially in elderly, and is also seen in swallowing conventional tablets and capsules. An estimated 35 % of the general population, and an additional 30 % of elderly institutionalized patients and 18 % of all persons in long-term care facilities, suffer from dysphagia. This disorder is associated with many medical conditions, including stroke, Parkinson's, AIDS, Thyroidectomy, head and neck radiation therapy, and other neurological disorders, including cerebral palsy. One study showed that 26 % of 1576 patients experienced difficulty in swallowing tablets. The most common complaint was tablet size, followed by surface, form and taste. The problem of swallowing tablets was more evident in geriatric and paediatric patients, as well as travelling patients who may not have ready access to water.

Advantages of Fast Disintegrating Tablets

Administration to patients who cannot swallow, such as the elderly, stroke victims, healthcare facility and bedridden patients; patients who should not swallow, such as those affected by renal failure; and patients who refuse to swallow, such as pediatric, geriatric and psychiatric patients.

- Rapid drug therapy intervention.
- Convenience and patient compliance, such as disabled bedridden patients and for travelling and busy people who do not have ready access to water.
- New business opportunities: product differentiation, line extension and life-cycle management, exclusivity of product promotion, and patent-life extension. .

Ideal Characteristics of Fast Disintegrating Tablets

- They should not require water for administration, yet dissolve or disintegrate in the mouth within a few seconds.
- They should be compatible with taste masking.
- They should be portable without fragility concerns.
- They should have a pleasing mouth feel.
- They should leave minimal or no residue in the mouth after oral administration.
- They should allow high drug loading.
- They should exhibit low sensitivity to environmental conditions such as humidity and temperature.
- They should be manufactured using conventional tablet processing and packaging equipments at low rate.[9-15]

Patented technologies

Table 1: Oral fast-dispersing tablet technologies

Technology	Company
a. Conventional tablet process with modifications	
WOWTAB®	Yamanouchi pharma technology, 1050 Arastradero Road, Palo Alto, CA,USA
ORASOLV®	Cima Labs, Inc., 10000Valley HILL Road, Eden Prairies MN, USA
EFVDAS®	Elan Corp., Monksland Athlone, country Westmeanth, Ireland
FLASHTAB®	Prographarm Chaueauneuf-En-Thymerain France
b. Freeze dying method	
ZYDIS®	R.P.Scherer, Frankland Road Swindon Uk
LYOC®	Farmalyoc, 5AV Charles Marting, Maisons-Alfort France
QUIKSOLV®	Janssen Pharmaceutica,1125 Trenton-Harbourton Road Tirusville,NJ USA
c. Floss formation	
FLASHDOSE®	Fuisz Technologies,14555 Avion At Lakeside Chantilly ,VA,USA

a. Conventional Tablet Formulation Methods with Modifications

With some modifications, conventional tablet processing methods and equipment can be used in the preparation of these fast-disintegrating dosage forms. The WOWTAB® (Yamanouchi Pharma Technologies, Palo Alto, CA, USA) tablet features sufficient hardness to maintain the physical characteristics of the dosage form during production and distribution, until it comes into contact with moisture, such as saliva in the mouth.

Tablets made by conventional compression methods usually possess sufficient hardness to withstand the handling and rigours of transportation. However, they lack fast disintegration properties in the oral cavity as they are not intended for this performance. Therefore, a fast disintegrating tablet with good mechanical strength that could be manufactured with conventional processing equipment was the objective of the formulation development programme.

It was noted that saccharides possess the qualities of fast dissolution in water or saliva and achieve the required tablet hardness upon compaction. However, any individual saccharide either possessed fast disintegration characteristics or good hardness upon compaction, but not both. For example, mannitol, lactose, glucose, sucrose, and erythritol showed very quick dissolution characters in the mouth and were identified as low moldable sugars. In contrast, maltose, sorbitol, trehalose, and maltitol showed adequate hardness upon compression and were highly moldable, although there in vivo disintegration time was very slow. As no single sugar possessed all the required characteristics, a new composition was created by granulating a low moldable sugar with a high moldable sugar. The tablets obtained by compression of the new composition, after undergoing a humidification and drying process, exhibited both the fast disintegration and adequate hardness required for oral fast disintegrating tablets. Simple physical mixing of a mannitol and maltose combination did not result in a tablet with the required qualities.

ORASOLV®, a direct compression technology, utilizes effervescence material and taste-masked active ingredients, and also requires only conventional manufacturing equipment. The inclusion of effervescence causes the dosage form to quickly disintegrate following contact with water or saliva. By definition, the effervescence material is a chemical reaction between an organic acid (citric acid, numeric acid or maleic acid) and a base (sodium

bicarbonate, potassium bicarbonate or magnesium bicarbonate), thereby resulting in the generation of carbon dioxide. The concept of effervescence is a well-known formulation art utilized in several dosage forms. However, the current technology uses this concept in a modified fashion to achieve fast-disintegrating dosage forms.

The micro particles are prepared by a novel technique involving the dispersion of active ingredient into suitable polymer dispersion together with other excipients such as mannitol and magnesium oxide. Typical polymers include ethyl cellulose, methyl cellulose, acrylate and methacrylic acid resins. The active material mannitol is added to the polymeric dispersion under stirring, followed by the addition of magnesium oxide. Mannitol and magnesium oxide are added to aid active ingredient release from the polymeric coating and are known as release promoters in the current technology. This mixture is dried for one hour at 58^0C, delumped, and dried for another hour at the same temperature. The material is then screened (8mesh) and dried for one hour at 60 ^{0}C.

The formed microparticles, effervescent agents and other excipients, including flavourants, colourants, and lubricants, are blended and compressed into tablets at 1.0-2.0 kg/cm^2 hardness. The tablets are fragile with in vivo disintegration times of less than one minute. Because the tablets are very soft, they are packed into foil-foil blisters using a specially designed packaging system.

b. Freeze Drying Process

ZYDIS® (R.P. Scherer, Swindon, UK), using freeze drying processes, is one of the first generations of fast disintegrating dosage forms. There are approximately 12 marketed ZYDIS® products, including lorazepam, piroxicam, loperamide, loratidine, enalapril and selegiline. These formulations are freeze-dried products of a combination of water-soluble matrix material with drug, which is preformed in blister pockets and freeze dried to remove the water by sublimation. The resultant structures are very porous in nature and rapidly disintegrate or dissolve upon contact with saliva. The process had undergone several modifications to accommodate drugs with different physicochemical characteristics, drug loading and particle size, and matrix modifications to result in an acceptable dosage form.[16]

LYOC® technology is patented by PHARMALYOC. Oil in water emulsion is prepared and placed directly in to blister cavities followed by freeze drying. Nonhomogeneity during freeze drying is avoided by incorporating inert filler to increase the viscosity finally the sedimentation. High proportion of filler reduces porosity of tablets due to which disintegration

is lowered.[17]

QUICKSOLV® technology is patented by Janssen Pharmaceutical. It utilizes two solvents in formulating a matrix, which disintegrates instantly. Methodology includes dissolving matrix components in water and the solution or dispersion is frozen. Then dry the matrix by removing water using an excess of alcohol (solvent extraction). Thus the product formed has uniform porosity and adequate strength for handling.

c. Floss Formation Techniques

FLASHDOSE® (Fuisz Technologies, Chantilly, VA, USA) dosage form utilizes the Shearform™ technology in association with Ceform TI™ technology as needed, to eliminate the bitter taste of the medicament. The Shear form technology is employed in the preparation of a matrix known as 'floss', which is made from a combination of excipients, either alone or in combination with drugs. The floss is a fibrous material similar to cotton-candy fibers, commonly made of saccharides such as sucrose, dextrose, lactose and fructose. For the preparation of sucrose fibers, temperatures ranging from 180^0F are employed. However, the use of other polysaccharides such as polymaltodextrins and polydextrose can be transformed into fibers at 30 % lower temperatures than those used for sucrose fiber production. This modification permits the safe incorporation of thermolabile drugs into the formulation.

MECHANISIM OF TABLET DISINTEGRATION

A. Swelling:

Although not all effective disintegrants swell in contact with water, swelling is believed to be a mechanism in which certain disintegrating agents (such as starch) impart the disintegrating effect. By swelling in contact with water, the adhesiveness of other ingredients in a tablet is overcome causing the tablet to fall apart.

B. Porosity and Capillary Action (Wicking):

Effective disintegrants that do not swell are believed to impart their disintegrating action through porosity and capillary action. Tablet porosity provides pathways for the penetration of fluid into tablets. The disintegrant particles (with low cohesiveness & compressibility) themselves act to enhance porosity and provide these pathways into the tablet. Liquid is drawn up or "wicked" into these pathways through capillary action and rupture the interparticulate bonds causing the tablet to break apart.

C. Deformation:

Starch grains are generally thought to be "elastic" in nature meaning that grains that are deformed under pressure will return to their original shape when that pressure is removed. But, with the compression forces involved in tableting, these grains are believed to be deformed more permanently and are said to be "energy rich" with this energy being released upon exposure to water. In other words, the ability for starch to swell is higher in "energy rich" starch grains than it is for starch grains that have not been deformed under pressure. It is believed that no single mechanism is responsible for the action of most disintegrants. But rather, it is more likely the result of inter-relationships between these major mechanisms.

D. Due to disintegrating particle/particle repulsive forces:

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non swellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking[18].

In recent years, several newer agents have been developed known as "Superdisintegrants". These newer substances are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. On contact with water the superdisintegrants swell, hydrate, change volume or form and produce a disruptive change in the tablet. Effective superdisintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high-dose drugs. Super disintegrants offer significant improvements over starch. But hygroscopicity may be a problem in some formulations. As day's passes, demand for faster disintegrating formulation is increased. So, pharmacist needs to formulate disintegrants i.e. Superdisintegrants which are effective at low concentration and have greater disintegrating efficiency and they are more effective intragranularly. And this superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration. Three major groups of compounds have been developed which swell to many times their original size when placed in water while producing minimal viscosity effects. Different commonly used superdisintegrants are

1. **Modified Starches-** Sodium Carboxy methyl Starch (Sodium Starch Glycolate)

It is Possible to synthesize sodium starch glycolate from a wide range of native starches,

but in practice potato starch is used as it gives the product with the best disintegrating properties. After selection of the appropriate starch source the second step is the cross linking of the potato starch. This is typically carried out using an FDA approved starch esterifying agent such as sodium trimetaphosphate or phosphorus oxychloride in alkaline suspension. The effect of introduction of the large hydrophilic carboxymethyl groups is to disrupt the hydrogen bonding within the polymer structure. This allows water to penetrate the molecule and the polymer becomes cold water soluble. The effect of the crosslinking is to reduce both the water soluble fraction of the polymer and the viscosity of dispersion in water. The optimum balance between the degree of Substitution and the extent of cross-linking allows for rapid water uptake by the polymer without the formation of a viscous gel that might impede dissolution.

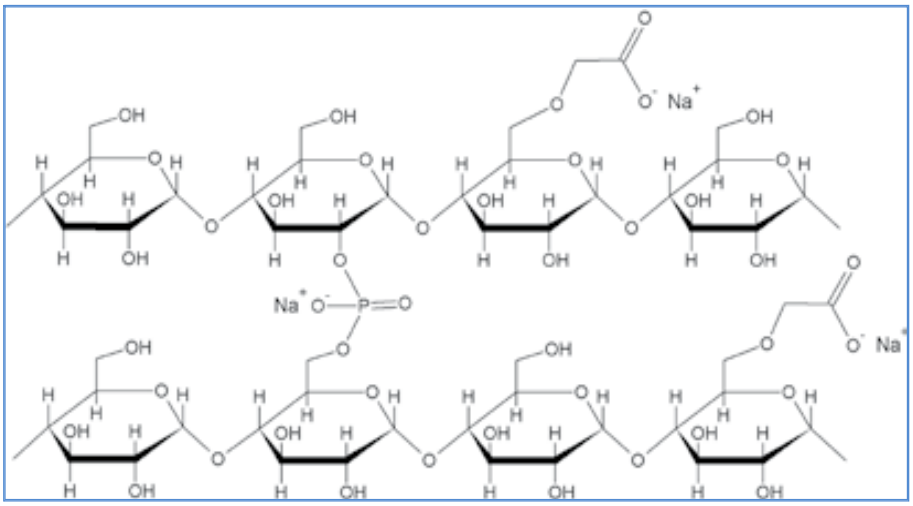


Figure 1: Basic Structure of Sodium Starch Glycolate

2. **Cross-linked polyvinylpyrrolidone** (crospovidone)

Crospovidone quickly wicks saliva into the tablet to generate the volume expansion and hydrostatic pressures necessary to provide rapid disintegration in the mouth. Unlike other superdisintegrants, which rely principally on swelling for disintegration, Crospovidone superdisintegrants use a combination of swelling and wicking. When examined under a scanning electron microscope, crospovidone particles appear granular and highly porous. This unique, porous particle morphology facilitates wicking of liquid into the tablet and particles to generate rapid disintegration. Due to its high crosslink density, crospovidone swells rapidly in water without gelling. Other superdisintegrants have a lower crosslink density and, as a result, form gels when fully hydrated, particularly at the higher use levels in ODT formulations. Unlike other superdisintegrants which are either poorly compressible or non-compressible, Crospovidone

disintegrants are highly compressible materials as a result of their unique particle morphology. In contrast to sodium starch glycolate and croscarmellose sodium, Crospovidone superdisintegrants exhibit virtually no tendency toward gel formation, even at high use levels. Disintegrants that gel can result in ODT and chewable products with an unpleasant, gummy texture. Crospovidone superdisintegrants provide the best overall sensory experience as well as rapid disintegration and robust tablets.

3. **Modified Cellulose** (croscarmellose sodium)

Croscarmellose sodium is described as a cross-linked polymer of carboxymethylcellulose. Apart from the differences between the starch and cellulose polymer backbones, there are Differences between the synthetic processes used to modify the polymer. Most importantly, the DS of croscarmellose sodium is higher than that of sodium starch glycolate, and the mechanism of crosslinking is different. The substitution is performed using Williamson's ether synthesis to give the sodium salt of carboxymethylcellulose. A key difference from the chemistry of SSG is that some of the carboxymethyl groups themselves are used to cross-link the cellulose chains, the process being accomplished by dehydration. Thus the cross-links are carboxyl ester links rather than phosphate ester links as in Primojel[19-24].

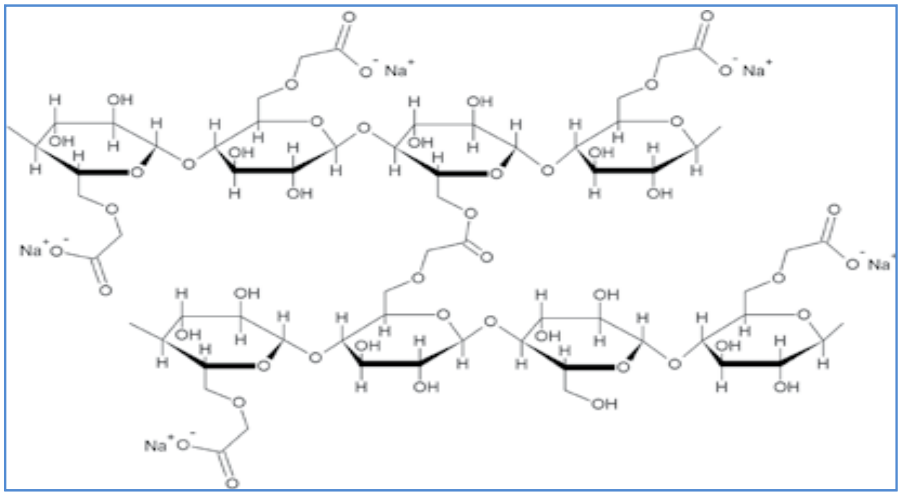


Figure 2: Basic Structure of Croscarmellose Sodium

4. Soy polysaccharide-

It is a natural super disintegrant that does not contain any starch or sugar so can be used in nutritional products.

5. Cross-linked alginic acid –

It is insoluble in water and disintegrates by swelling or wicking action. It is a hydrophilic

colloidal substance, which has high sorption capacity. It is also available as salts of sodium and Potassium.

6. Gellan gum –

It is an anionic polysaccharide of linear tetrasaccharides, derived from Pseudomonas elodea having good superdisintegrant property similar to the modified starch and celluloses.

7. Xanthan gum –

Xanthan Gum derived from Xanthomonas campestris is official in USP with high hydrophilicity and low gelling tendency. It has low water solubility and extensive swelling properties for faster disintegration.

8. Calcium Silicate –

It is a highly porous, lightweight superdisintegrant, which acts by wicking action.

Ion exchange resins -The INDION 414 has been used as a superdisintegrant for ODT. It is chemically cross-linked polyacrylic, with a functional group of – COO – and the standard ionic form is K+. It has a high water uptake capacity. It is a high purity pharmaceutical grade weak acid cation exchange resin supplied as a dry powder. It is an extremely effective tablet disintegrant which provides the necessary hardness and chemical stability to the tablet. The product swells up to a very great extend when in contact with water or gastrointestinal fluids causing rapid disintegration without the formation of lumps. It is a high molecular weight polymer, therefore it is not absorbed by the human tissues and totally safe for human consumption. It has several advantages, such as[25-30.]

Advantages:

- Remarkable tendency on wetting causing rapid disintegration.
- No lump formation on disintegration.
- Compatible with commonly used therapeutical agents and excipients.
- Work equally effective in hydrophilic and hydrophobic formulations.
- Provides good mechanical strength to the tablet facilitating easy packing and transportation.
- Does not stick to the punches and dyes.
- Although there are many superdisintegrants, which show superior disintegration, the search for newer disintegrants is ongoing and researchers are experimenting with modified natural products, like formalin casein, chitin, chitosan, polymerized agar acrylamide, xylan,

smecta, key jo-clay, crosslinked carboxymethyl guar and modified tapioca starch. Studies have suggested that the water insoluble superdisintegrants show better disintegration property than the slightly water soluble agents, since they do not have a tendency to swell. Superdisintegrants that tend to swell show slight retardation of the disintegration property due to formation of viscous barrier. There is no particular upper limit regarding the amount of superdisintegrant as long as the mechanical properties of the tablet are compatible with its intended use. The superdisintegrant may be used alone or in combination with other superdisintegrants. Commercially available super disintegrants are listed in the table given below[31-33].

Table 2: Various Super Disintegrants and Their Properties

Superdisintegrants	Commercially available grades	Mechanism of action	Special comment
Crosslinked cellulose	Crosscarmellose® Ac-Di-Sol®, Nymce ZSX® Primellose®, Solutab®, Vivasol®, L-HPC.	Swells 4-8 folds in < 10 seconds. Swelling and wicking both.	Swells in two dimensions. Direct compression or Granulation Starch free.
Crosslinked PVP	Crosspovidon M® Kollidon® Polyplasdone®	Swells very little and returns to original size after compression but act by capillary action.	Water insoluble and spongy in nature so get porous tablet.
Crosslinked starch	Explotab® Primogel®	Swells 7-12 folds in < 30 seconds.	Swells in three dimensions and high level serve as sustain release matrix.
Crosslinked alginic acid	Alginic acid NF	Rapid swelling in aqueous medium or wicking action.	Promote disintegration in both dry and wet granulation.
Soy polysaccharides	Emcosoy®		Does not contain any starch or Sugar. Used in nutritional products.
Calcium silicate		Wicking action.	Highly porous, Light weight.

ANTI CANCER

Cancer is a disease characterized by uncontrolled multiplication and spread of abnormal forms of the body's own cells. The branch of medicine concerned with the study, diagnosis, treatment and prevention of cancer is Oncology. Cancer may affect people at all ages, even fetuses, but the risk of most varieties increase with age. [34] All cancers begin in cells, the body's basic unit of life. The body is made up of many types of cells. These cells grow and divide in a controlled way to produce more cells as they are required to keep the body healthy. When cell become old or damaged, they die and are replaced with new cells. However, sometimes this orderly process goes wrong. The genetic material [DNA] of a cell can become damaged, producing mutations that affect normal cell growth and division. When this happens, cells do not die when they should and new cells form when the body does not need them. The extra cells may form a mass of tissue called a tumor. Targeted drug delivery is considered as a method in which drug-carrier complex,

Cancer is an uncontrolled growth of cells resulting in lack of differentiation and ability to invade local tissues and metastasis which are reproduce individually throughout the body. During metastasis, cancer cells enter the blood stream and are carried to distant parts of the body where they form other similar growths. Synthetic drugs are available for the treatment of cancer but they are not free from unfavorable effects. Chemotherapy and radiation therapy are major clinical treatment used for the control of early stages of tumor but these methods have severe side effects. Nature has provided human a variety of useful sources mainly plants for discovery and development of drugs against dreadful diseases

IMATINIB

Imatinib is one of the first cancer therapies that has shown a potential for a novel approachin cancer treatment. Imatinib represents a therapeutic breakthrough as a targeted therapy in the form of selective tyrosine kinase inhibitors (TKIs) specifically BCR-ABL, c-KIT, PDGFRA. It has become the first line drug in management of several cancers. Apart from itsremarkable success in CML, it has also shown promising results in the treatment of gastro- intestinal stromal tumors, clonal eosinophilic disorders, Philadelphia chromosome positive acute lymphatic leukemia and in steroid-refractory chronic graft versus-host disease because of its anti-PDGFR action. Introduction of Imatinib has radically improved the outcome of patients and has geared up further research into development of designer drugs with molecular targets.

The first clinical trial of Imatinib took place in 1998 and the drug received FDA approval in May 2001. Lyndon, Druker, and the other colleagues were awarded the Lasker-DeBakey Clinical Medical Research Award in 2009 for "converting a fatal cancer into a manageable condition" and the Japan Prize in 2012 for their part in "the development of a new therapeutic drug targeting cancer-specific molecules." Encouraged by the success of Imatinib in treating CML patients, scientists explored its effect in other cancers and it was found to produce a similar miracle effect in other cancers where tyrosine kinases were overexpressed[70]

2. REVIEW OF LITERATURE TO IMATINIB

- **Sunita A Chaudhary et, al, (2010)[35]** The present investigation is to formulate Orally Disintegrating Tablets (ODTs) of Rizatriptan were prepared by direct compression using super disintegrants such crospovidone, croscarmellose sodium, and sodium starch glycolate with incorporation of diluents like lactose, MCC and mannitol. To decrease the disintegration time further, modified diluents like spray dried lactose, Avicel PH 102 and Orocell 200.used along with the super disintegrants for the preparation of ODTs. Further trial was done in combinations of Orocell with Avicel PH 102. Among them Avicel PH 102 and orocell in 35:65 ratio showed less time of disintegration and rapid dissolution.
- **Pravin Chaudhari et, al, (2011)[36]** In order to achieve fast disintegration of Rizatriptan Benzoate proper formulation is needed. Tablets were prepared using various super disintegrants like Ac-Di-Sol, Primojel, Polyplasdone and Tulsion 339 and were formulated by direct compression method and were evaluated for thickness, weight variation, drug content, hardness, friability, disintegration time, water absorption ratio and dissolution. The hardness was found to be 3 kg, with disintegration time of 15 seconds, and showed 100% release within 1.5 minutes for tablets containing the super disintegrant Polyplasdone and hence considered superior as compared to other super disintegrants.
- **Akhila Alladi et, al, (2012)[37]** The aim of the present study is to formulate and evaluate taste masked Imatinib orally disintegrating tablet by using different taste masking agents and different super disintegrants in different ratios. The oral disintegrating tablets of Imatinib were prepared using different super disintegrants and the effect of different super disintegrants at different concentration on in-vitro release was studied. Imatinib release from ODT was directly proportional to the concentration of the superdisintegrant used. The optimized formulation was found to release the drug in minimum time and is found to be stable.
- **Ronald Peter, et al., (2014)[38]** In the present work, Flunarizine hydrochloride, an anti-migraine drug has been formulated into fast dissolving tablets by sublimation method using camphor and menthol as sublimating agents and treated agar as superdisintegrant. The blend was evaluated for angle of repose, bulk density, tapped density, compressibility index and hausner's ratio, thickness, hardness, friability, weight variation, content uniformity, wetting time and water absorption ratio, In-vitro disintegration time, dissolution study and FTIR studies. We could conclude that, superdisintegrant, menthol was better compared to camphor.
- **S.Vidhyadhara et, al, (2015)[39]** The aim of present work is to formulate and evaluate

fast dissolving tablets of Rizatriptan Benzoate prepared by effervescent and sublimation methods using effervescent agents like sodium bicarbonate & citric acid, super disintegrants like Croscarmellose sodium, Avicel PH 112 as diluents and menthol as sublimating agent. The prepared tablets were evaluated for uniformity of weight, thickness, friability, content uniformity, hardness, disintegration time, wetting time and for invitro drug release. Among all the formulations the tablets prepared by sublimation methods using menthol and Croscarmellose sodium as super disintegrant and Avicel PH 112 as diluents showed faster disintegration and rapid drug release.

