FORMULATION AND *IN-VITRO* EVALUATION OF ORALLY ADMINISTERED GASTRO-RETENTIVE FLOATING TABLETS OF IMATINIB

Dissertation submitted to

THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY

Chennai - 600032

In partial fulfilment of the requirements for the award of the Degree of

MASTER OF PHARMACY
In

PHARMACEUTICS

Submitted by

SUJITKUMAR SAJJA

(Register No: 26114515)

Under the Guidance of

Mrs.RAJARAJESWARI HARIHARAN, M.pharm.,

PROFESSOR

DEPARTMENT OF PHARMACEUTICS

K.K. COLLEGE OF PHARMACY

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PRINCIPAL

Prof. A.MEENA, M.Pharm, (Ph.D),

K.K. COLLEGE OF PHARMACY,

CHENNAI – 600122.

DIRECTOR

Prof. Dr. V. VAIDHYALINGAM, M.Pharm., Ph.D.,

K.K. COLLEGE OF PHARMACY,

CHENNAI – 600122.

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HEAD OF DEPARTMENT
Prof. Dr. K. SENTHIL KUMARAN, M.Pharm.,Ph.D.,

DEPARTMENT OF PHARMACEUTICS,

K.K. COLLEGE OF PHARMACY,
CHENNAI .600 122.

CERTIFICATE

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GUIDE

Mrs. RAJARAJESWARI HARIHARAN, M.pharm.,

PROFESSOR,

K.K. COLLEGE OF PHARMACY,

CHENNAI-600122.

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The completion of this dissertation is not only fulfilment of my dreams but also the dreams of my parents who have taken a lot of pain for me in completion of higher studies successfully , whose full hearted co-operation , love and moral support encouraged me to finish the course successfully.

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Place: *Sujitkumar Sajja*

Date:

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LIST OF ABBREVIATIONS

GIT	: Gastro Intestinal Tract
CR-GRDF	: Controlled Release Gastro-retentive Dosage Form
GRT	: Gastric Residence Time
CYP	: Cytochrome P
CR	: Controlled Release
CML	: Chronic Mylogenous Leukemia
GISTs	: Gastro Intestinal Stromal Tumors
HPMC	: Hydroxy Propyl Methyl Cellulose
SBC	: Sodium Bi Carbonate
MCC	: Micro Crystalline Cellulose
HBS	: Hydro Dynamically Balanced
FDDS	: Floating Drug Delivery Systems
MMC	: Migrating