- **Surrndea Babu et, al, (2016)[40]** The present work is done on preparing fast dissolving tablets of Imatinib. Among the various method of preparation fast dissolving tablets were prepared by using super disintegrants like CCS, CP and SSG by direct compression. The prepared tablets of Imatinib were evaluated for precompression parameters like angle of repose, bulk density, tapped density, Carr's index and post compression parameters like the hardness, friability and weight variation, drug content, disintegration time, and In Vitro dissolution studies. Among the various fast dissolving tablets of Imatinib F6 formulation was optimized. F6 maximum drug release in 20 min.

- **R. Nazemoon et, al, (2017)[41]** The present research work was to formulate and evaluate the oral fast disintegrating tablets of sumatriptan succinate. The tablets are prepared by direct compression method. The formulations were optimized by incorporating varying composition of Carboxy methyl cellulose (Avicel PH 102), mannitol as diluent, crospovidone as super disintegrants magnesium stearate as lubricant, Micro crystalline cellulose as a glidant. All the excipients are tested for compatability with model drug, which revealed that there was no physical and chemical interaction occurred. The preformulation parameters analyzed for prepared tablet blend before compression. The effect of these variables on drug release also studied. All the formulations showed low weight variation with disintegration and wetting time less than three minutes and rapid in vitro dissolution. The present study demonstrated potentials for rapid absorption, improved bioavailability, effective therapy and patient compliance.

- **Abeer Ahmed Kassem et, al, (2017)[42]** Development of sublingual fast dissolving lyophilized Imatinib tablets, to enhance its pre-gastric absorption and so alleviating the

gastrointestinal dysmotility that is commonly associated with migraineurs**.** Physical properties, wetting time, in vitro dissolution and disintegration behaviour were investigated. A combination of PVP, gelatin and chitosan in different ratios with mannitol were developed and characterized for further improvement. Optimized formula was examined by scanning electron microscope (SEM), differential scanning calorimetry (DSC) and Fourier-transform infrared spectroscopy (FTIR). Sublingual instantly dissolving Almo-lyotab was successfully developed and may constitute an advance in the management of acute migraine attacks.

- **Talele Swati G. et, al, (2015)[43]** The present study was aimed to formulate and evaluate mouth dissolving films of Imatinib malate using polymers HPMC E-15, HPMC E-4 and gelatin as the film forming agents. The fast dissolving oral films were designed using optimal design and numerical optimization techniques were applied to find out best formulations. The films were prepared by solvent casting method. They were evaluated for physicochemical characterization such as thickness uniformity of weight, drug content, folding endurance surface pH percentage elongation, tensile strength all of which showed satisfactory results The formulation were also subjected to invitro disintegration and in vitro drug release .The stability studies showed that there was no appreciable change parameters when stored at three different temperatures .

2.1 REVIEW OF LITERATURE FOR FAST DISSOLVING TABLET

- **Yunxia bi *et al.*,(1996)[44]** have formulated tablets which rapidly disintegrate in the oral cavity using Microcrystalline cellulose and Low-substituted Hydroxypropyl cellulose as disintegrants and Ethanzamide and Ascorbic acid as poorly and easily water soluble model drugs, respectively.

- **Y. X. Bi, H. Sunada, *et al.*,(1999)[45]** have prepared rapidly disintegrating tablets using microcrystalline cellulose as diluents, and cross-linked sodium Carboxymethyl cellulose (Ac-Di-sol) Erythritol are selected as response variables, tablet porosity and parameters representing the characteristics of formulations were selected as controlling factors and the relation was determined by the polynomial regression method.

- **Hisakadzy Sunada *et al.*, (2002)[46]**have developed rapidly disintegrating tablets using both direct compression and wet compression methods. Tablet properties, such as, porosity, tensile strength, wetting time and disintegrating time were evaluated, and the formulation and disintegration mechanisms of the tablets were evaluated.

- **Kaushik D. *et al.*,(2004)[47]** have worked on the "Development of Melt in Mouth dissolving tablets by sublimation Technique" This was indicative of the fact that the volatile salt was completely removed from the tablets resulting in the creation of pores in the tablets, which were responsible for the rapid disintegration of tablets in the oral cavity.

- **Madhugalkar AR et al., (2007)[48]** studied the efficiency of Indion 414 and Amberlite IRP88 as superdisintegrants in the mouth dissolving tablets of Nimesulide. Formulations also contain camphor. Tablets were prepared by wet granulation method. The compressed tablets were stored at 50 ^{0}C for two hours to bring about sublimation of camphor. The tablets were evaluated for parameters like hardness, friability, weight variation, drug content Invitro dispersion time, Invivo dispersion time and drug release. Indion 414 was found best compared to Amberlite IRP88.

- **Malke S et al**., **(2007)[49]** Fast dissolving tablets of oxcarbazepine were prepared containing Avicel pH 102 as a diluent and Ac-Di-Sol as a superdisintegrants by wet granulation process. A modified disintegration method was used for studying disintegration. Since the drug is poorly water soluble, drug release was tested in various media and the effect of surfactants on drug release was studied.

- **Shirsand S.B. et al., (2008)[50]** Fast dissolving tablets of clonazepam were prepared by direct compression method with a view to enhance patient compliance. Three superdisintegrants viz., crospovidone, croscarmellose sodium and sodium starch glycolate in different ratios with microcrystalline cellulose (Avicel pH-102) along with directly compressible mannitol

(pearlitol SD 200) to enhance mouthfeel. The prepared batches of tablets were evaluated for hardness, friability, drug content uniformity, wetting time, water absorption ratio and in-vitro dispersion time. Based on in-vitro dispersion time three formulations were tested for the invitro drug release pattern in (pH-6.8 phosphate buffer) and drug excipients interaction (IR spectroscopy). Among the three promising formulations the formulation prepared by using 10% w/w of crospovidone and 35%w/w of microcrystalline cellulose emerge the best of all formulations.

- **Mulla ja et al., (2008)**[51]deve1oped fast dissolving tablets of promethazine HCL using direct compression after incorporating super disintegrants such as Ac-di-sol,Explotab and polyplasdone XL in different concentrations. The tablets were evaluated for different pharmacoepial tests. Tablets containing Ac-Di-Sol showed better disintegrating character along with good release.

- **Patel B *et al.*, (2009)**[52]fast dissolving tablets of glipizide were prepared by direct compression method .Two superdisintegrants viz, crospovidone and croscarmellose sodium with different binders viz, pvp k-30 and pregelatinized starch were used. The prepared batches of tablets were evaluated for hardness, friability, weight variation, disintegration, wetting time, drug content and in vitro dissolution studies. Based on evaluating parameters. Stability studies were carried out at 25 ^{0}C / 60% RH and 40 ^{0}C / 75 % RH for optimized formulation for 2 months. Stability studies on the optimized formulation indicate that there was no significant change found in physical appearance, disintegration time and wetting time of the tablets.

- **Jain C.P. *et al.*, (2009)**[53]Fast dissolving tablets of valsartan were prepared using different super disintegrants by direct compression method. FDTs were evaluated for physical chemical properties and in-vitro dissolution. Effect of disintegrant on disintegration behaviour of tablet in artificial saliva, pH 5.8 was evaluated. Wetting time of formulations containing Crospovidone was least and tablets showed fastest disintegration. The drug release from FDTs increased with increasing concentration of super disintegrants and was found to be highest with formulations containing Crospovidine.

- **Rangasamy M *et al.*,(2009)**[54] Fast dissolving tablets of terbutaline sulfate were prepared by the direct compression method after incorporating super disintegrants such as Explotab, Ac-Di-Sol and Polyplasdone XL in different concentrations. The prepared tablets were evaluated for weight variation, thickness, hardness, friability, wetting time, drug content, water absorption ratio, in-vitro dispersion time, in-vitro disintegration time and in-vitro drug release. Among all, the formulation F9 (containing 5 % w/w concentration of polyplasdone XL) was the best

formulation, which release up to 99.33 % of the drug in 10 min.

- **Manivannan Rangasamy *et al.*,(2009)[55]** Studied the effect of different super disintegrants on "Fast dissolving tablets of terbutaline sulfate were prepared by the direct compression method after incorporating super disintegrants such as Explotab, Ac-Di-Sol and Polyplasdone XL in different concentration. Among all 5 % w/w concentration of polyplasdone XL has showed better release up to 99.33 % of the drug in 10 mins.

- **Bhalerao AV *et al.*,(2009)[56]**worked on the development and evaluation of clonazepam fast disintegrating tablets using superdisintegrants. Different combinations of superdisintegrants such as crosscarmellose sodium, sodium starch glycolate, crospovidone were used. Directly compressible mannitol and aspartame were used to enhance the mouth feel and taste. Lactose was used as diluents. The tablets were prepared by direct compression technique on rotary tablet machine. Amongst all DRUG : PVP K30 (1:4) ratio and combination of 5 % w/w croscarmellose sodium and 5 % w/w of sodium starch glycolate showed least dispersion time of 8 seconds and faster dissolution.

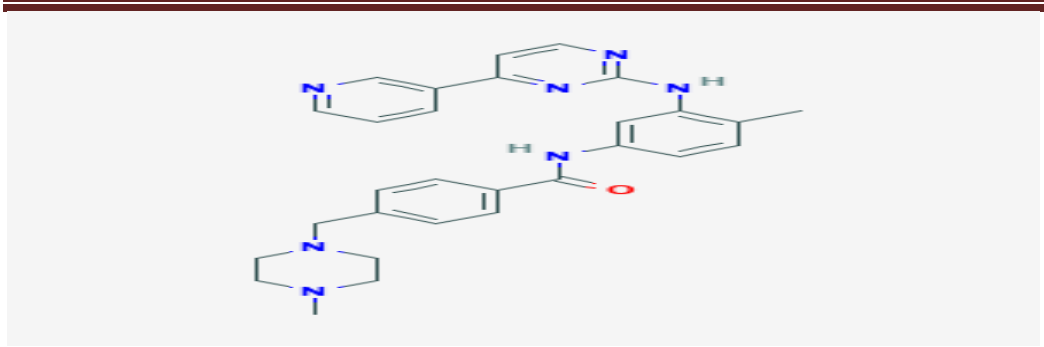
- **Ashish Masih, et al., (2017)[57]** Fast dissolving tablets emerge as one of the popular and widely accepted dosage forms, especially for pediatric patients because of incomplete development of the muscular and nervous system and a case of geriatric patients suffering from Parkinson's disorder or hand tremors. Fast dissolving tablets are designed to dissolve in saliva remarkably faster, within a few seconds and those are real fast-dissolving tablets. FDTs formulations contain super disintegrants to enhance the disintegration of tablets.

3.1 DRUG PROFILE

IMATINIB:

Description:

stromal tumors.



Chemical Name : N-(4-Methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide

Molecular formula : $C_{29}H_{31}N_7O$

Molecular weight : 493.6 g/mol

Description : It is a white to slightly yellow crystalline powder that is water soluble.

Dose: 100 mg to 400mg/day

Half-life: 18 to 40 hours.

Physico-chemical properties:

Melting point : 226°C

Solubility : soluble in water, Slightly soluble in dichloro methane and methanol Soluble in DMSO and Acetone

Category : Anti-Cancer drug.

Storage : Storage at room temperature, protected from moisture and heat.

Mechanism of action:

Imatinib mesylate is a protein-tyrosine kinase inhibitor that inhibits the Bcr-Abl tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukemia (CML). It inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as fresh leukemic cells from Philadelphia chromosome positive chronic myeloid leukemia.

Imatinib also inhibits the receptor tyrosine kinases for platelet derived growth factor (PDGF) and stem cell factor (SCF) - called c-kit. Imatinib was identified in the late 1990s by Dr Brian J. Druker. Its development is an excellent example of rational drug design. Soon after identification of the bcr-abl target, the search for an inhibitor began. Chemists used a high-throughput screen of chemical libraries to identify the molecule 2-phenylaminopyrimidine. This lead compound was then tested and modified by the introduction of methyl and benzamine groups to give it enhanced binding properties, resulting in imatinib.

Pharmacokinetics:

Absorption:

The pharmacokinetics in CML and GIST patients are similar. Imatinib is well absorbed with mean absolute bioavailability is 98% and maximum plasma levels achieved within 2-4 hours of dosing

Distribution:

Imatinib is actively cleared from the blood into the liver, where it is metabolized extensively. Possible candidates for this active transport are OATP1B3, OCTN2, and OCT1, predominantly located at the basolateral membrane of hepatocytes

Metabolism:

Metabolism of imatinib **occurs in the liver** and is mediated by several isozymes of the cytochrome P450 system, including CYP3A4 and, to a lesser extent, CYP1A2, CYP2D6, CYP2C9, and CYP2C19. The main metabolite, N-demethylated piperazine derivative, is also active.

Excretion:

Renal excretion accounts for less than 10% of imatinib excretion, increased plasma exposure and decreased clearance in imatinib-treated cancer patients with impaired renal function. his finding may be due to increased levels of circulating uremic toxins. One such toxin inhibits OATP1B3 function in a rodent model, supporting the possibility that uremic toxins can directly reduce hepatic uptake of imatinib by OATP1B3. Further elucidation of this mechanism is needed. Extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported in association

with drugs in this class have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation.

Imatinib elimination is predominately in the feces, mostly as metabolites. 81% of the dose is eliminated within 7 days, in feces (68% of the dose) and urine (13% of the dose). Unchanged imatinib accounted for 25% of the dose (5% urine, 20% faces), the remainder being metabolites.

Duration of action: Upto 24hrs

Protein binding: 95.5%

Volume of distribution: 435L

Pka value: 12.45

Log p: 4.38

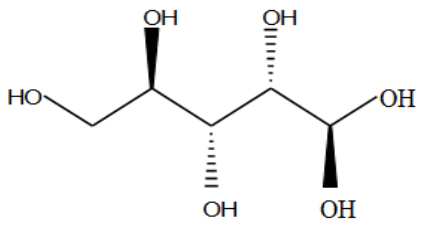
Elimination: <0.5% unchanged drug in urine

37% -52% in urine as metabolites

3.2 EXCIPIENTS

MANNITOL [59]:

1. Description : It is a hexahydric alcohol related to mannose and isomeric with sorbitol. It occurs as a white, odorless, crystalline powder or free flowing granules. It has a sweet taste as glucose and half as sweet as sucrose and imparts cooling sensation in the mouth.



2. Empirical Formula: $C_6 H_{14} O_6$

3. Molecular Weight: 182.17

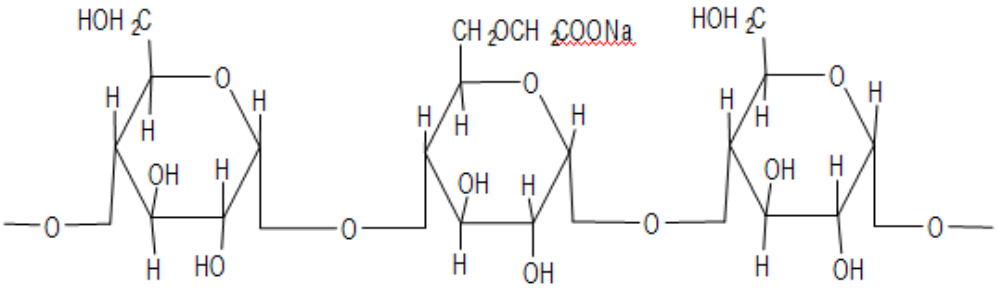
4. Solubility: It is soluble in alkalis, methanol, and water and practically insoluble in ether.

5. Melting point: 166-168 ^{0}C

6. Usage: It is used as a diluent (10-90% w/w) in tablets formulations,
Direct compressible agent,
Used as an excipient in manufacture of chewable tablets,
Therapeutically used as an osmotic diuretic.

SODIUM STARCH GLYCOLATE [60]

1. Synonyms : Sodium carboxy methyl starch, explotab, primojel.



2. Description: It is white to off - white, odorless, tasteless, free flowing powder. It consists of oval or spherical granules.

3. Functional category: Tablet and capsule disintegrate.

4. Solubility: At 2 % w/ v it disperses in cold water and settles in the form of highly saturated layer. Insoluble in organic solvents.

Sparingly soluble in ethanol.

5. pH: 5.5 to 7.5

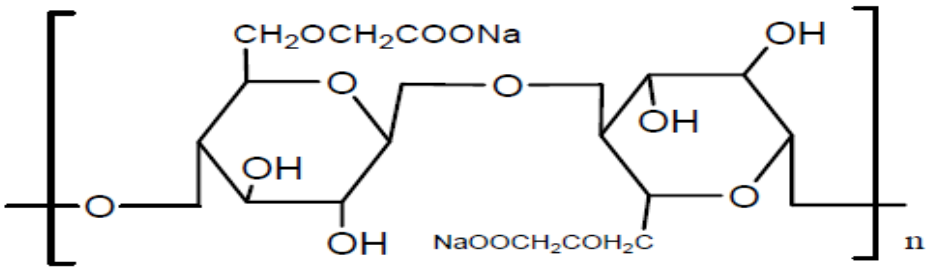
6. Storage conditions : It is stable and it should be stored in well closed container to protect it from wide variations in humidity and temperature that may cause caking.

7. Safety : It is used in oral pharmaceutical formulations, and is generally regarded as non toxic and non irritant type of material. However, oral ingestion of large quantities may be harmful.

8. Applications : It is widely used in oral pharmaceuticals as the disintegrant in capsule and tablet formulations in the concentration of 2 to 8%. Disintegration occurs of by rapid uptake of the water followed by rapid enormous swelling.

CROSSCARMELLOSE SODIUM[61]

1. Synonyms : AC-Di-sol, cross linked carboxyl methylcellulose sodium, explocel.



CROS CARMELLOSE SODIUM

2. Description : It is odourless, white or greyish white powder.

3. Functional category : Tablet and capsule disintegrant.

4. Solubility : Insoluble in water, although croscarmellose sodium rapidly swells to 4-8 times its original volume on contact with water.

5. Bulk density : 0.529 g/cm ^{3}

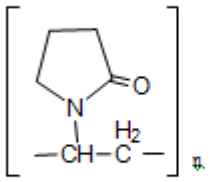
6. Tapped density : 0.819 g/cm ^{3}

7. Incompatibilities : Efficacy of croscarmellose sodium may be slightly reduced in tablet formulations contain hygroscopic excipients such as sorbitol.

8. Applications : It is widely used in oral pharmaceutical formulations as a disintengrant for capsules tablets & granules. In capsules it is used as a disintegrant in the concentration of 10 to 25 % and tablets in the concentration of 0.5 to 5.0.

CROSPOVIDONE [62]

1. Synonyms : cross linked povidone, kollidon CL, polyvinyl pyrrolidone



CROSPOVIDONE

2. Description : It is a white to creamy white, finely divided, free flowing practically tasteless, odourless or nearly odourless hygroscopic powder

3. Functional category : Tablet disintegrants.

4. pH : 5.0 to 8.0 .

5. Density : 1.22 gm/ cm^3

6. Solubility : Practically insoluble in water and organic solvents

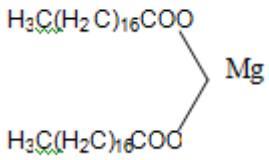
7. Storage conditions : Since crospovidone is a hygroscopic it should be stored in air tight containers in dry place.

8. Incompatibilities : Crospovidine is compatible with the most inorganic and organic pharmaceutical ingredients. When exposed to the high water level it may form molecular adducts with some materials.

9. Applications : It is a water insoluble tablet disintegrants and dissolution agent used at 2-5% concentration in tablets it rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. It can also be used as a solubility enhancer.

MAGNESIUM STEARATE [63]

1. Synonyms : Metallic stearate, Magnesium Salt.
2. Structural Formula : $[CH_3(CH_2)_{16}COO]_2Mg$



3. Description : Fine white, precipitated or milled, impalatable powder of low bulk density. Odour and taste are slight but characteristic. The powder is unctuous and readily adheres to skin.
4. Functional Category : Tablet or Capsule lubricant.
5. Solubility : Practically insoluble in water, alcohol, ethers.

Slightly soluble in warm benzene and the warm ethanol (95 %).

6. Melting point : 117^0 to $150\ ^0C$
7. Storage conditions : Stable and should be stored in a cool, dry place in a well closed containers.
8. Applications : It is widely used in cosmetics, foods and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentration between 0.25 - 0.5 % w/w.

TALC[64.]

1. Synonyms : Talcum Powder, French chalk, Soap Stone, Mineral.

2. Description : Talc occurs as a white to gray-white, fine crystalline powder. It has a smooth feel and is odorless.

3. Functional category : Talc used in paper industry.

4. pH : 7.5−9.5

5. Solubility : Talc is not soluble in water, but is slightly soluble in dilute mineral acids.

6. Storage conditions : Store Between 15°C-25°C. Protect from Sunlight and Heat.

7. Applications : Talc is used in many industries such as paper making, plastic, rubber, food, electric cable, pharmaceutical, cosmetics.

4. AIM &OBJECTIVES

AIM:

The main aim of present work is to formulate fast disintegrating tablets by direct compression technique containing Imatinib, and the application of direct compression results in increasing the absorption by decreasing t max, solubility by using different super disintegrants like crospovidone, croscarmellose sodium, sodium starch glycolate, which give more rapid onset of action compared to oral conventional dosage form to improve patient compliance.

OBJECTIVES:

Rationale behind the Selection of Drug:

- Imatinib belongs to class I drug in BCS classification i.e. High solubility and high permeability.
- Imatinib is anti-cancer drug, which is used in the treatment of treat certain types of leukemia.
- One of the major problems with this drug is its High solubility in biological fluids, which results into poor absorption after oral administration.
- The solubility of Imatinib in aqueous medium is 0.121 mg/ml in water.
- Absolute bioavailability of the Imatinib was 98% and biological half-life is only 18-48 hours.
- By increasing the disintegration of Imatinib, its absorption and dissolution is increased. So it offers rapid onset of action and we can decrease t_{max}

From the above points, it is clear that, Imatinib is suitable drug to formulate into fast disintegrating tablet and may provide a better therapeutic profile than that of conventional dosage form.

5. PLAN OF WORK

Scheme of proposed work is as follows:

- To study the pre-formulation parameters of pure drug almotriptan.
- Evaluation of pre-formulation parameters for powder blend.
- Formulation of Imatinib fast dissolving tablet by direct compression.
- Evaluation of post compression parameters.
- Evaluation of In-vitro dissolution studies.
- Applying of kinetic plots.

6. METHODOLOGY

Materials used:

6.1 Table 3: List of chemicals used:

S. No.	INGREDIENTS AND REAGENTS	MANUFACTURER / SUPPLIERS
1.	Imatinib	Arizest Pvt Ltd, Bangalore.
2.	Crospovidone	Ozone international, Mumbai
3.	Croscarmellose sodium	Himedia laboratories, Mumbai.
4.	PVP K 30	Himedia laboratories, Mumbai.
5.	Sodium starch glycolate	Himedia laboratories, Mumbai.
6.	Magnesium Stearate	Himedia laboratories, Mumbai.
7	Talc	Sd fine –chem limited, Mumbai.
8	Mannitol	Kemphasal pharmaceuticals.

6.2 Table 4: List of instruments used

S. No.	NAME OF INSTRUMENT	MANUFACTURING COMPANY
1.	Digital Balance	Shimadzu corporation, Japan.
2.	Tablet hardness tester	Monsanto tablet hardness tester.
3.	Friability tester	Veego tablet friability test apparatus
4.	Dissolution apparatus USP XXIII	Electrolab tablet dissolution apparatus-08L.
5.	Double beam UV Spectrophoto-meter	Agilent Technologies, Carry 60 UV/VIS spectrometer.
6.	Rotary tablet punching machine	Yogesh Pharma Machinery Pvt.Ltd, Ahmedabad
7.	Ultra sonicator	Toshiba (India), New delhi.
8.	FT-IR Spectrophotometer	Agilent Technologies, carry 630 FT-IR

METHODOLOGY

6.3 Preformulation studies

Preformulation testing is an investigation of physical and chemical properties of drug substances alone and when combined with pharmaceutical excipients. It is

the first step in the rational development of dosage form.

Compatibility studies (Fourier Transform Infrared Spectroscopic studies)

One of the requirement for the selection of suitable excipients or carrier for pharmaceutical formulation is its compatibility. Therefore in the present work a study was carried out by using FT-IR spectrophotometer to find out if there is any possible chemical interaction of Imatinib with Crospovidone, Sodium starch glycolate, Croscarmellose sodium.

Procedure:

To study the compatibility of various formulation excipients with Imatinib, solid admixtures were prepared by mixing the drug with each formulation excipient separately in the ration of 1:1 and stored in air tight containers at 30 $\pm 2^0$c/65±5%RH. The solid admixtures were characterized using Fourier transform infrared spectroscopy (FT-IR).

6.4 Construction of standard curve for Imatinib

Imatinib can be estimated spectrometrically at 285 nm as it obeys Beer's – Lambert's law limit is the range of 10 – 50 μg/ml.

Preparation of reagents (procedure)

Preparation of standard drug solution

Stock solution

100mg of Imatinib was dissolved in 100 ml of 0.1N HCL, to get a solution of 1000μg/ml concentration.

Standard solution

1 ml of stock solution was made to 10ml with 0.1N HCL thus giving a concentration of 100 μg/ml. Aliquot of standard drug solution ranging from 1 ml, 2 ml, 3 ml, 4 ml, 5 ml were transferred in to 10ml volumetric flask and were diluted up to the mark with 0.1N Hcl. Thus the final concentration ranges from 10-50 μg/ml. Absorbance of each solution was measured at 285 nm against 0.1N Hcl as a blank. A plot of concentrations of drug versus absorbance was plotted.

Preparation of 0.1N Hcl[65]:

8.5ml of Hcl was taken in 1000 ml volumetric flask containing about 700 ml distilled water and volume was made up to the mark with distilled water.

Method of preparation of tablets by direct compression:

The formulation of the various tablets tried to select the best tablet with enhanced solubility and bioavailability.

The steps in direct compression are:

Step-1: All the materials were sifted according to the following indications:

Part-1: Sift the active ingredient mixture through the following mesh:

Material	Mesh size
Imatinib	Mesh #40
Optimized Imatinib and Mannitol	Mesh #40

Part-2: Sift the direct compressible vehicles through the following mesh

Material	Mesh size
MCC	Mesh #30

Part-3: Sift the disintegrates through the following mesh

Material	Mesh size
Croscarmellose	Mesh #30
Crospovidone	Mesh #30
Sodium starch glycolate	Mesh #40

Part-4: Sift the lubricants and glidants through the following mesh

Material	Mesh size
Mg. stearate	Mesh #60
Talc	Mesh #60

Step-II Preparation of Blend:

Loaded sifted Part-2 material into a Polyethylene bag and mixed for 5 min. and to this added part-1 sifted material and mixed for 10 min. loaded the part-3 and part-4 materials into another polyethylene bag and mixed for 5 min. and this mixed material was transferred into a former polyethylene bag and mixed for 10 min.

Step-III Compression:

Imatinib blend was compressed using 12 stationary rotary punching machines until desired hardness was obtained.

TABLET FORMULATIONS

Table 5 : Formulae for the preparation of tablets: (per tablet)

SL.O	Ingredients (in mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Imatinib	400	400	400	400	400	400	400	400	400
2.	CP	5	7.5	10	---	---	---	---	---	---
3.	CCS	---	---		5	7.5	10	---	---	---
4.	SSG	---	---	---	---	---	---	5	7.5	10
5.	Magnesium Stearate	1	1	1	1	1	1	1	1	1
6.	Talc	70	70	70	70	70	70	70	70	70
7.	Mannitol	24	21.5	19	24	21.5	19	24	21.5	19

6.5 Characterization of Granules[66]

Prior to compression, granules were evaluated for their characteristic parameters such as:

(i) Angle of Repose

(ii) Bulk density

(iii) Hausner's Factor

(iv) Compressibility index

(v) Drug content uniformity

(i) Angle of Repose

The angle of repose of granules, was determined by the fixed funnel and freestanding cone method, according to the method reported by Raghuram et al., * where by accurately weighed granules (5gm were carefully poured through the funnel with its tip at 2 cm height (h) until the apex of the conical heap so formed just reached the tip of the funnel. The mean diameter (r1, of the base for the powder cone was measured and angle of repose (0) was calculated using the following equation.

$$\tan\theta = h/r$$

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

Where, θ = angle of repose

h = height

r = radius

Table: 6: Limitations of angle of repose

Angle of repose(Ɵ) (degrees)	Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

(ii) Bulk Density

Both loose bulk Density and tapped bulk density were determined, according to the method reported by raghuram et al, where by a quantity (20g) of granules from each formula, previously lightly shaken to break any agglomerates cylinder. After the initial volume was observed, the cylinder was allowed to full under its own weight onto a have surface from the height of 2.5cm at 2-Second intervals. The tapping was continued until no further change in the volume was noted loose bulk density (LBD) and tapped bulk density (TBD) were

calculated using the following formulas

LBD = Weight of the powder/ volume of the packing

TBD = weight of the powder / tapped volume of the packing

iii) Hauser's Ratio

It indicates the flow properties of the powder and it measured by the ratio of TBD to the LBD

$$\text{Hauser's Ratio} = \frac{\text{TBD}}{\text{LBD}}$$

Table: 7: Limitations of hauser'ratio

S.NO	Hauser's Ratio	Property
1	0 - 1.2	Free flowing
2	1.2 – 1.6	Cohesive powder

iv) Compressibility index (Carr's index)

To analyze flow ability, the Carr's index was calculated on the basis of the LBD and TBD. The compressibility index of the granules was determined by Carr's index

Carr's index (%) = [BD – LBD) x 100)] / TBD

Table: 8: Limitations of carr's index

% Carr's Index	Properties
5 – 12	Free Flowing
12 – 16	Good
18 – 21	Fair
23 – 35	Poor
33 – 38	Very Poor

>40	Extremely poor

(v) Drug content uniformity

Standard preparation

An accurately weighed amount of pure Imatinib (5mg) is transferred into 50ml volumetric flask. It was dissolved and made up to volume with 0.1 N Hcl and absorbance was measured at 283 nm.

Sample preparation

A Tablet is powdered and transferred to 50 ml volumetric flask. Then the volume was made up with, 0.1NHcl and shaken or 25 min to ensure complete solubility of the drug. Then the solution was filtered. The sample solution absorbance was measured at 283 nm in UV-Visible spectrophotometer are shown in table-20.

Calculation

The amount of Imatinib present in tablets can be calculated using the formula:-

$A_t / A_s X Sw / 100 x 100$

A_t = Absorbance of sample preparation

A_s = Absorbance of standard preparation

S_w = Weight of Imatinib working standard (mg)

6.6 Characterization of Tablets[67]

The properties of the compressed matrix tablet, such as Hardness, Friability, weight variation & Drug content Uniformity, were studied.

i) Hardness Test

For each formulation, the hardness of 5 tablets was determined using a Monsanto hardness tester, mean and SD were calculated

ii) Friability Test

For each formulation, 6 tablets were weighed. The tablets were placed in a friabilator (Roche

friabilator) and subjected to 25 rpm in 4 minutes. The tablets were then dedusted and reweighed. The friability was calculated as the percentages of weight loss.

$$F = 100 (1-wo/wt)$$

Where,

Wo = weight of tablets before friability test

Wt = weight of tablets after friability test

iii) Weight variation Test

To study weight variation, to tablets of each formulation were weighed using an electronic balance and the test was performed according to the USP official limits of percentage deviation of tablet are presented in the table.

Weight variation Tolerance for uncoated Tablets

Table: 9: Limitations of weight variation

Average weight of Tablets (mg)	Maximum percentage Difference Allowed
130 or less	10

130 – 324	7.5
More than 324	5

% maximum positive deviation = (w_H-A/A) x 100

% minimum negative deviation = (A-WL/A) x 100

where

W_H = Highest weight in mg

WL = Lowest weight in mg

A = Average weight of tablet in mg.

iv) Drug content uniformity:

Standard preparation

An accurately weighed amount of pure Imatinib (5mg) is transferred into 50ml volumetric flask. It was dissolved and made up to volume with 0.1 N Hcl and absorbance was measured at 283 nm.

Sample preparation

A Tablet is powdered and transferred to 50 ml volumetric flask. Then the volume was made up with, 0.1NHcl and shaken or 25 min to ensure complete solubility of the drug. Then the solution was filtered. The sample solution absorbance was measured at 285 nm in UV-Visible spectrophotometer are shown in table-20.

Calculation

The amount of Imatinib present in tablet can be calculated using the formula:

$$A_t/As \times S_w/100 \times 100/S_t \times A_v$$

Where,

A_t = Absorbance of sample preparation

A_s = Absorbance of Standard preparation

S_w = weight at Imatinib working standard (mg)

S_t = weight of Imatinib tablet (mg)

Av = Average weight of tablet (mg)

6.7 In-Vitro Drug Release Studies (Dissolution studies)

Dissolution Parameters:

Medium: 0.1N HCL.

Apparatus: USP-Type 2 (Paddle)

RPM: 50

Temperature: $37^0 \pm 0.5^0$ C

Dissolution Medium: 900 ml

Procedure:

The release of Imatinib from the fast disintegrating tablet was studied up to 30 min in 900 ml of 0.1 N HCL as dissolution medium using a USP dissolution paddle assembly at 50 rpm and $37^o \pm 0.5^o$ C. An aliquot (1 ml) was withdrawn at specific time intervals, filtered and diluted to 10 ml with the dissolution medium, and drug content was determined by UV-visible spectrophotometer at 285 nm. An equal volume of fresh dissolution medium was replaced to maintain the dissolution volume

Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

6.8 Kinetic Analysis of In – Vitro Release Rates of Fast Disintegrating Tablets of Imatinib [68,69]

The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows: -

1. Zero – order kinetic model – Cumulative % drug released versus time.
2. First – order kinetic model – Log cumulative percent drug remaining versus time.
3. Higuchi's model – Cumulative percent drug released versus square root of time.
4. Korsmeyer equation / Peppa's model – Log cumulative percent drug released versus log time.

1. Zero order kinetics:

Zero order release would be predicted by the following equation:-

$$A_t = A0 - K_0t$$

Where,

A_t = Drug release at time 't'.

A_0 = Initial drug concentration

K_0 = Zero – order rate constant (hr^{-1}).

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys Zero – order release kinetics, with a slope equal to K^0.

2. First Order Kinetics:

First – order release would be predicted by the following equation:-

$$\text{Log } C = \log C_0 - K_t / 2.303$$

Where,

C = Amount of drug remained at time't'.

C_0 = Initial amount of drug.

K = First – order rate constant (hr^{-1}).

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line, indicating that the release follow first order kinetics. The constant 'K' can be obtained by multiplying 2.303 with the slope values.

3. Higuchi's model:

Drug release from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation.

$$Q = [D\varepsilon / \tau (2 A - \varepsilon Cs) Cst]^{1/2}$$

Where,

Q = Amount of drug released at time't'.

D = Diffusion coefficient of the drug in the matrix.

A = Total amount of drug in unit volume of matrix.

Cs = the solubility of the drug in the matrix.

ε = Porosity of the matrix.

τ = Tortuosity.

τ = Time (hrs) at which 'q' amount of drug is released.

Above equation may be simplified if one assumes that 'D', 'Cs', and 'A', are constant. Then equation becomes:

$$Q = Kt1^{/2}$$

When the data is plotted according to equation i.e. cumulative drug release versus square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K' (Higuchi's 1963).

4. Korsmeyer equation / Peppa's model:

To study the mechanism of drug release from the sustained – release matrix tablets of Imatinib, the release data were also fitted to the well – known exponential equation (Korsmeyer equation / peppa's law equation), which is often used to describe the drug release behavior from polymeric systems.

$$M_t / M_a = Kt^n$$

Where,

M_t / M_a = the fraction of drug released at time 't'.

K = Constant incorporating the structural and geometrical characteristics of the drug / polymer system.

N = Diffusion exponent related to the mechanism of the release.

Above equation can be simplified by applying log on both sides,

And we get:

$$\text{Log } M_t / M_a = \text{Log } K + n \text{ Log } t$$

When the data is plotted as log of drug released versus log time, yields a straight line with a slope equal to 'n' and the 'K' can be obtained from y – intercept. For Fickian release

'n' = 0.5 while for anomalous (non – Fickian) transport 'n' ranges between 0.5 and 1.0. The result of in – vitro drug release study of all the formulation as shown below.

Table: 10 Mechanism of Drug Release as per Korsmeyer Equation / Peppa's Model

S. No.	N Value	Drug release
1.	n <0.5	Fickian release
2.	0.5 >n < 1	Non – Fickian release
3.	n > 1	Case II transport

7. RESULTS

In order to achieve the development of anti-cancer dosage forms, **Imatinib** was used as a model drug for the therapy of cancer, which was formulated by direct compression method employing different concentrations of fast disintegrating agents for fast release of drug, talc as diluent's and magnesium stearate as lubricant.

In the present study Nine formulations (F1-F9) with variable concentrations of fast disintegrating agents (croscarmellose sodium, crospovidone, sodium starch glycolate) were prepared and evaluated for various physico-chemicals parameters, and In-vitro drug release studies. On the basis of In-vitro release studies the best formulation (F9) was selected
(table 28).

To know the mechanism of drug release from these formulations, the data were treated according to first-order release, Higuchi's, and Korsmeyer equation / Peppa's model et al's equations along with zero order (cumulative amount of drug released verses time).

7.1 Preformulation studies (Compatibility studies):

Compatibility studies were performed by using FT-IR spectrophotometer. The IR Spectrum of pure Imatinib drug was compared with the IR spectrum of physical mixture of Imatinib (SSG, CP, and CCS).

There is no appearance or disappearance of any characteristics peaks. This shows that there is no chemical interaction between the drug and the excipients.

The presence of peaks at the expected range confirms that the materials taken for the study are confirmed.

Table 11: Characteristic peaks of drug in FT-IR spectra

S.No	Wave in cm	Functional group
1	3200-3400	Secondary Amine(-NH-)
2	3300-3500	Hydroxyl Group (OH)
3	1680-1740	Carboxyl Group (C=O)
4	2900-3100	Aromatic Stretching(C-H)
5	1475-1575	Aromatic Bending(C-H)

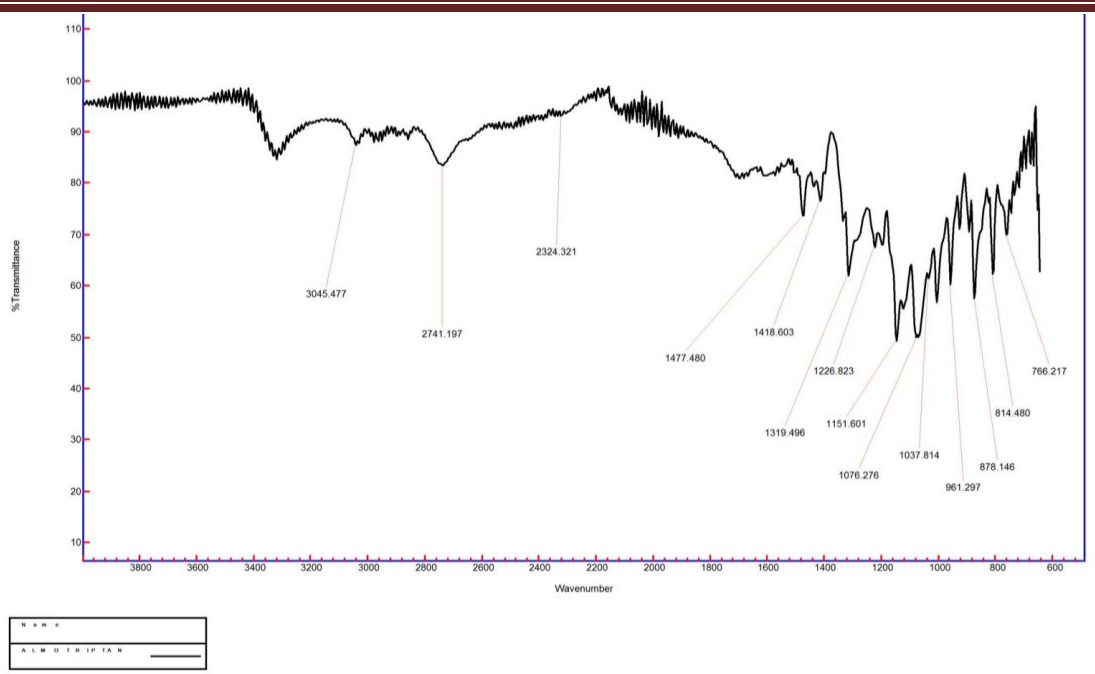


Figure 3: FTIR Spectra of Pure Imatinib

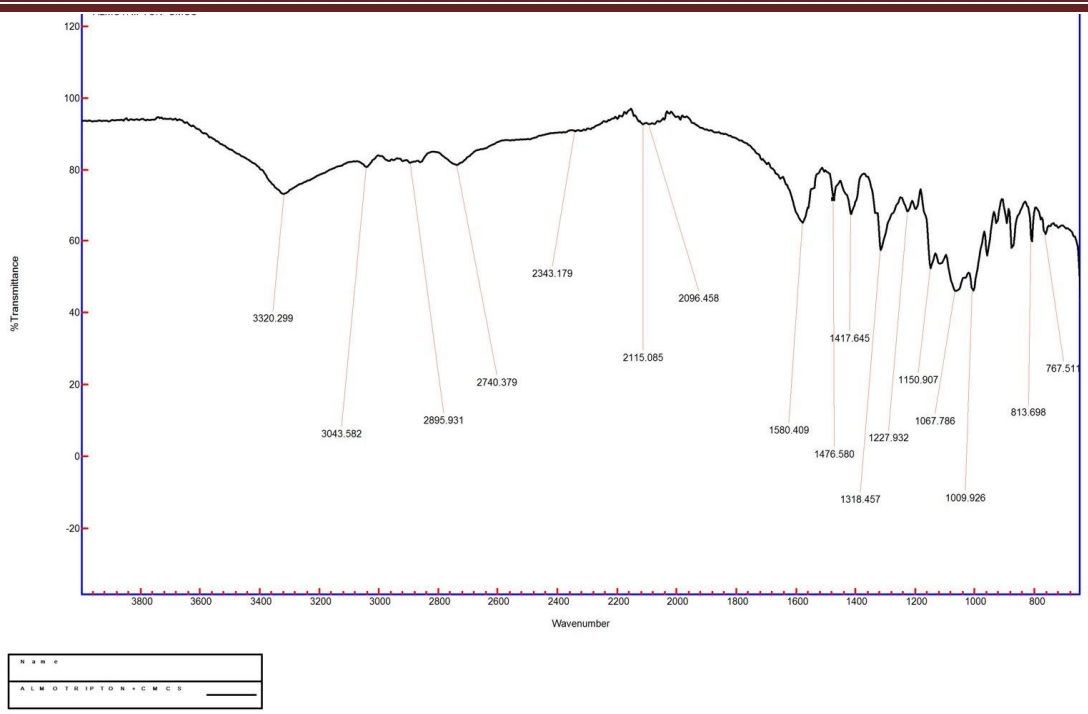


Figure 4 : FTIR Spectra Imatinib and Croscarmellose sodium

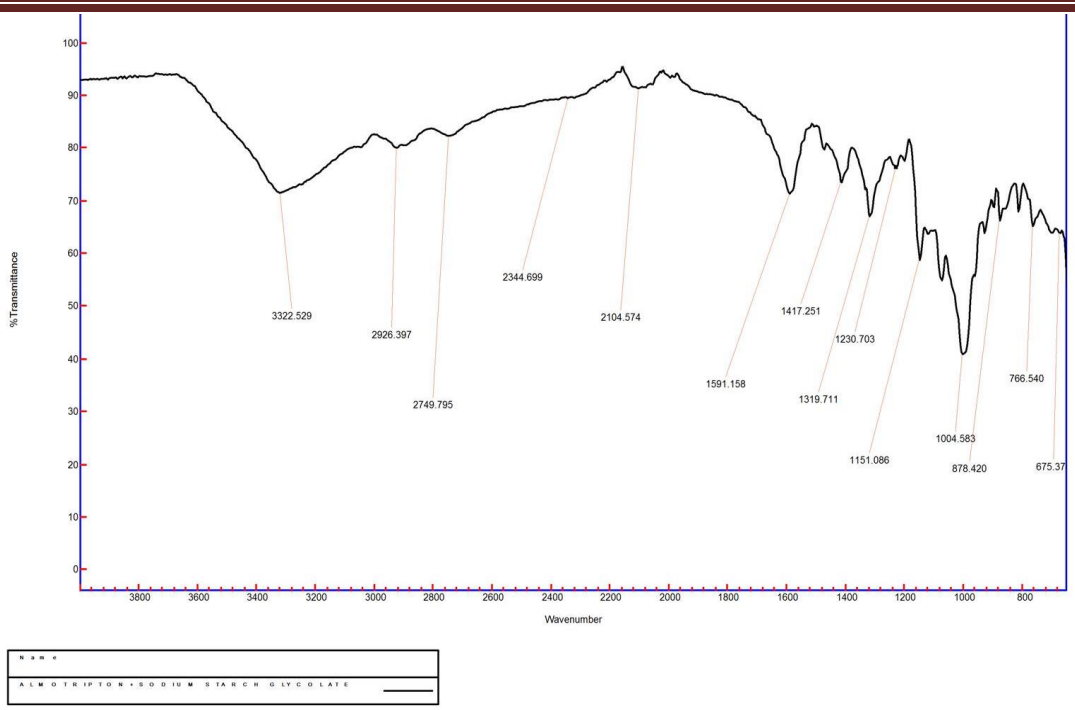


Figure 5: FTIR Spectra Imatinib and Sodium starch glycolate

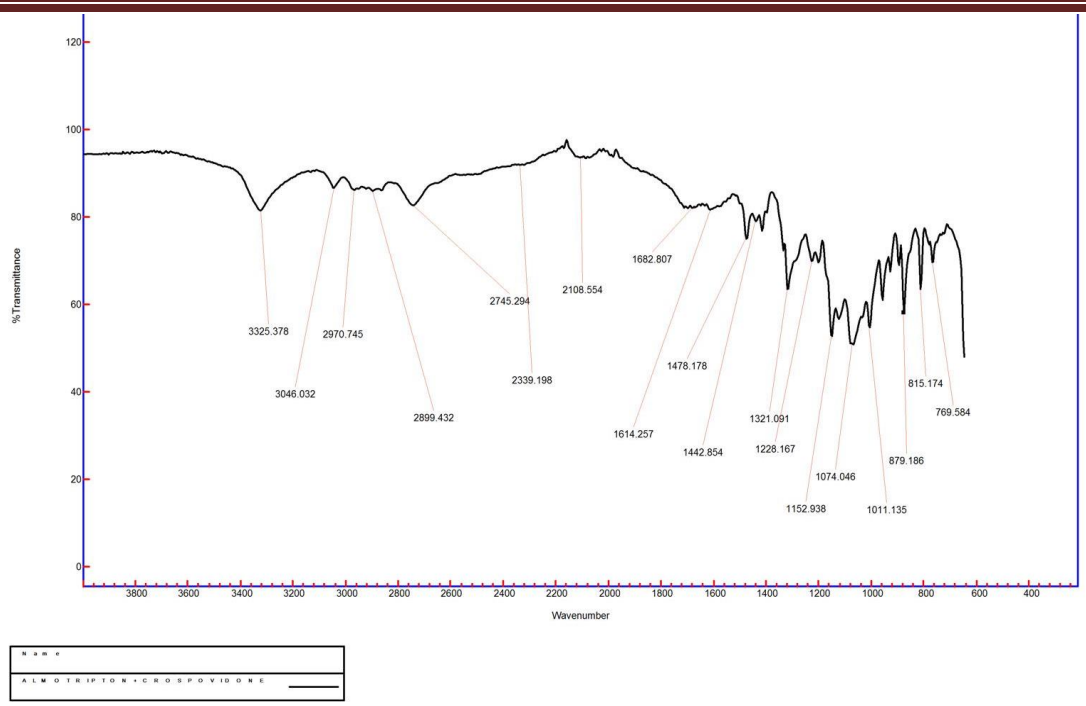


Figure 6: FTIR Spectra Imatinib and Crospovidone

Standard calibration curve of Imatinib:

Standard Curve of Imatinib was determined by plotting absorbance (nm) verses concentration (mcg/ml) at 285 nm and it is follows the Beer's law. The results were obtained, are as follows.

Table 12: Calibration curve of Imatinib in 0.1N Hcl

S.no	Concentration(mg/ml)	Absorbance(285 nm)

1	0	0
2	10	0.129
3	20	0.253
4	30	0.397
5	40	0.510
6	50	0.649
Slope		0.0129
Regression		0.9994

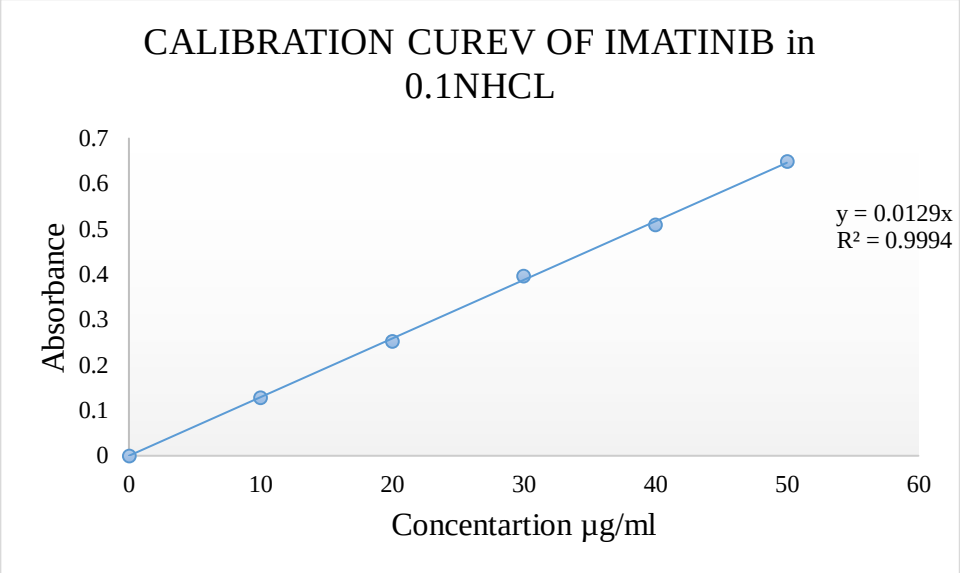


Figure: 7 Standard calibration curve of Imatinib in 0.1 N Hcl

7.2 Evaluation of blend characteristics of fast disintegrating tablets of Imatinib

The blended granules of different formulation were evaluated for angle of repose, loose bulk density (LBD), tapped bulk density (TBD), compressibility index, Hauser's ratio and drug content uniformity. The results of these evaluations are as follows:-

1. Angle of repose:

Angle of repose ranged from 28° 00"± 1.1868 to 29°65"±1.837. The results were found to be below 30^0 and hence the blend was found to have good flow property. (Table-13).

2. Bulk density and tapped density:

Bulk and tapped densities are used for the measurement of Compressibility index. The LBD and TBD ranged from 0.3969± 0.004 to 0.4150±0.004 and 0.4652±0.007 to 0.4832± 0.006 respectively. (Table -14).

3. Compressibility index (Carr's index):

The compressibility index (%) ranged from 13.763± 0.861to 14.922± 1.145(Table -14). The blend was found to have free flowing property as the result were found to be below 18%.

4. Hauser's Ratio:

The Hauser ratio ranged from 1.160± 0.011to 1.176± 0.016 (Table - 14). The result indicates the free flowing properties of the granules.

Table: 13 Angle of repose for blend of Imatinib formulations

S.NO	Formulation Code	Height (h) (Cms)	Radius (r) (Cms)	h/radius	$\theta^* = \tan^{-1}$ h/r
1	F1	1.38± 0.0836	2.59± 0.0480	0.5324± 0.0421	28.005± 1.1868
2	F2	1.44± 0.0547	2.59± 0.0518	0.5565± 0.0319	29.095± 1.3901
3	F3	1.52± 0.0836	2.74± 0.0285	0.5550± 0.0359	29.031± 1.5818
4	F4	1.40± 0.0707	2.63± 0.0480	0.5328± 0.0359	28.030± 1.6043
5	F5	1.52± 0.0836	2.67± 0.0570	0.5699± 0.0422	29.654± 1.8371
6	F6	1.52± 0.0836	2.70± 0.0395	0.5634± 0.0387	29.374± 1.6930
7	F7	1.42± 0.0636	2.60± 0.0260	0.5461±0.0415	28.639±1.5480
8	F8	1.46± 0.0570	2.64± 0.0812	0.5530±0.0312	29.942±1.6250

9	F9	1.50±0.0838	2.67±0.0127	0.5617±0.0349	29.322±1.8795

* All values are expressed as mean ± S.D, n= 3

Table: 14 Evaluation of properties of the blended powder for formulations of Imatinib

S.No	Formulation Code	Volume before tapping (V_o) ml	Volume after tapping (V) ml	Loose Bulk Density	Tapped Bulk Density	Carr's index	Hauser's Ratio
1.	**F1**	48.2± 0.447	41.4± 0.547	0.4150± 0.004	0.4832± 0.006	14.107± 0.908	1.164± 0.012
2.	**F2**	48.8± 0.447	41.6± 0.547	0.4099± 0.003	0.4808± 0.006	14.753± 0.889	1.173± 0.012
3.	**F3**	49.4± 0.547	42.6± 0.547	0.4049± 0.004	0.4695± 0.006	13.763± 0.861	1.160± 0.011
4.	**F4**	49.6± 0.547	42.2± 0.836	0.4033± 0.004	0.4740± 0.009	14..922± 1.145	1.176± 0.016
5.	**F5**	50.0± 0.707	42.6± 0.547	0.4001± 0.005	0.4695± 0.006	14.794± 0.971	1.174± 0.013
6.	**F6**	50.4± 0.547	43.0± 0.707	0.3969± 0.004	0.4652± 0.007	14..682± 1.071	1.172± 0.015
7	**F7**	48.6± 0.520	41.8± 0.472	0.4210± 0.002	0.4635± 0.004	14.742± 0.704	1.172± 0.012
8	**F8**	49.2±	42.6±	0.4110±	0.4601±	14.671±	1.168±

		0.602	0.836	0.003	0.003	0.871	0.016
9	**F9**	50.1± 0.447	44.0± 0.547	0.4001± 0.004	0.4580± 0.004	14.528± 1.124	1.170± 0.014

* All values are expressed as mean ± S.D, n= 3

7.3 Physical evaluation of oral fast disintegrating tablets of Imatinib

Imatinib fast disintegrating tablets were evaluated for various physical parameters namely– Hardness, Weight variation, Friability, Drug Content uniformity test etc.

1. Hardness test:

The hardness of all batches ranged from 4.5-6.5 Kg/cm^2 (Table 15).

2. Friability test:

The percentage friability of all batches ranged from 0.047 % to 0.094 % (Table 16).

3. Weight variation test:

The percentage weight variations for all formulations are present in table- 17. All the formulations (F1-F9) passed weight variation test as per the Pharmacopoeias limits of 5%. (Table 17).

4. Drug content uniformity:

Drug content was found to be uniform among the all formulations and ranged from 99.234±0.463 to 99.530±0.410 (Table- 18).

Table:15 Physical evaluation of fast disintegrating tablets of Imatinib

Hardness (kg/cm^2)

S. No.	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	4.5	6.5	5.0	5.5	4.5	6.0	5.5	6.0	4.5
2.	5.0	6.5	6.0	6.0	5.0	6.5	5.0	5.5	5.5
3.	6.5	5.0	5.5	5.5	5.0	5.5	6.0	6.0	4.5
4.	6.5	4.5	5.0	6.0	5.5	5.0	6.5	5.5	5.5
5.	6.5	5.0	5.5	4.5	6.0	5.0	6.5	5.5	5.5
Avg.	**5.8**	**5.5**	**5.4**	**5.5**	**5.2**	**5.6**	**5.8**	**5.7**	**5.1**

Table:16 Friability test for fast disintegrating Imatinib tablets

Formulation Code	Weight of 6 tablets before test (gms)	Weight of 6 tablets after test (gms)	Friability $F = 100(1-w_0/ w_t)$

F1	3.017	3.011	0.120 %
F2	3.011	3.009	0.066 %
F3	2.999	2.995222	0.133 %
F4	3.015	3.011	0.132 %
F5	3.012	3.007	0.166 %
F6	3.014	3.007	0.232 %
F7	3.015	2.950	0.110 %
F8	3.090	3.150	0.125 %
F9	3.010	3.015	0.130 %

Table:17 Weight variation test for fast disintegrating tablets of Imatinib

S. No.	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	510	505	510	510	490	510	505	500	510
2.	510	510	510	490	500	500	520	490	480
3.	510	510	510	510	500	510	510	505	510
4.	490	480	490	510	490	490	480	490	490
5.	510	410	520	510	510	510	500	505	500

6.	480	410	520	500	480	520	490	480	480
7.	510	500	490	500	500	510	500	500	510
8.	520	490	520	510	510	520	500	510	500
9.	510	510	500	500	500	500	505	480	490
10.	510	510	520	510	500	510	510	500	510
11.	510	490	510	510	500	500	510	480	490
12.	500	510	510	520	520	510	510	500	500
13.	510	500	510	510	510	520	510	500	510
14.	490	500	490	510	500	510	510	500	510
15.	510	510	510	510	510	510	520	500	500
16.	500	500	500	500	510	500	505	500	510
17.	510	510	510	510	480	510	520	500	510
18.	500	510	500	510	520	500	505	490	490
19.	520	490	520	500	510	510	510	490	500
20.	510	510	510	510	500	510	520	505	505
Average weight	505.5	502.5	508.0	507.0	502.0	508.0	506.0	508.2	5108.2
% Maximum Positive deviation	4.90	2.56	4.02	4.3	6.16	4.02	4.60	4.54	3.55
% Minimum Negative deviation	5.24	7.69	9.3	4.7	7.13	2.68	2.26	2.34	1.33

Table: 18 Content uniformity for Imatinib fast disintegrating tablets

S. No.	**Formulation Code**	**Standard absorbance**	**Sample absorbance**	**Working standard weight (mg)**	**% Drug Content * ± S.D.**
1.	F1	0.3657	0.3532	100	96.58
2.	F2	0.3657	0.3567		97.50
3.	F3	0.3657	0.3593		98.24
4.	F4	0.3657	0.3579		97.86
5.	F5	0.3657	0.3627		99.17
6.	F6	0.3657	0.3553		97.15
7.	F7	0.3657	0.3612		98.70
8.	F8	0.3657	0.3632		99.30
9.	F9	0.3657	0.3602		98.40

7.4 In -vitro drug release for fast disintegrating tablets of Imatinib

The fast disintegrating tablets were prepared and evaluated on trial basis. Total nine

formulations (F1-F9) prepared by using croscarmellose sodium, crospovidone, sodium starch glycolate.

The release of Imatinib from the fast disintegrating tablet was studied in 900 ml of 0.1 N Hcl as dissolution medium using a USP dissolution paddle assembly at 50 rpm and 37^{o} ± 0.5^{o} C. Drug content was determined by UV-visible spectrophotometer at 285 nm. Dissolution studies were performed for30 min. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

Table: 19 In-vitro Release Profile for Imatinib fast disintegrating tablet - Formulation (F1)

Time (min)	Absorbance (nm)	Concentration (mg/ml)	Amount of Drug Release(mg/900ml)	Cumulative % Drug Release
0	0	0	0	0
5	0.345	26.74	240.6	60.17
10	0.401	34.88	279.9	70.4
15	0.457	35.42	327.9	82
30	0.498	38.68	347.7	87

In vitro Dissolution Profile and Kinetic Plots of Formulation (F1)

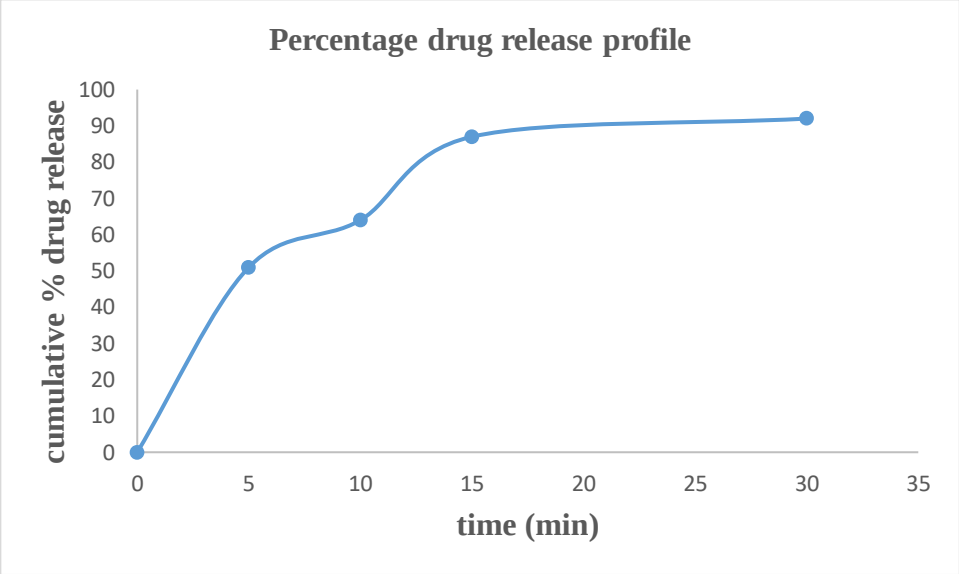


Figure: 8 Percentage drug release profile for F1

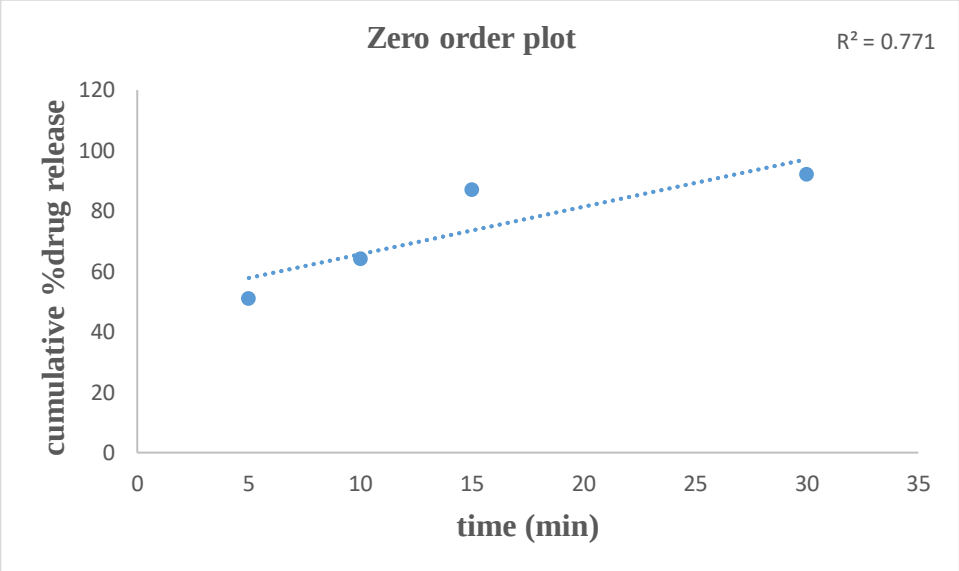


Figure: 9 Zero order plot for F1

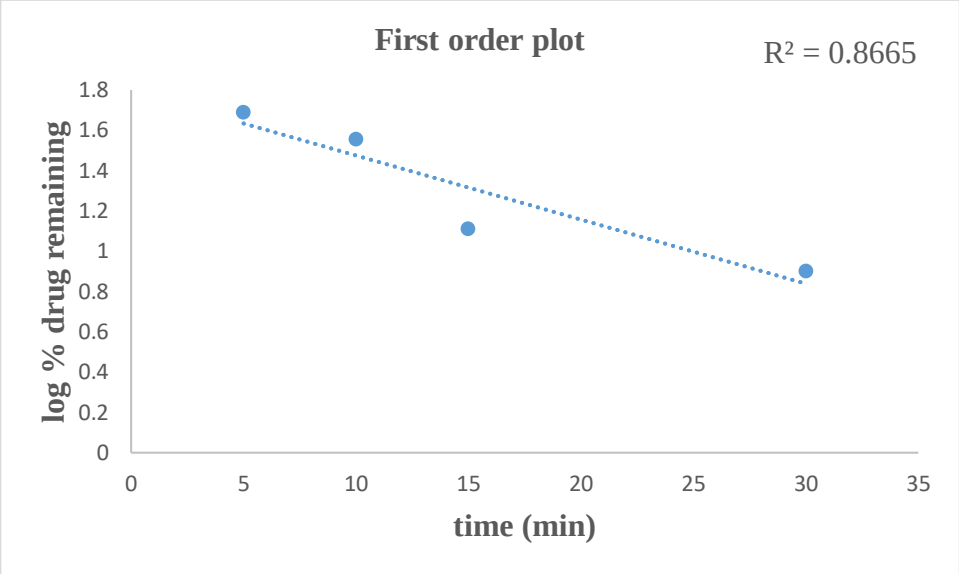


Figure: 10 First order plot for F1

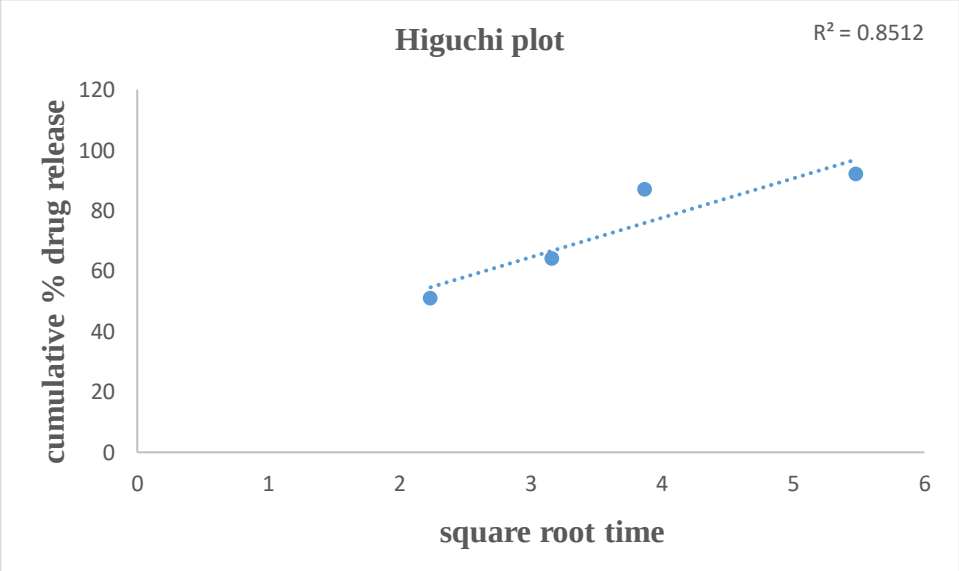


Figure: 11 Higuchi plot for F1

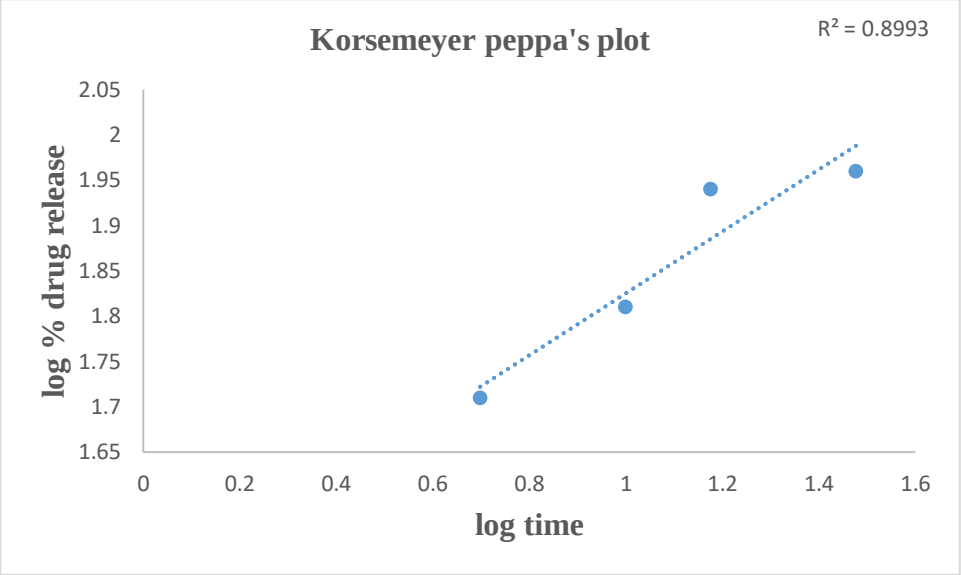


Figure: 12 Korsemeyer plot for F2

Table: 20 In-vitro Release Profile for Imatinib fast disintegrating tablet - Formulation (F2)

Time (min)	Absorbance (nm)	Concentration (mg/ml)	Amount of Drug Release(mg/900ml)	Cumulative % Drug Release
0	0	0	0	0
5	0.346	26.8	243	61
10	0.410	31.78	286	72.2
15	0.511	39.5	356.5	89
30	0.552	42.79	385.1	96

In vitro Dissolution Profile and Kinetic Plots of Formulation (F2)

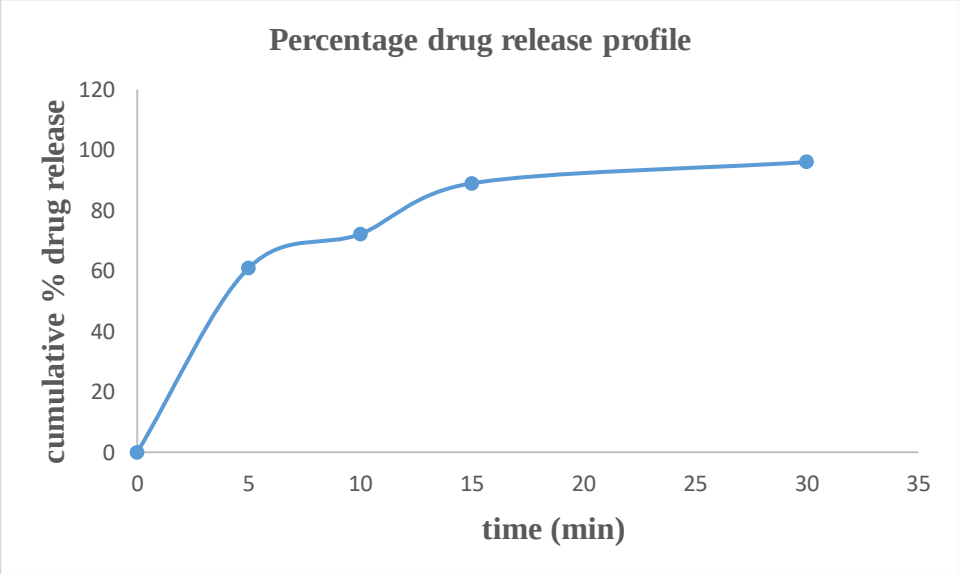


Figure: 13 Percentage drug release profile for F2

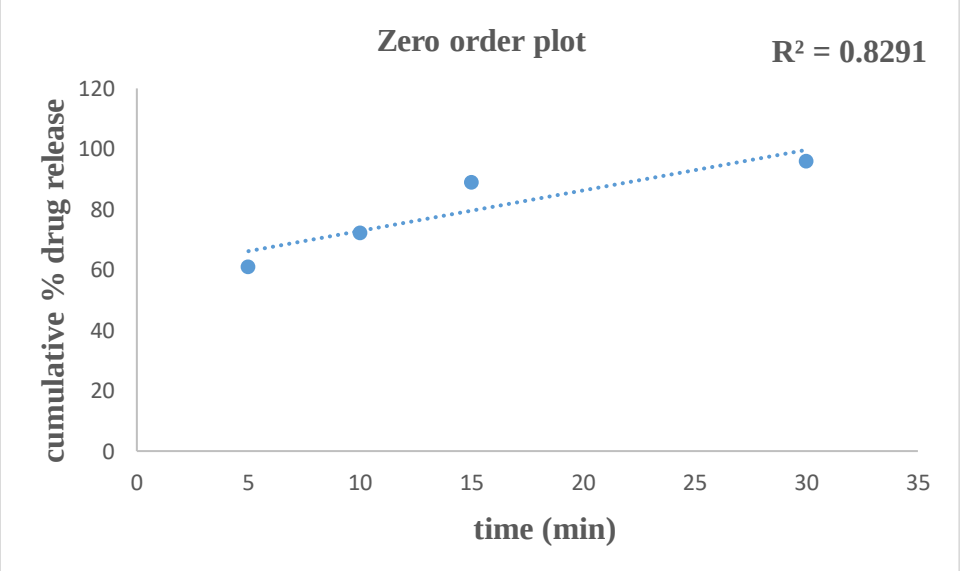


Figure: 14 Zero order plot for F2

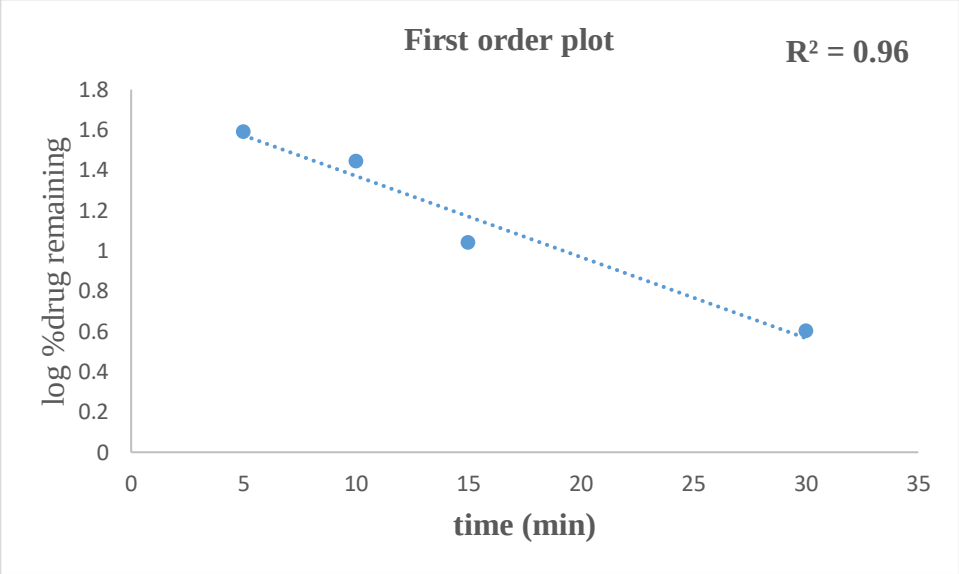


Figure: 15 First order plot for F2

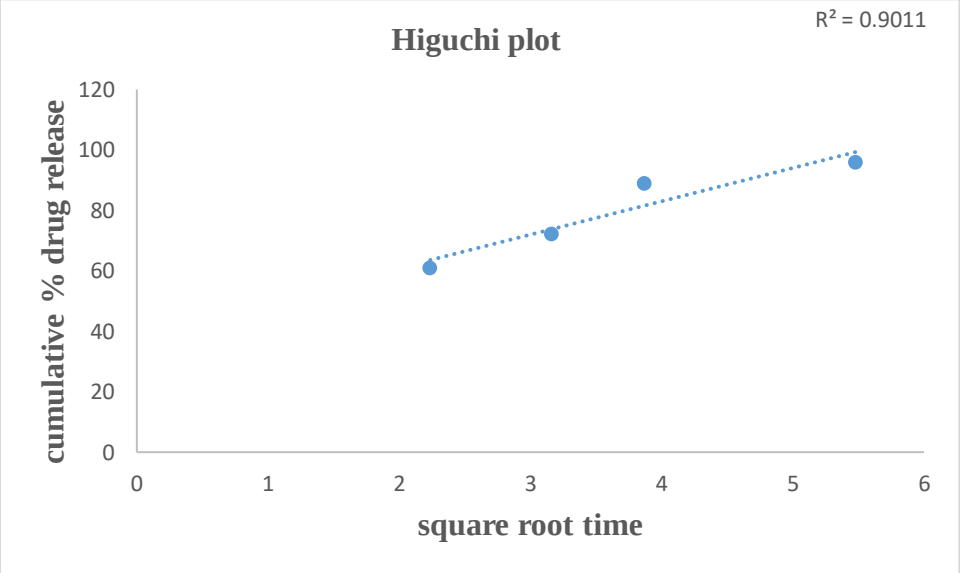


Figure: 16 Higuchi plot for F2

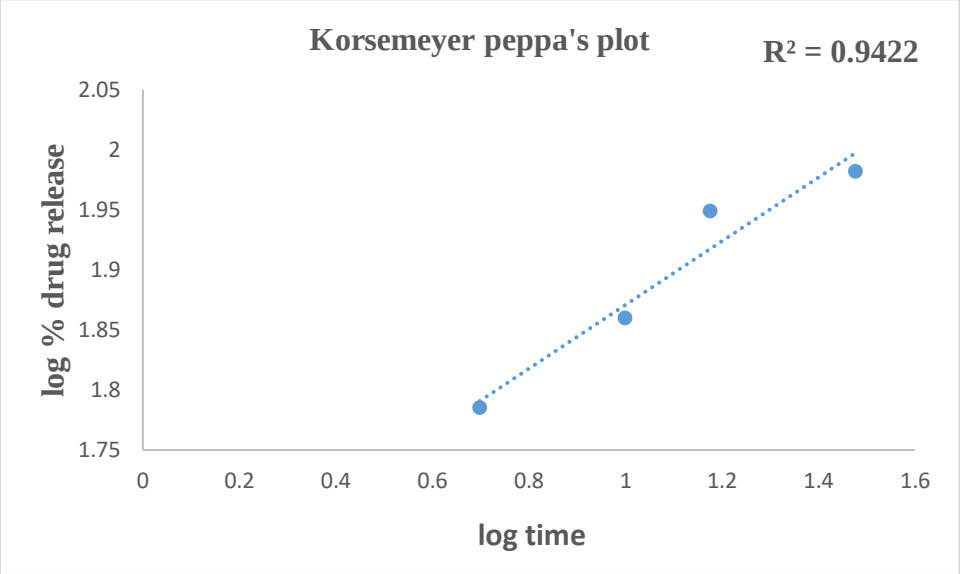


Figure: 17 Korsemeyer plot for F2

Table: 21 In-vitro Release Profile for Imatinib fast disintegrating tablet - Formulation (F3)

Time (min)	Absorbance (nm)	Concentration (mg/ml)	Amount of Drug Release(mg/900ml)	Cumulative % Drug Release
0	0	0	0	0
5	0.332	24.9	224.6	57
10	0.401	31.8	286.4	71
15	0.492	40.8	355	87.5
30	0.559	43.4	392	97

In vitro Dissolution Profile and Kinetic Plots of Formulation (F3)

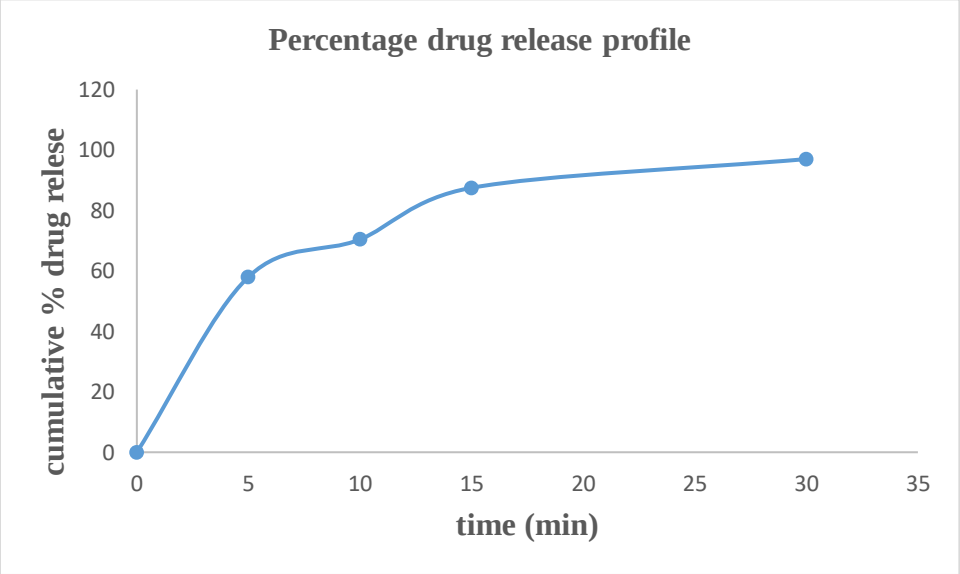


Figure: 18 percentage drug release profile for F2

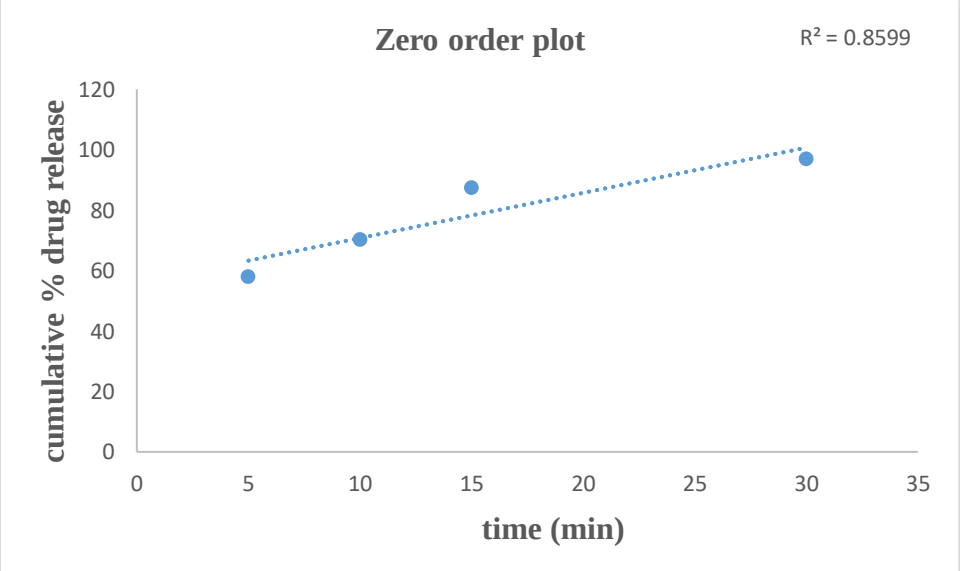


Figure: 19 Zero order plot for F3

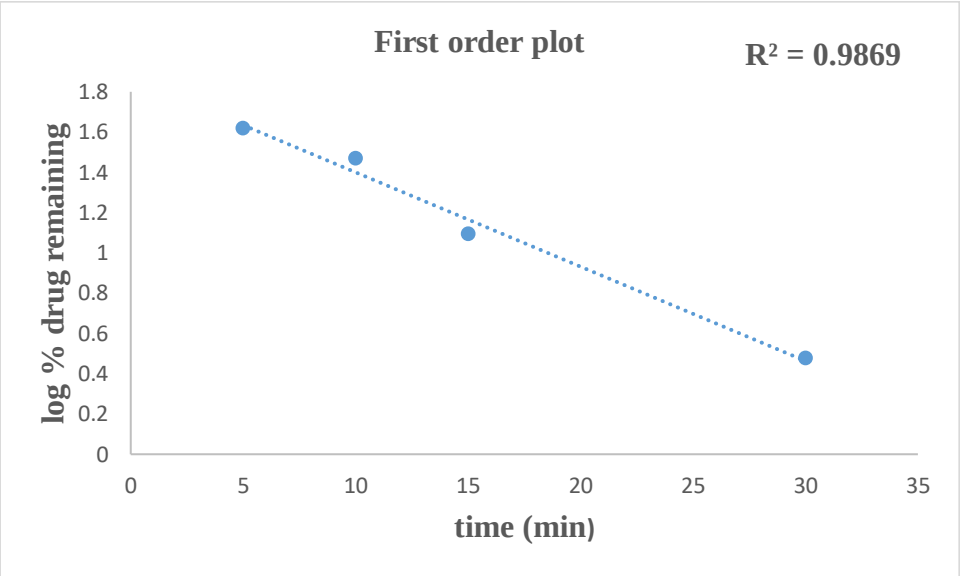


Figure: 20 First order plot for F3

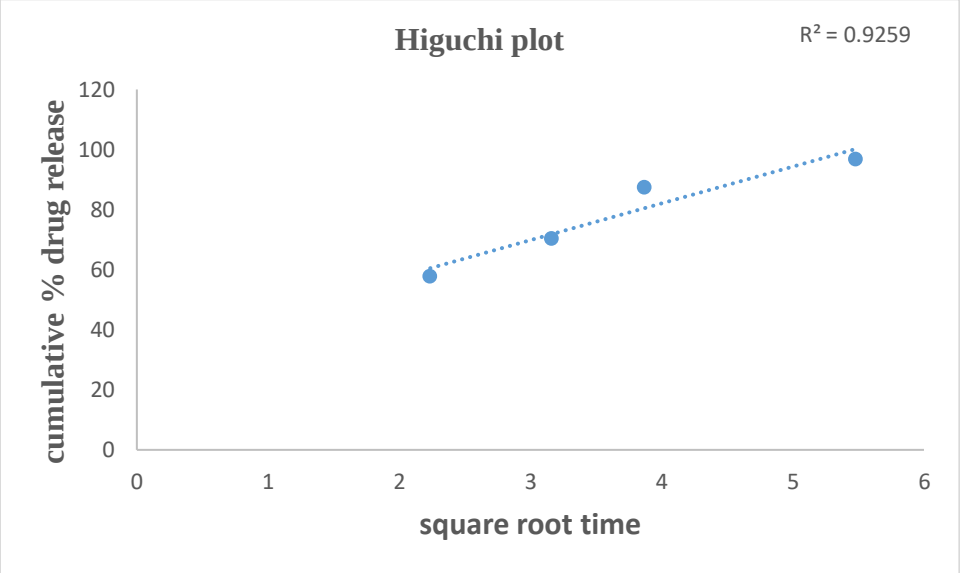


Figure: 21 Higuchi plot for F3

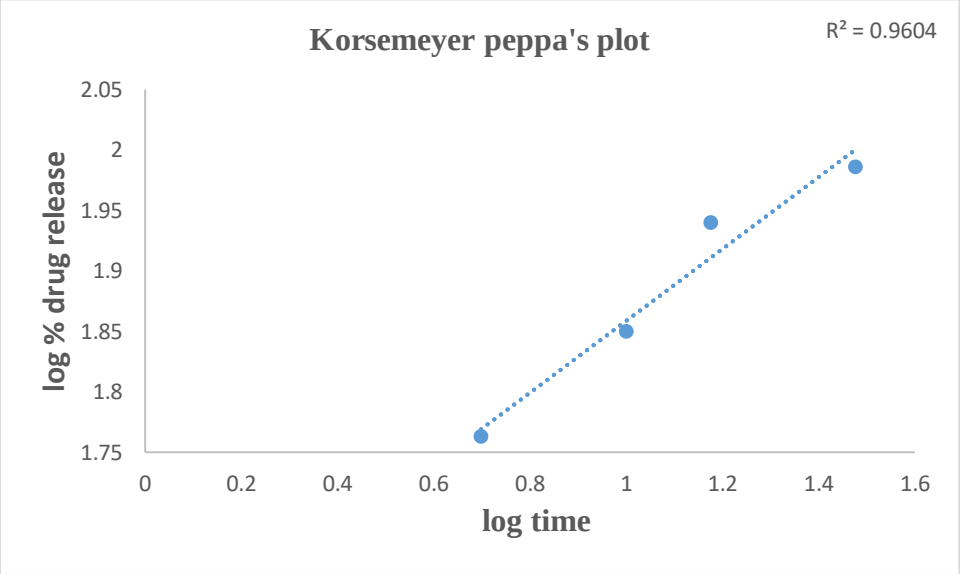


Figure: 22 Korsemeyer plot For F3

Table: 23 In-vitro Release Profile for Imatinib fast disintegrating tablet - Formulation (F4)

Time (min)	Absorbance (nm)	Concentration (mg/ml)	Amount of Drug Release(mg/900ml)	Cumulative % Drug Release
0	0	0	0	0
5	0.337	25.6	231	60
10	0.408	32	287	73
15	0.492	40.8	355	87.5
30	0.534	41.3	373	94

In-vitro Release Profile for Imatinib FD tablet - Formulation (F4)

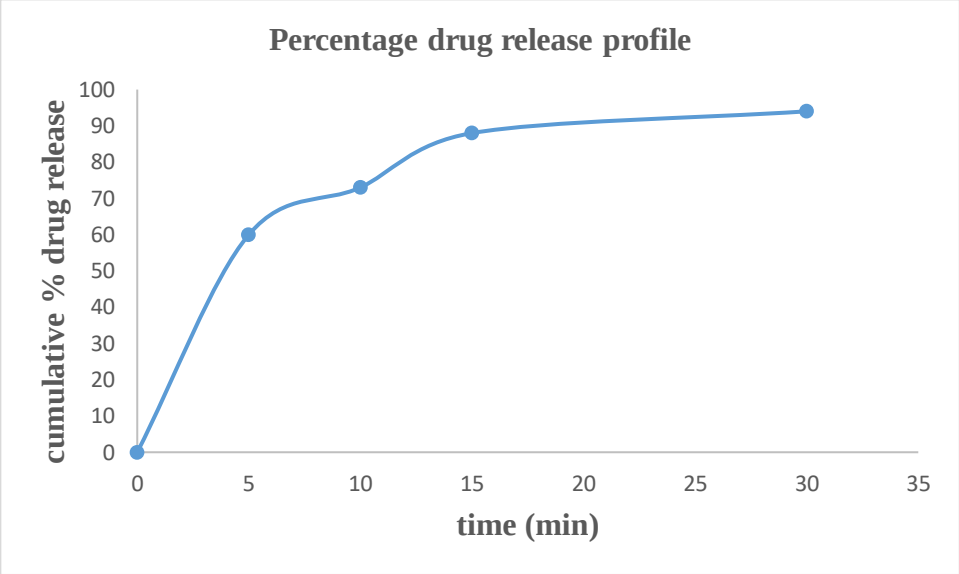


Figure: 23 Percentage drug release profile for F4

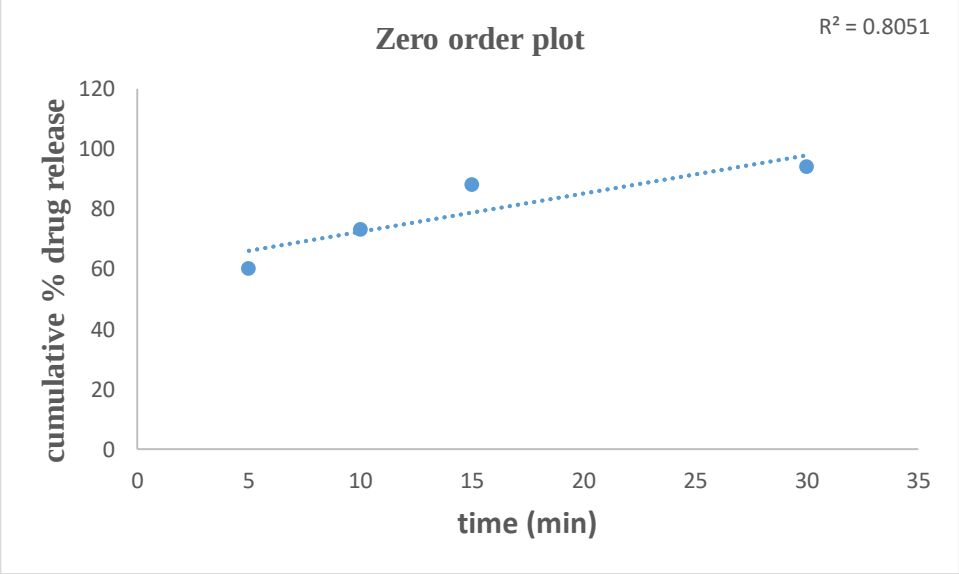


Figure: 24 Zero order plot for F4

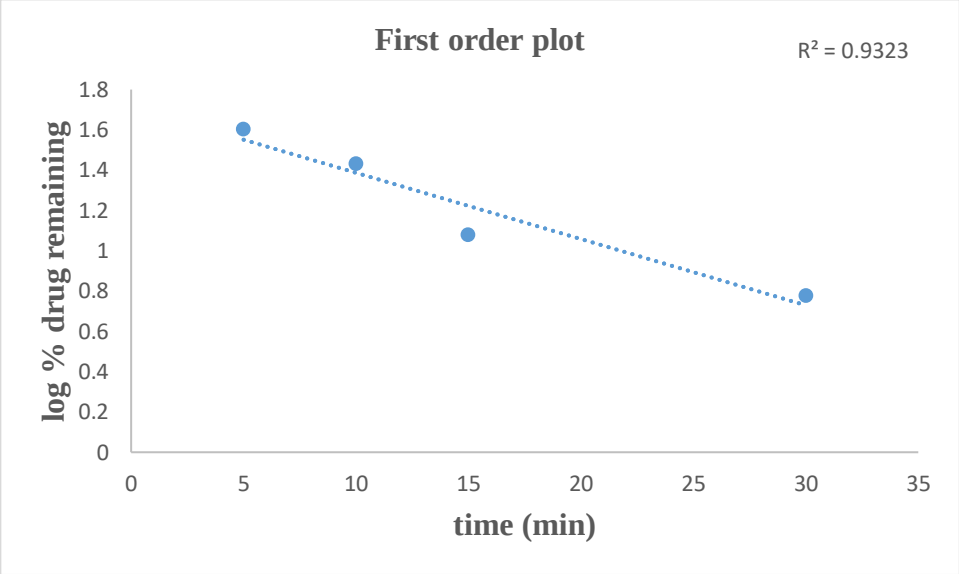


Figure: 25 First order plot for F4

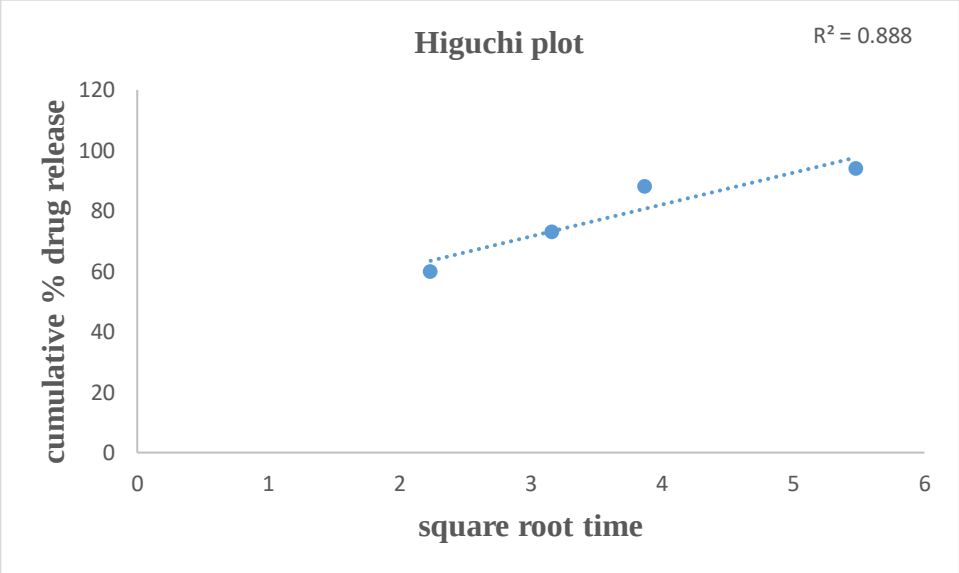


Figure: 26 Higuchi plot for F4

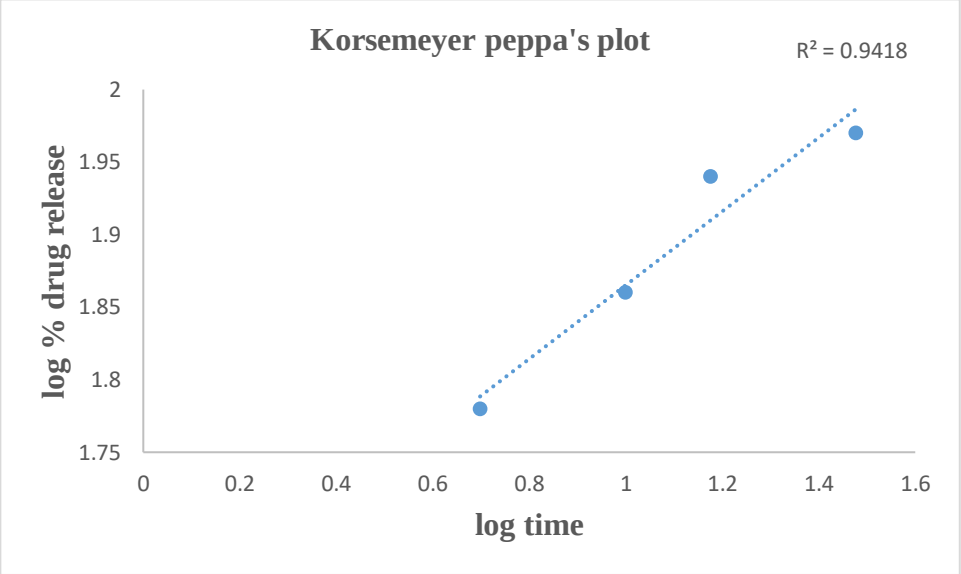


Figure: 27 Korsemeyer plot for F4

Table: 24 In-vitro Release Profile for Imatinib fast disintegrating tablet - Formulation (F5)

Time (min)	Absorbance (nm)	Concentration (mg/ml)	Amount of Drug Release(mg/900ml)	Cumulative % Drug Release
0	0	0	0	0
5	0.358	27.8	250	62
10	0.443	35.4	308	77
15	0.525	42.4	372	93
30	0.558	45.1	381	95

In vitro Dissolution Profile and Kinetic Plots of Formulation (F5)

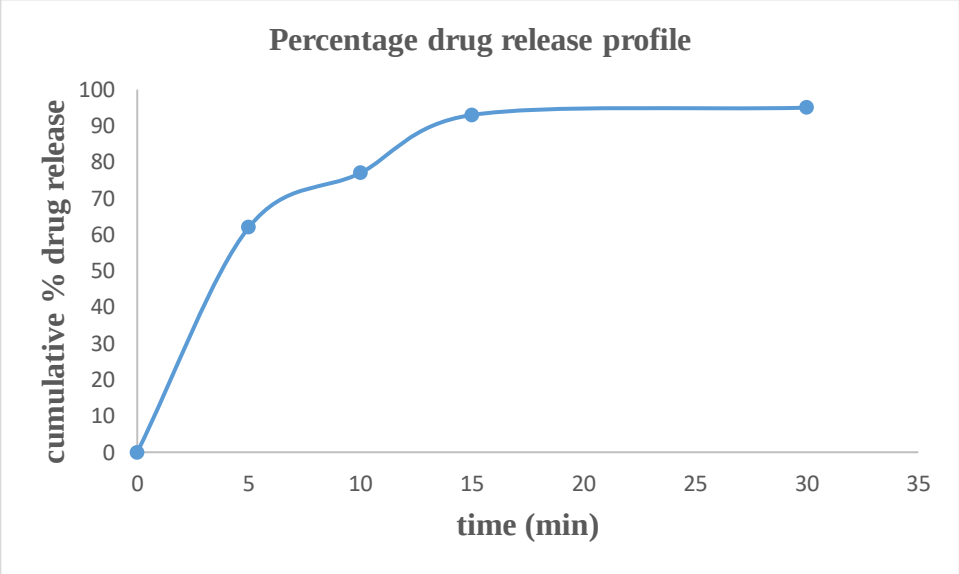


Figure: 25 Percentage drug release profile for F5

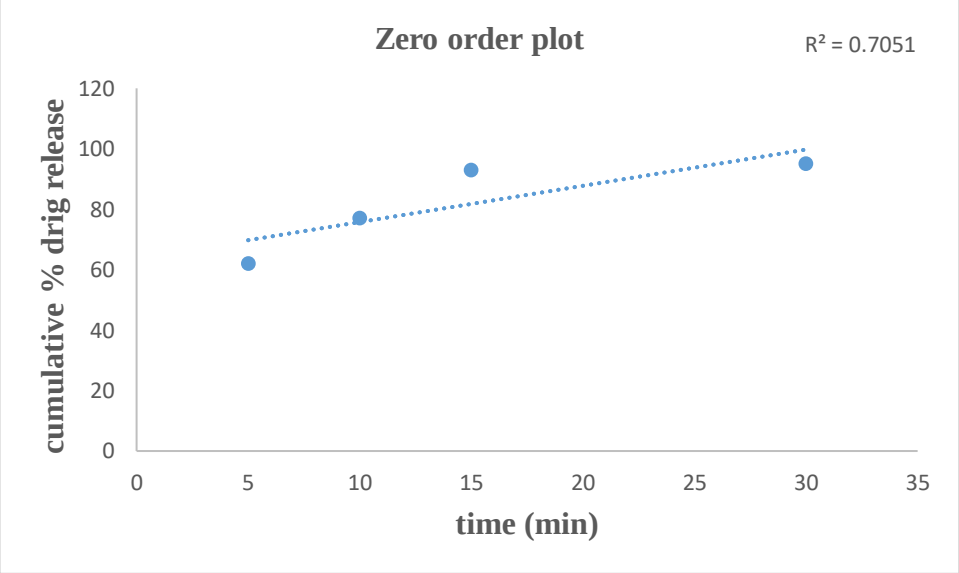


Figure: 26 Zero order plot for F5

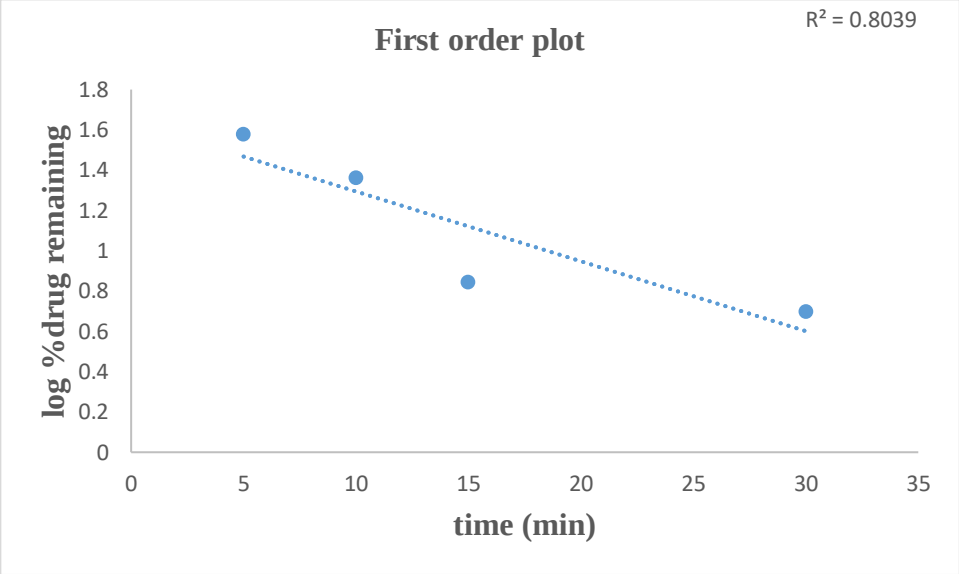


Figure: 27 First order plot for F5

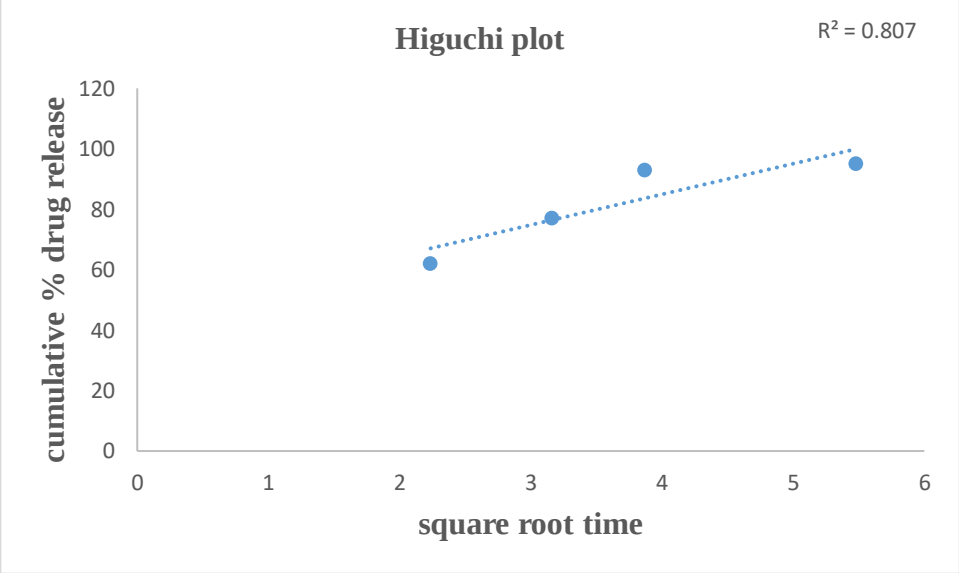


Figure: 28 Higuchi plot for F5

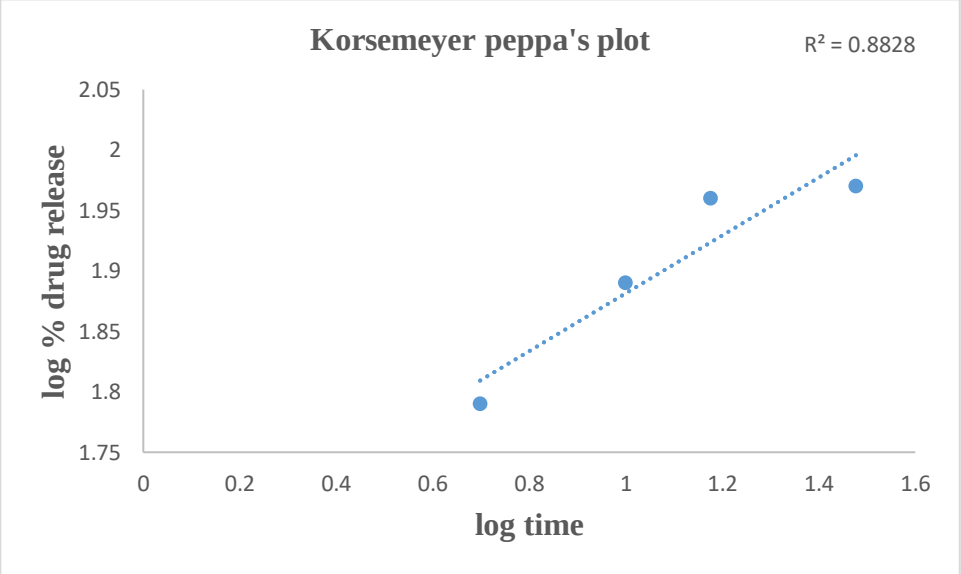


Figure: 29 Korsemeyer plot for F5

Table: 25 In-vitro Release Profile for Imatinib fast disintegrating tablet - Formulation (F6)

Time (min)	Absorbance (nm)	Concentration (mg/ml)	Amount of Drug Release(mg/900ml)	Cumulative % Drug Release
0	0	0	0	0
5	0.363	28.4	261	64
10	0.461	37	330	83
15	0.525	42.4	381	94
30	0.559	43.4	392	97

In vitro Dissolution Profile and Kinetic Plots of Formulation (F6)

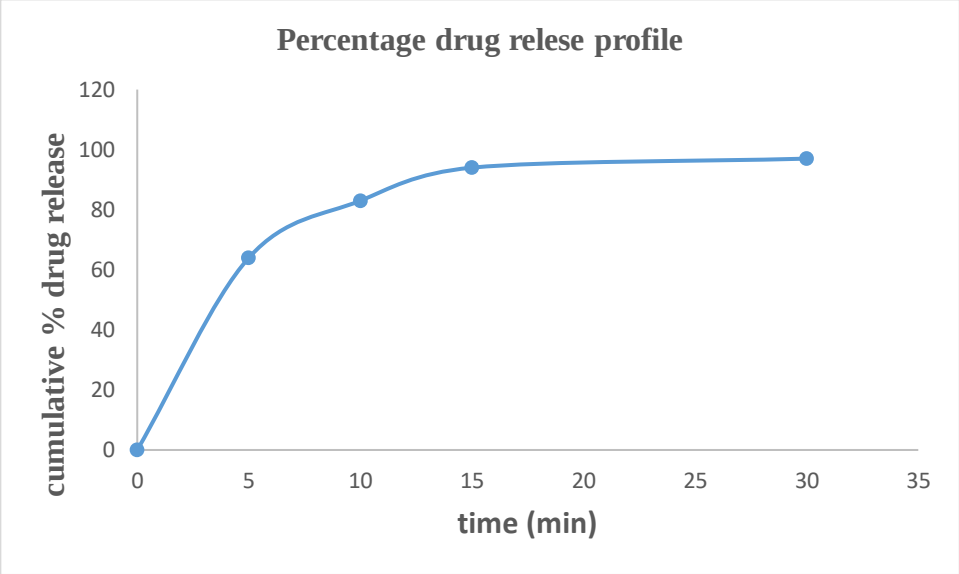


Figure: 30 Percentage drug release profile for F6

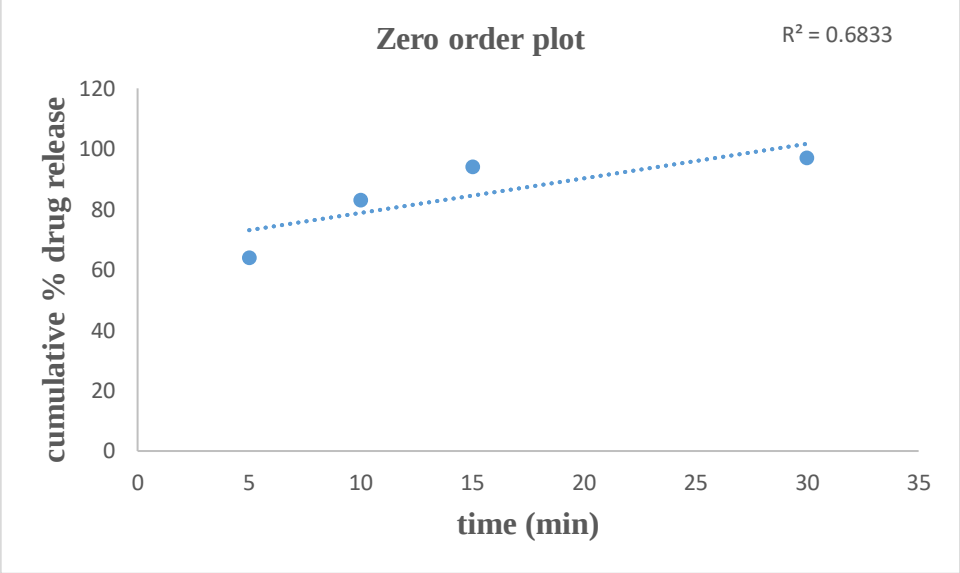


Figure: 31 Zero order plot for F6

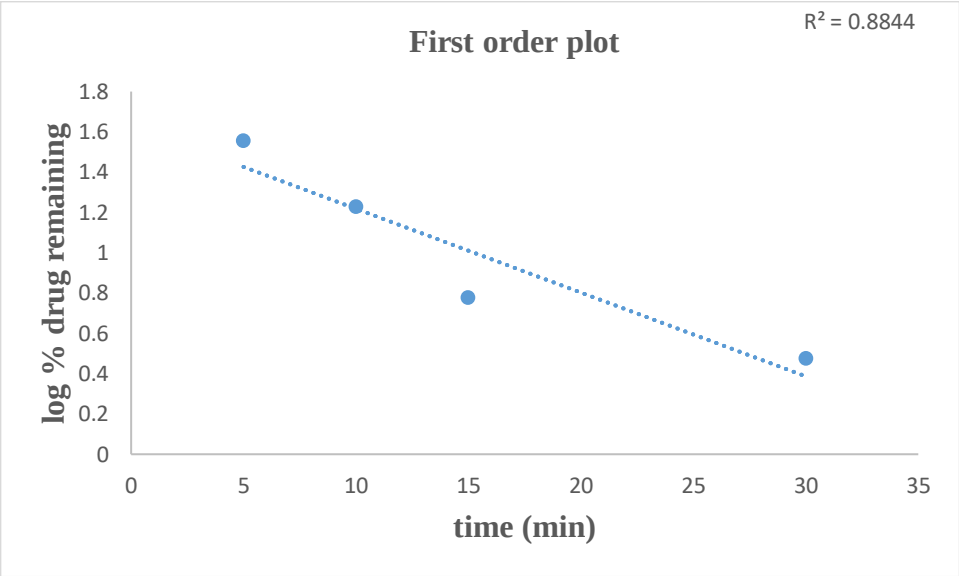


Figure: 32 First order plot for F6

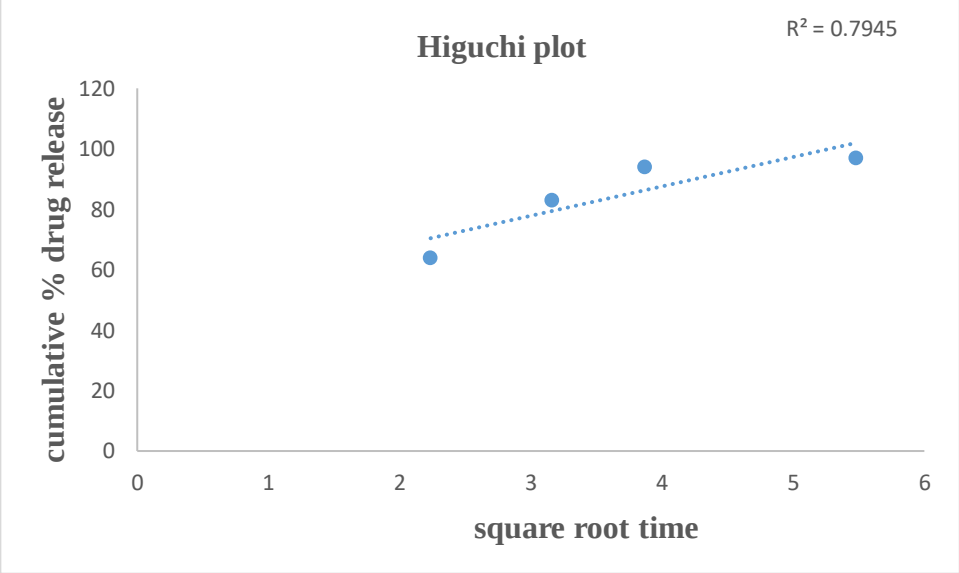


Figure: 33 Higuchi plot for F6

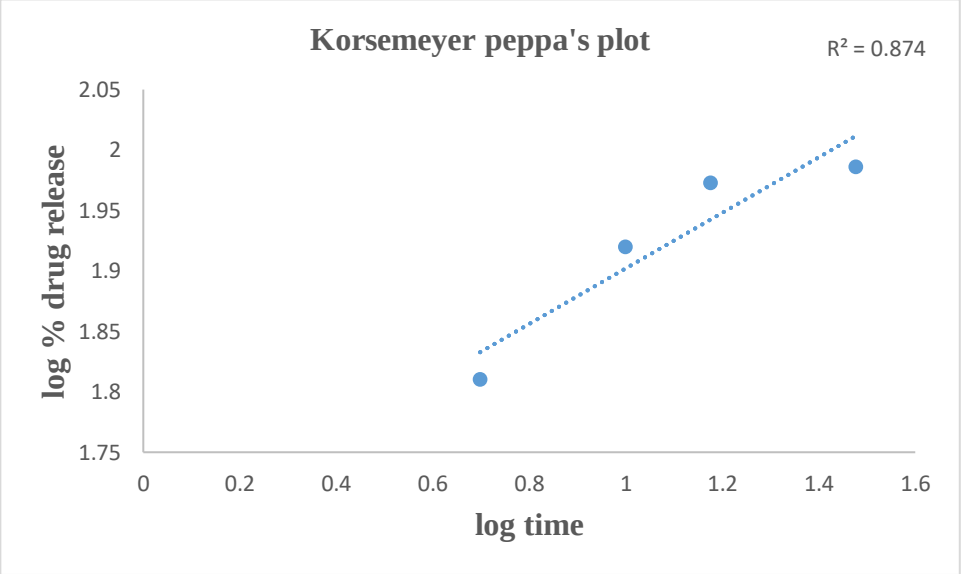


Figure: 34 Korsemeyer plot for F6

Table: 26 In-vitro Release Profile for Imatinib fast disintegrating tablet - Formulation (F7)

Time (min)	Absorbance (nm)	Concentration (mg/ml)	Amount of Drug Release(mg/900ml)	Cumulative % Drug Release
0	0	0	0	0
5	0.335	26	235	58.82
10	0.363	28.4	261	63.7
15	0.492	40.8	355	86.4
30	0.552	42.79	385.1	96

In vitro Dissolution Profile and Kinetic Plots of Formulation (F7)

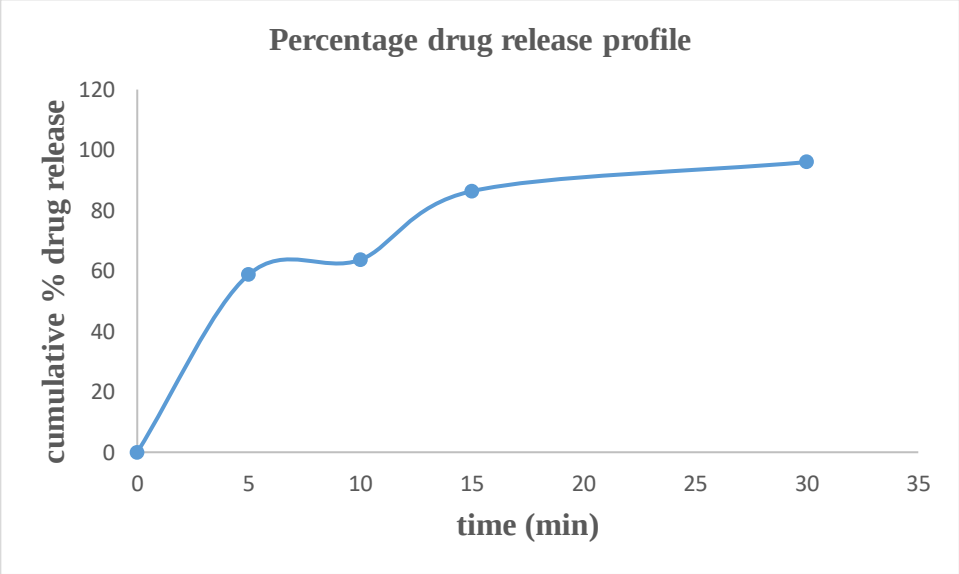


Figure: 35 Percentage drug release profile for F7

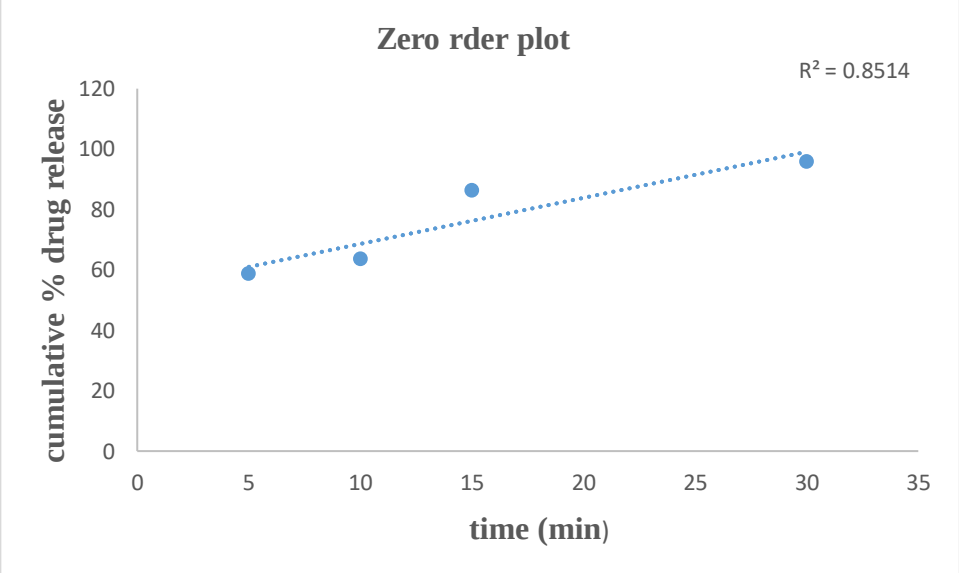


Figure: 36 Zero order plot for F7

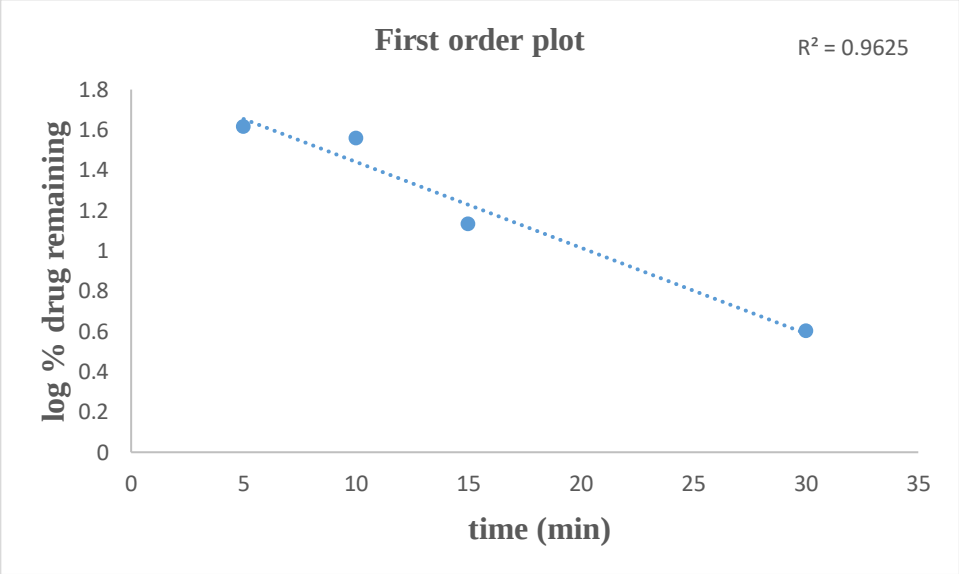


Figure: 37 First order plot for F7

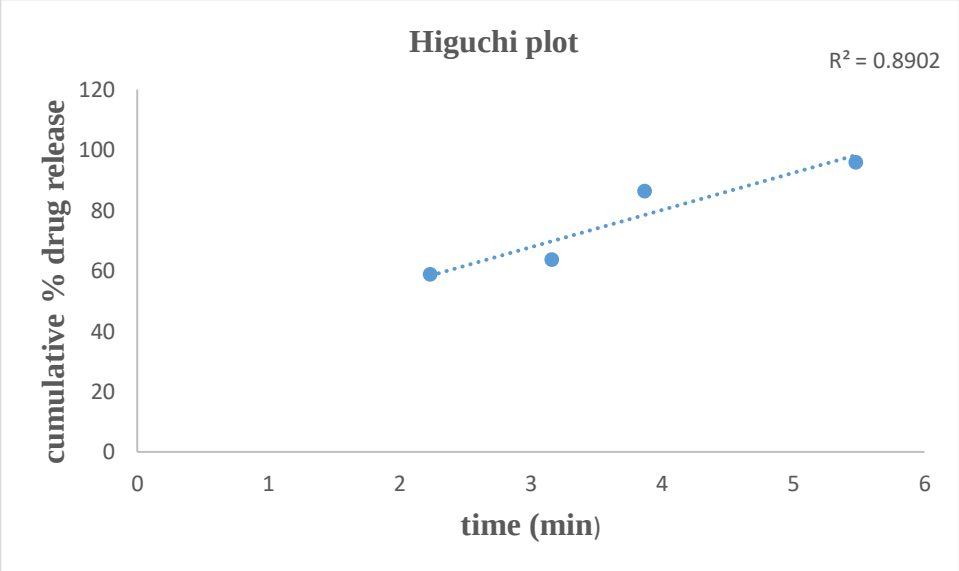


Figure: 38 Higuchi plot for F7

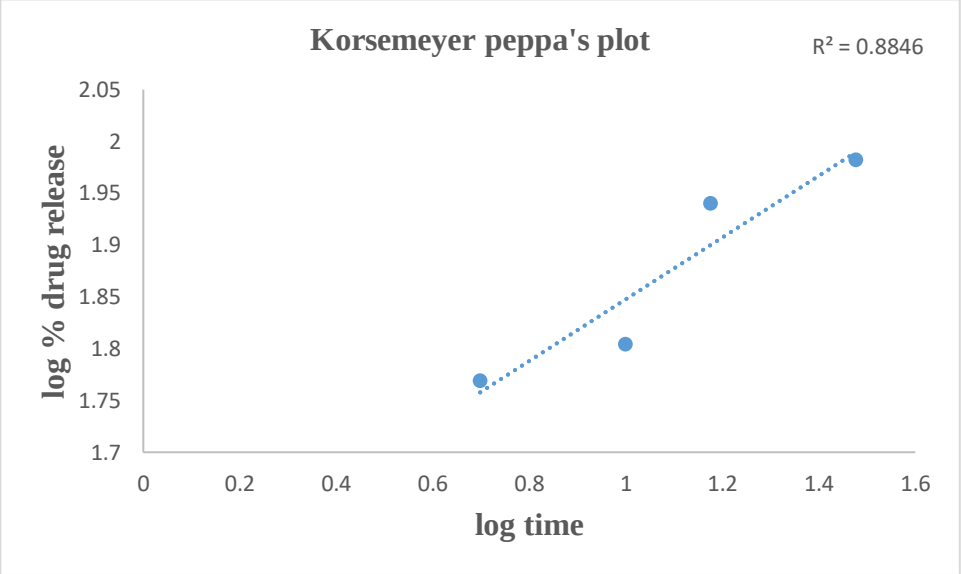


Figure: 39 Korsemeyer plot for F7

Table: 27 In-vitro Release Profile for Imatinib fast disintegrating tablet -Formulation (F8)

Time (min)	Absorbance (nm)	Concentration (mg/ml)	Amount of Drug Release(mg/900ml)	Cumulative % Drug Release
0	0	0	0	0
5	0.365	28.5	257	64
10	0.443	35.4	308	77
15	0.526	40.8	367	92
30	0.570	44	392	99

In vitro Dissolution Profile and Kinetic Plots of Formulation (F8)

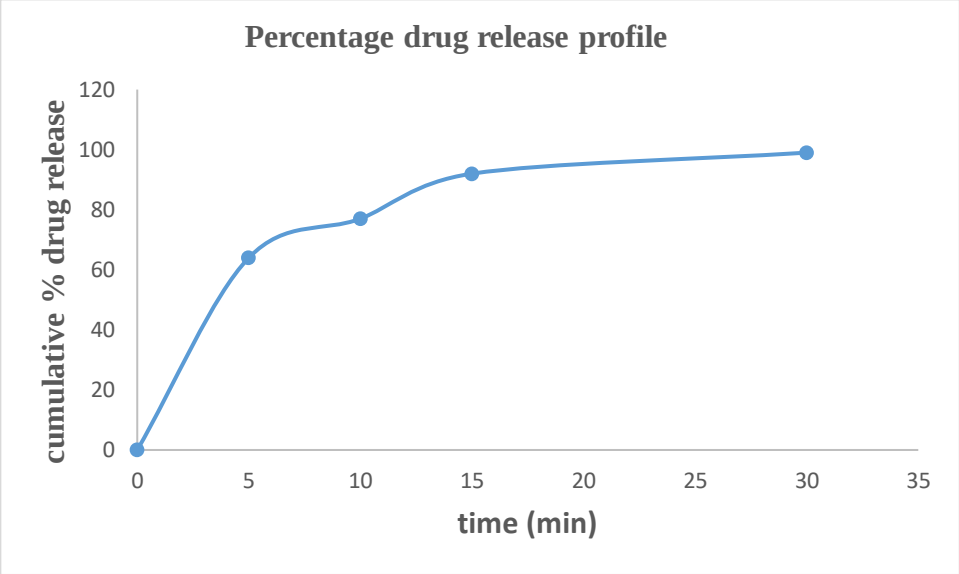


Figure: 40 Percentage drug release profile for F8

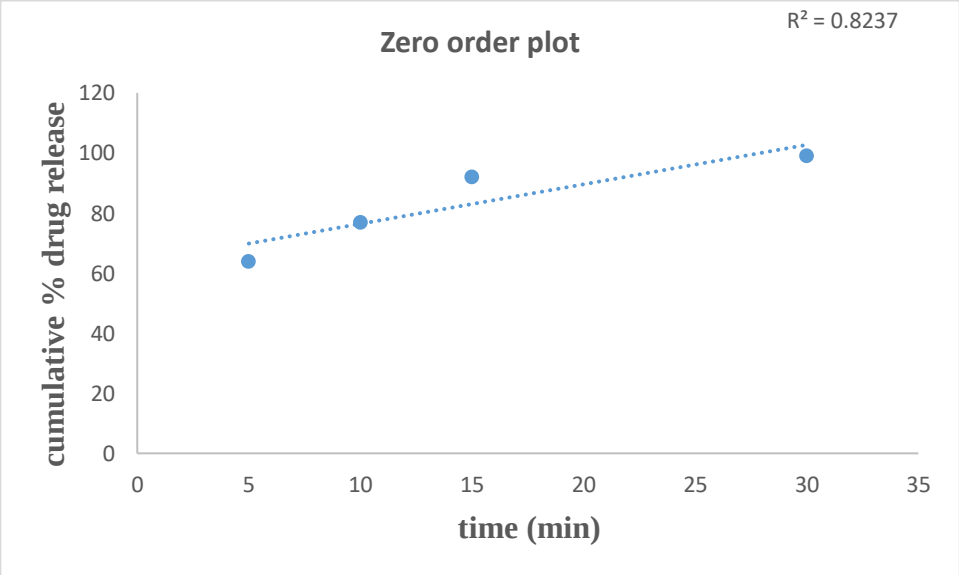


Figure: 41 Zero order plot for F8

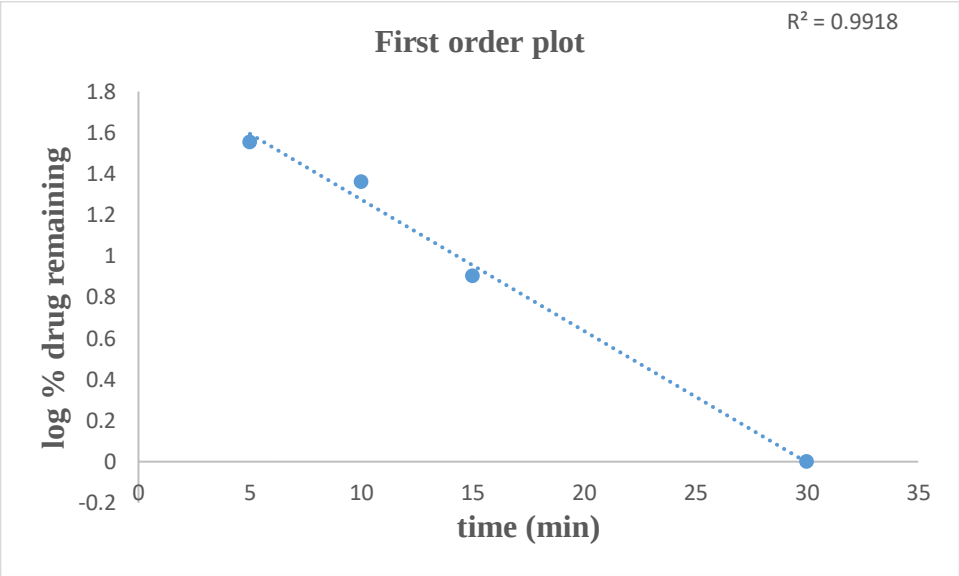


Figure: 42 First order plot for F8

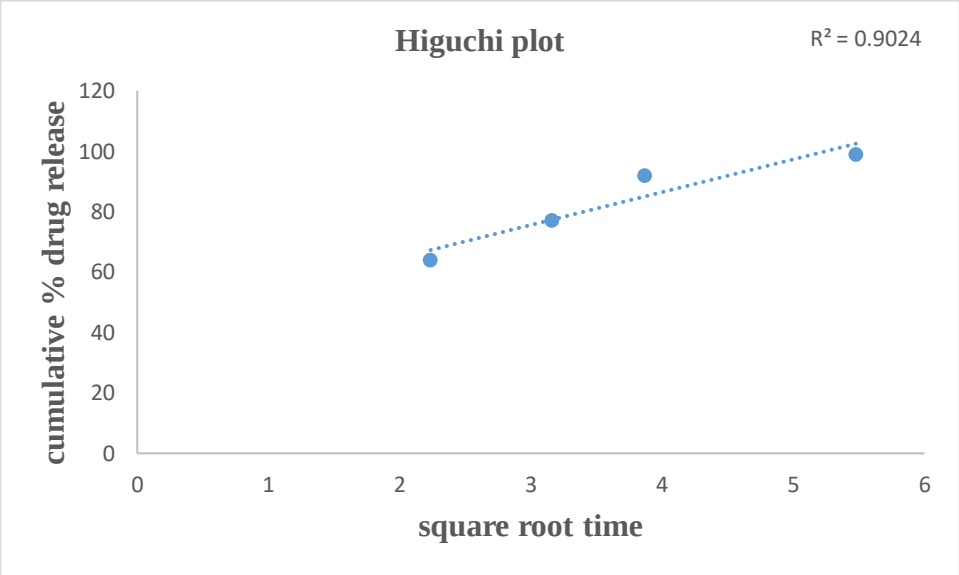


Figure: 43 Higuchi plot for F8

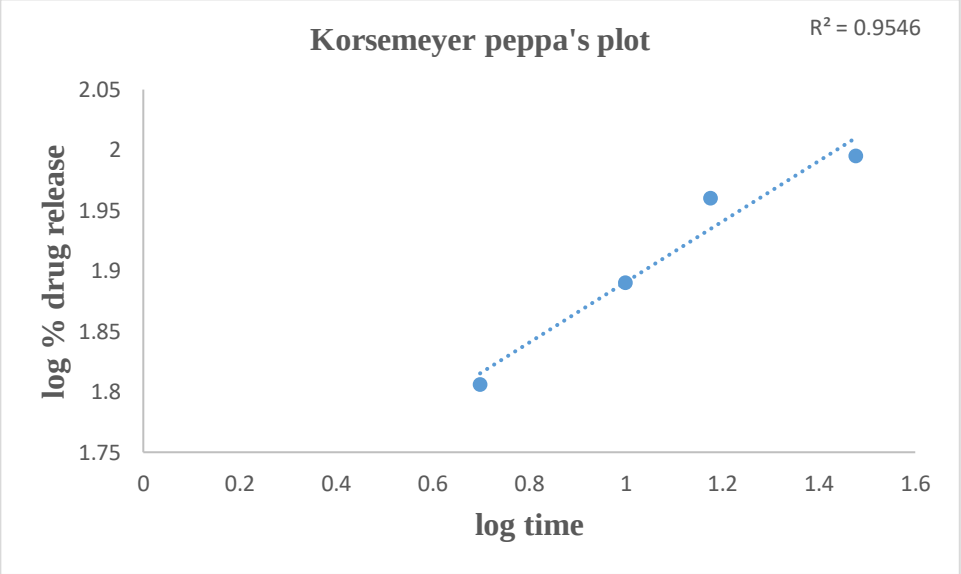


Figure: 44 Korsemeyer plot for F8

Table: 28 In-vitro Release Profile for Imatinib fast disintegrating tablet - Formulation (F9)

Time (min)	Absorbance (nm)	Concentration (mg/ml)	Amount of Drug Release(mg/900ml)	Cumulative % Drug Release
0	0	0	0	0
5	0.394	30.5	275	69
10	0.469	36.4	328	82
15	0.538	41.8	376	94
30	0.573	44.4	399	100.3

In vitro Dissolution Profile and Kinetic Plots of Formulation (F9)

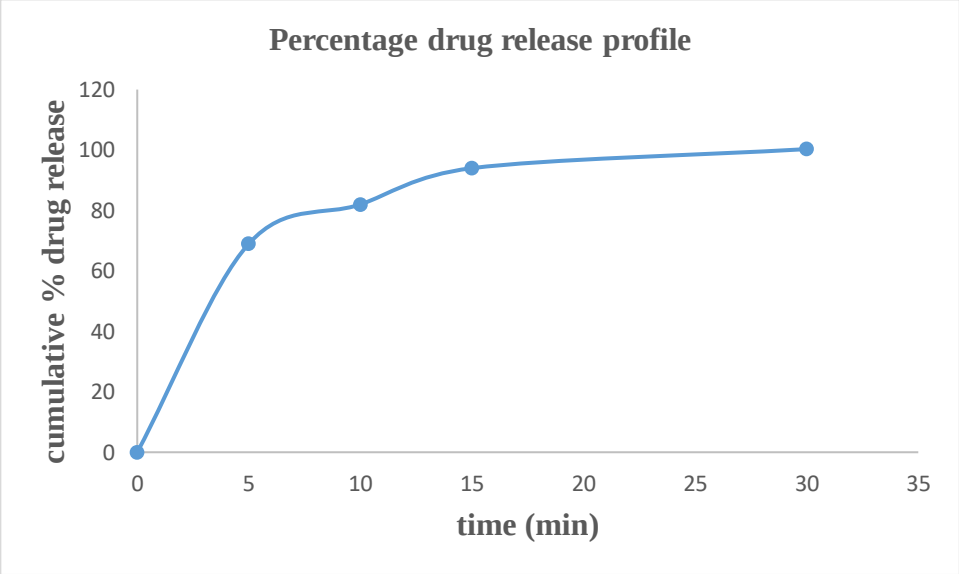


Figure: 45 Percentage drug release profile for F9

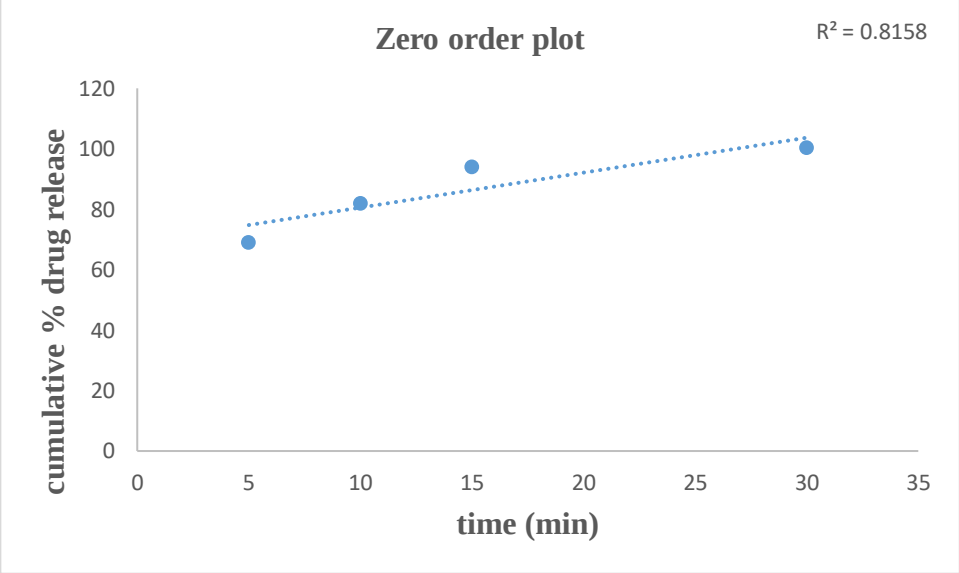


Figure: 46 Zero order plot for F9

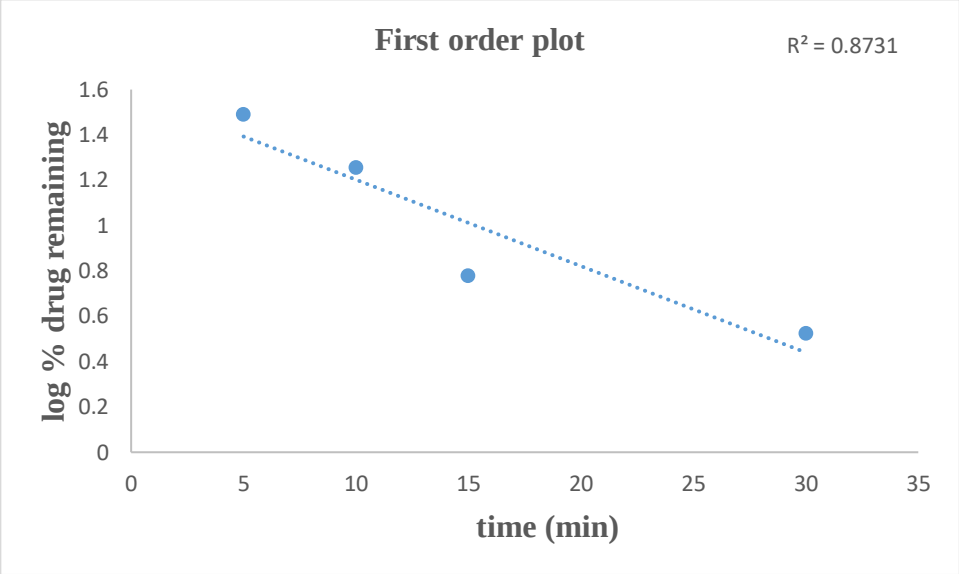


Figure: 47 First order plot for F9

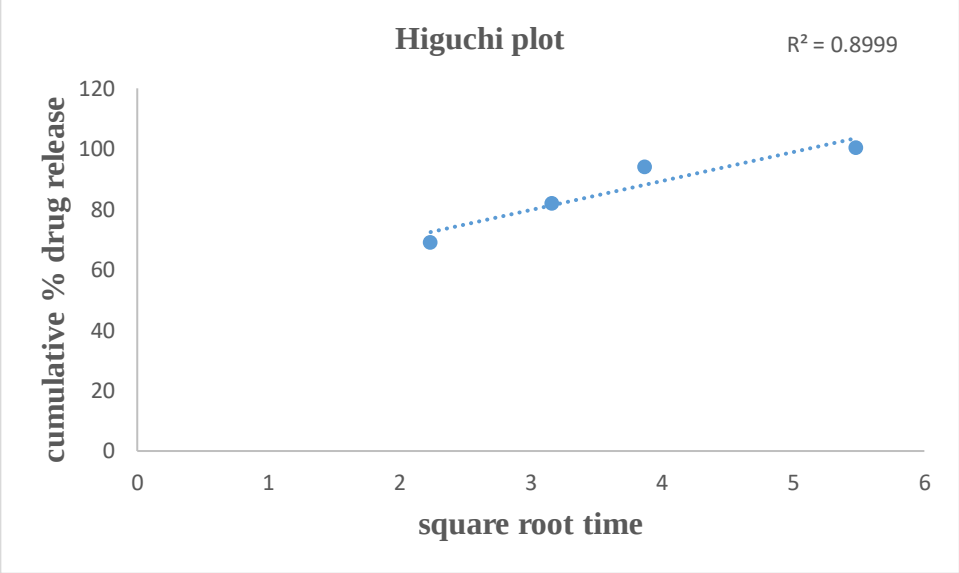


Figure: 48 Higuchi plot For F9

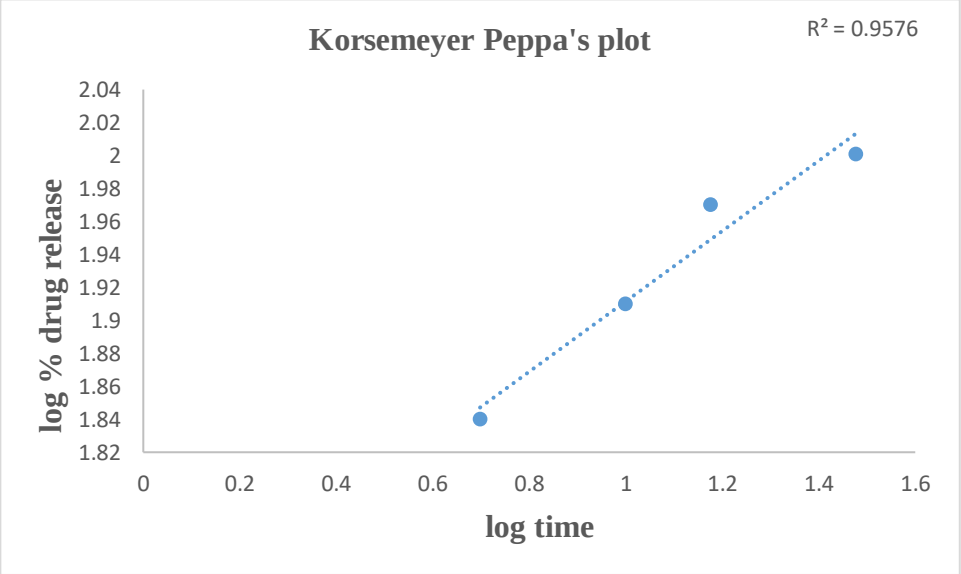


Figure: 49 Korsemeyer plot for F9

Table-29 Kinetic values obtained from different plots of Formulation (F1– F9)

Formulation code	Zero order plot		First order plot		Higuchi plot	Korsemeyer peppa,s plot		Possible mechanism of drug release
	R^2	Zero order rate constant	R^2	First order rate constant		R^2	N	
F1	0.771	1.5714	0.8665	-0.0318	0.8512	0.8993	0.3413	Fickian transport
F2	0.8219	1.34	0.96	-0.0402	0.9011	0.9422	0.2652	Fickian transport
F3	0.8599	1.4943	0.9869	-0.0468	0.9259	0.9604	0.2972	Fickian transport
F4	0.8051	1.2714	0.9323	-0.0329	0.888	0.9418	0.2542	Fickian transport
F5	0.7051	1.2	0.8039	-0.0347	0.807	0.8828	0.2392	Fickian transport
F6	0.6833	1.1429	0.8844	-0.0412	0.7942	0.874	0.2297	Fickian transport
F7	0.8514	1.5237	0.9625	-0.0426	0.8902	0.8846	0.2977	Fickian transport
F8	0.8237	1.3143	0.9918	-0.0639	0.9024	0.9546	0.2502	Fickian transport
F9	0.8158	1.1557	0.8731	-0.0381	0.8999	0.9576	0.2132	Fickian transport

8. DISCUSSION

Imatinib is one of the first cancer therapies that has shown a potential for a novel approach in cancer treatment. Imatinib represents a therapeutic breakthrough as a targeted therapy in the form of selective tyrosine kinase inhibitors (TKIs) specifically BCR-ABL, c-KIT, PDGFRA. It has become the first line drug in management of several cancers.Conventional formulation of Imatinib is administered single time a day (100 to 400 mg daily) because of its high half-life ($t_{1/2}$ = 18-40 hrs.).

Imatinib, with all evident advantages proved to be suitable candidates for development of a fast dissolving dosage form. In the present study, developing a oral fast dissolving dosage form of Imatinib an anti-Cancer drug with using super disintegrating agents (crospovidone, croscarmellose sodium and sodium starch glycolate). Hence in the present work, an attempt has been made to formulate the fast dissolving tablets of Imatinib using 3 different types of fast dissolving agents with different ratios such as (5mg, 7.5mg, 10mg).

Characterization of Bulk Drug and Effect of various formulation Excipients:

FT-IR spectra of pure Imatinib and its physical mixtures (1:1 ratio w/wt) with the excipients used in this study. The characteristic peak of carbonyl group at 1680-1740 cm^{-1}, NH_2 group at 3200-3400 cm^{-1} and hydroxyl group at 3300-3500 cm^{-1} present in the entire spectrum indicates the stable structure of Imatinib in the solid admixtures.

Physical properties of Granules:

The granules for the tablet preparation were prepared according to the formula given in (Table 5). The granules of different formulations were evaluated for angle of repose, LBD, TBD, Compressibility index, Hauser's factor and drug content (Table 13, 14, 15). The results of angle of repose range from 28.005 to 29.942 indicate good flow properties of the granules. This was further supported by lower compressibility index values (Table-14). Generally, compressibility index values from 14.10 to 14.92 (up to 16%) result in good to excellent flow properties. The Hauser's ratio of granules of all formulations was <1.2 indicates free flowing. The drug content in the weighed amount of granules of all formulations was found to be uniform. Other parameter, such as bulk density, tapped density was found to be within acceptable limits (Table 14). All these results indicate that the granules possessed satisfactory flow-properties, compressibility and drug-content. Finally, both fast disintegrating level and fast disintegrating type did not affect the physical properties of the prepared granules.

Physical properties of Tablets:

The tablets of different formulations were subjected to various evaluations tests such as Hardness, Friability, and uniformity of weight, drug content and in vitro – dissolution. In a weight variation test, the pharmacopoeia limit for the percentage deviation for tablets above 324mg is ±10%. The average percentage deviation of all tablet formulations was found to be within the limit, and hence all formulations passed the test for uniformity of weight as per official requirements. Good uniformity in drug content was found among different batches of the tablets, and the percentage batches of drug content were more than 98%. In the present study, the percentage friability for all the formulations was below 1%, indicating that the friability is within the prescribed limits. All the tablet formulations showed acceptable pharmacopoeia limit specifications for weight variation, drug content, hardness and friability.

In-vitro Release Studies:

The in vitro drug release characteristics were studied in 900ml of 0.1NHcl for 30min, using USP. XXIII Dissolution apparatus type II (paddle) method.

The results of dissolution studies indicate that F1, F2, F3 released 92%, 96%, and 97% of Imatinib at the end of 30 min. Formulation F1, F2, F3 formulated with crospovidone by gradual increasing the ratio of crospovidone (5mg, 7.5mg, 10mg) shows increasing in drug release at the end of 30min by using mechanism of wicking.

The results of dissolution studies indicate that F4, F5, F6 released 94%, 95%, and 97% of Imatinib at the end of 30 min. Formulation F4, F5, F6 formulated with croscarmellose sodium by gradual increasing the ratio of croscarmellose sodium (5mg, 7.5mg, 10mg) shows increasing in drug release at the end of 30min by using mechanism of minimum of gelling and wicking due to fibrous structure.

The results of dissolution studies indicate that F7, F8, F9 released 96%, 99%, and 100.3% of Imatinib at the end of 30 min. Formulation F7, F8, F9 formulated with sodium starch glycolate by gradual increasing the ratio of sodium starch glycolate (5mg, 7.5mg, 10mg) shows increasing in drug release at the end of 30min by using mechanism of rapid and extensive swelling with minimum gelling.

It is noticed that all the 9 formulations show maximum release at the end of 30 minutes by increasing the concentration of super disintegrating agents (crospovidone, croscarmellose sodium and sodium starch glycolate).

By comparing all these 9 formulations by using In-vitro drug release. The In-vitro drug release reveals that formulation F7, F8, F9 which is formulated with SSG shows better result in

all the ratios by comparing with F1-F6.

In formulation F1-F3 formulated with crospovidone shows less invitro drug release (all 3 ratios of fast disintegrating agents). Because crospovidone is insoluble in water and also the average particle size greater than sodium starch glycolate.

In formulation F4-F6 formulated with CCS shows better invitro drug release (all 3 ratios of fast disintegrating agents when compared with F1-F3 (formulated with crospovidone). Because they have less particle size than crospovidone. Even though it is insoluble in water they rapidly swell 4-8 times to its original volume and contact with water.

In formulation F7-F9 formulated with sodium starch glycolate shows best invitro drug release (all 3 ratios of fast disintegrating agents). This is due to rapid and extensive swelling with minimum gelling of sodium starch glycolate. Average particle size of sodium starch glycolate (38nm-42nm) which is less than croscarmellose sodium and crospovidone. In contact with water SSG swells up to 300 times to its original volume which is less than croscarmellose sodium/crospovidone and gives translucent suspension in water.

Hence F9 formulation shows a best formulation with maximum drug release of 100.3% at the end of 30 minutes.

To know the mechanism of drug release from these formulations, the data were treated according to first-order release, Higuchi's, and korsmeyer equation / peppa's model et al's equation along with zero order release pattern. The release rate kinetic data for all the other equations can be seen (Table 29). The formulations F1-F9 showed higher Regression values for first order plots indicating that drug release followed first order kinetics. The in vitro release profiles of drug from all the formulations could be best expressed by Higuch's equation, as the plots showed high linearity Regression 0.7945 to 0.9259. To confirm the diffusion mechanism, the data were fit into korsmeyer, et al's equation, with slope (n) values ranging from 0.2132 to 0.3413. This indicates that the release of drug follows Fickian transport. It means in release of drug from the tablet dissolution and diffusion both mechanisms are used. Padmavathi College of Pharmacy

9. CONCLUSION

It is evident from the result of formulation F9 which is formulated with sodium starch glycolate (10mg) shows maximum and better release at the end of 30min, when comparatively with F1-F8. This may be due to their rapid swelling mechanism, less particle size, and also the cost of sodium starch glycolate is less when compared to crospovidone, croscarmellose sodium. Thus the work proves that sodium starch glycolate is better super disintegrating agent in the In-vitro drug release and it is cost effective. The formulation F1-F9 exhibited fickian drug release mechanism.

9. BIBLIOGRAPHY

1. D.M.Brahmankar, Sunil B. Jaiswal, "Biopharmaceutics and Pharmacokinetics A Treatise", 1std, Vallabh Prakasan, Delhi, 2005; p: 27,5-6.

2. James Swarbrick., James C Boylan., "Encyclopedia of Pharmaceutical Technology", 2nd edition, Vol-1:8, 2002; p: 698-734.

3. Christian Leuner., Jennifer Dressmann., "Improving drug solubility for oral delivery using solid dispersions. European Journal of Pharmaceutics and Biopharmaceutics", 2000, p: 50, 47-48.

4. Leon Shargel., Andrew B.C, "Applied Biopharmaceutics and Pharmacokinetics", Appleton-Century-Crofts, 4th Ed, 1985. p:134.

5. H.A. Gare Kani., F. Sadeghi., A. Badiee., S.A. Mostafa and A.R. Rajabisiahboomi., "Crystal habit modifications of Ibuprofen and their Physicochemical Characteristics". Drug Development and Industrial Pharmacy, 2001, p: 27(8): 803-809.

6. Leon Shargel., Andrew B.C, "Applied Biopharmaceutics and Pharmacokinetics", Appleton-Century-Crofts, 4th Ed, 1985. p :135.

7. D.M.Brahmankar, Sunil B. Jaiswal, "Biopharmaceutics and Pharmacokinetics A Treatise", 1std, Vallabh Prakasan, Delhi, 2005; p: 27, 29-30.

8. Nandita G. Das and Sudip K. Das., "Formulation of Poorly Soluble Drugs". Drug Delivery Report Spring/Summer, 2006, p: 52-55.

9. Devarajan, Padma V, Gore SP. "Melt-in-mouth tablets- innovative oral drug delivery systems". Express Pharma Pulse. 2000; p: 7(1):16-18.

10. Reddy L.H., Ghosh B, Rajneesh. "Fast dissolving drug delivery systems: A Review of Literature". Indian J Pharm Sci. 2002; p: 64(4):331-36.

11. Kuchekar B S, Bhise S B, Armugam V. "Design of fast dissolving tablets". Ind. J. Pharm. Edu. 2001; p: 35(4):150-152.

12. Tetsuya O et al. "Design of rapidly disintegrating oral tablets using acid-treated yeast cell wall: A Technical Note". AAPS PharmSciTech 2003; p: 44.

13. Beatrice P." Formulation design of carbamazepine fast-release tablets prepared by melt granulation technique". Int. J. Pharma 256 (2003) p: 53.

14. Abdelbary G et al. "The preparation of orally disintegrating tablets using a hydrophilic waxy binder". Int. J. Pharma 278 (2004) p: 423.

15. Okuda Y et al. "A new formulation for orally disintegrating tablets using a suspension spray-coating method". Int. J. of Pharma 382 (2009) p: 80.

16. Sastry SV, Nyshadham JR, Joseph AF. "Recent technological advances in oral drug delivery - a review", PSTT 2000; p: 3(4).

17. Bandari S, Mittapalli RK, Gannu R, Rao YM. "Orodispersible tablets: an overview". Asian J Pharm Jan 2008; p: 66-78.

18. Lachman L, Liberman HA. Theory and Practice of Industrial Pharmacy, Third Edition, 1990, pp 293-294.

19. Rudnic, EM, Lausier JM, Chilamkarti RN, Rhodes CT. Studies on the utility of cross-linked polyvinylpyrrolidone as a tablet disintegrant, Ind. Pharm, 6, 1980, 291 – 309.

20. Shah NH, Lazarus JH, Sheth CI, Jarowski PR. Carboxymethylcellulose: Effect of degree of polymerization and substitution on tablet disintegration and dissolution, J. Pharm. Sci., 70(6), 1981, 611 – 613.

21. Bolhuis GK, Arends-Scholte AW, de Vries JA. Disintegration efficiency of sodium starch glycolates prepared from different sodium starch glycolates, Eur. J. Pharm. Biopharm, 40(5), 1994, 317 – 320.

22. Rudnic EM, Kanig JL, Rhodes CT. Effect of molecular structure variation on the disintegrant action of sodium starch glycolate, J. Pharm. Sci, 74(6), 1982, 647 – 650.

23. Bolhuis GK, van Kamp HV, Lerk CF, Gielen JW, Arends AW , Effect of variation if degree of substitution, cross-linking and purity on the disintegration efficiency of sodium starch glycolate, Acta Pharm. Technol, 30(1), 1984, 24 – 32.

24. Zhao N, Augsburger LL. The influence of product brand to brand variability on superdisintegrants performance, a case study with croscarmellose sodium. Pharm. Dev. and Technol, 11, 2006, 179 –185

25. Smallenbroek AJ, Bolhguis GK, Lerk CF. The effect of particle size of disintegrants on the disintegration of tablets, Pharmaceutisch Weekblad, 3, 1981,172 – 175.

26. List PH, Muazzamm UA .Swelling – A driving force in tablet disintegration, Pharm. Ind, 41, 1979, 1075 –1077.

27. Caramella C, Novel methods for disintegrants characterization, Part 1, Pharm. Technol. Int, 2(9), 1990, 30 – 37.

28. Shangraw R, Wallace J, Bowers F, "Morphology and Functionality in Tablet Excipients

for Direct Compression," Pharm. Technol. 5, 1981, 44–60.

29. Shangraw R, Mitrevej A, Shah M, "A New Era of Tablet Disintegrants," Pharm. Technol, 4, 1980, 48–57.

30. European Pharmacopeia, European Directorate for the Quality of Medicines, 5, 2006, 3151.

31.Cremer K. "Orally Disintegrating Dosage Forms Provide Life Cycle Management Opportunities," Pharm. Technol. Formulation and Solid Dosage 2003,22–28.

32. Parakh SR, Gothosakar AV, "A Review of Mouth Dissolving Tablet Technologies," Pharm. Technol. 27 (11), 2003, 92–100.

33. Duriez X, Joshi AA, "Starches A Versatile Source," Pharma Form. Qual. 6 (3), 2004, 48–50.

34. http://archives.who.int/eml/wmf/2004/English/Antimigraine%20drugs.pdf.

35. Sunita A Chaudhary, Tejal A Mehta, Ankit B Chaudhary "Formulation, Development and Evaluation of fast disintegrating tablets of Rizatriptan benzoate using novel adjuvants" International Journal of ChemTech Research Coden(USA): IJCRGG Vol.2, No.2, pp 1026-1030, April-June 2010

36. Pravin Chaudhari, Smita Kolhe, Dhananjay More "Formulation Development Studies of Rizatriptan Benzoate Fast Disintegrating Tablet" RJPBCS Volume 2 Issue 1, January – March 2011.

37. Akhila Alladi, N. Damodharan "Formulation, taste masking and evaluation of almotriptan oral disintegrating tablets" IJPSR, 2012; Vol. 3(10): 3940-3946, accepted 26 September, 2012

38. Ronald Peter, N. Shashank Nayak, S. Shwetha, K. Kamath and AR. Shabaraya "Formulation and Evaluation of Fast Dissolving Tablets of Flunarizine HCl by Sublimation Method Using Treated Agar As Superdisintegrant" Int J Pharm Sci, Vol. 3 (2) Apr-Jun 2014

39. S. Vidyadhara, R. L. C. Sasidhar, T. Balakrishna, S. Vikas and M. Bhaskar "Design and evaluation of fast dissolving tablets for rizatriptan benzoate" Scholars Research Library, *Der Pharmacia Lettre, 2015, 7 (11):80-85.*

40. Surrndea Babu, D. Ramakrishna "Formulation and invitro evaluation of almotriptan fast dissolving tablets" Journal *of Pharmacreations Vol-3(2) 2016 [128 133].*

41. R. Nazemoon, N. Sowjanya, S. Seeivallika Rani, P. Ramya, M. Nagamani "Formulation and evaluation of oral fast disintegrating tablets of sumatriptan succinate" *International*

Journal of Research in Pharmaceutical and Nano Sciences. 6(3), 2017, 111 - 117.

42. Abeer Ahmed Kassem ,Gihan Salah Labib "Flash dissolving sublingual almotriptan malate lyotabs" International Journal of Pharmacy and Pharmaceutical Sciences, Vol 9, Issue 1, 2017, *08 Nov 2016*

43. Talele Swati G. , Harak Yogesh, Bakliwal Akshada A., Chaudhari G.N. "Formulation and evaluation of mouth dissolving film of almotriptan malate", *J. Pharm. BioSci. 3(2015)42---52,* 28 Sep 2015

44. Yunxia Bi, Hisakazu Sunada, Yorinobu yonezaywa, Kazumi Danjo, Akinobo Otsuka. Preparation and evaluation of a compressed tablet rapidly disintegrating in the oral cavity. Chem. Pharm. Bull. 1996; p: 44(11) 2121-2127.

45. Y. X. Bi, H. Sunada, Yonezawa Y, Danjo K. Evaluation of rapidly disintegrating tablets prepared by direct compression method. Drug development and Industrial pharmacy 1999; p: 25(5): 571-581.

46. Hisakadzy Sunada, Yunxia Bi. "Preparation, Evaluation and optimization of rapidly disintegrating tablets". Powder technology 2002; p: 122,188-198.

47. Kaushik D, Saini TR and Dureja H "Development of melt in mouth tablets by sublimation technique"Journal of ph anna ceutica I research vol- 3, No- 2, 2004; p: 04: 35-37.

48. Madgulkar AR, Bhalekar MR, Joshi VS, Wable N. "Comparative study of efficiency of Indion 414 and Amberlite IRP 88 as super disintegrants in mouth dissolve tablets:. Ind Drugs 2007; p: 44(6):455-7

49. Malke S, Shidaye S, Kadam VJ." Formulation and evaluation of oxcarbazepine fast dissolve tablets". Ind J Pharm Sci 2007; p: 69(2):211-4.

50. Shirsand SB, Sarasija S. "Design and evaluation of fast dissolving tablets of clonazepam". Ind J Pharm Sci 2008; p: 70(6):788-91

51. Mulla JA, Dasankoppa FS, Vilas GJ, Sholapur HP. "Fast dissolving tablets of promethazine: A novel oral formulation for the treatment of fractionated radiotherapy induced nausea and emesis". Ind Drugs 2008; p: 45(4):314-7.

52. Patel B, Patel D, Patel C. "Development and in-vitro evaluation of fast dissolving tablets of glipizide". Int J Pharm Sci Nov-Dec 2009; p: 1(1):145-50.

53. Jain CP, Naruka PS. "Formulation and evaluation of fast dissolving tablets of valsartan". Int J Pharmacy Pharm Sci Jul-Sep 2009; p:1(1):219-26.

54. Rangasamy M. Ayyasamy B. "Design and evaluation of fast dissolving tablet of terbutaline

sulphate". Asian J Pharm Jul-Sep 2009; p: 215-7.

55. Manivannan Rangasamy, Balasubramaniam Ayyasamy, Senthil Kumar Raju, Sandeep Gummadevelly. Design and evaluation of the fast dissolving tablet of terbutaline sulfate. Asian Journal of Pharmaceutics; 2009; p: 07:215-217.

56. Bhalerao AV, Deshkar SS, Shirolkar SV, Gharge VG, and Deshpande AD. Development and evaluation of clonazepam fast disintegrating tablets using superdisintegrants. Research Journal Of Pharmacy and Technology.2 (2): 2009; p: 04: 375 - 377.

57. Ashish masish, Amar Kumar, Shivan singh, Ajay kumar tiwari "Fast dissolving tablets: A Review" Vol 9, Issue 2, 2017, *23 Jan 2017*.

58. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021001s008s009lbl.pdf

59. Raymond C. Rowe, Paul J. Sheskey and Paul J. Weller, "Handbook of Pharmaceutical Excipients", 4th ed, The pharmaceutical press, London, 2003; p: 373- 377.

60. Raymond C. Rowe, Paul J. Sheskey and Paul J. Weller, "Handbook of Pharmaceutical Excipients", 4th ed, The pharmaceutical press, London,2003; p: 581- 583.

61. Raymond C. Rowe, Paul J. Sheskey and Paul J. Weller, "Handbook of Pharmaceutical Excipients", 4th ed, The pharmaceutical press, London, 2003; p: 181-183.

62. Raymond C. Rowe, Paul J. Sheskey and Paul J. Weller, "Handbook of Pharmaceutical Excipients", 4th ed, The pharmaceutical press, London, 2003; p: 184-185.

63. Raymond C. Rowe, Paul J. Sheskey and Paul J. Weller, "Handbook of Pharmaceutical Excipients", 4th ed, The pharmaceutical press, London, 2003; p: 354-355.

64. Raymond C. Rowe, Paul J. Sheskey and Paul J. Weller, "Handbook of Pharmaceutical Excipients", 4th ed, The pharmaceutical press, London, 2003; p: 161-163.

65. Indian pharmacopoeia 2007, volume – 1:477-480.

66. CVS Subramanyam., "Micromeritics in Text Book of Physical Pharmaceutics" 2nd edition, Vallabh Prakashan Publishers, 2003; p: 215, 226-227, 222-224

67. Leon Lachman., Herbert A. Lieberman., Joseph L. Kang., Tablets in., "The theory and practice of Industrial Pharmacy", 3 rd edition, 1987; p: 299, 300.

68. Korsmeyer R.W., Gurny R. Peppas, "Mechanism of solute release from porous hydrophilic polymers", *In.J Pharm.*, 1983, Page: 25-35.

69.Higuchi.T, "Mechanism of sustained action medication: Theoretical analysis of rate of release of solid drug dispersed in solid matrix", *J Pharm Sci.*, 1963, Page: 1145-149.

70. Kadivar A,Kamalidehgan B,Javar HA,Davoudi ET,Zaharuddin ND,Sabeti b,et al.Formulation ond in vitro ,in vivo evaluation of effervescent floating sustained release Imatinib mesylate tablet.2015;10(6)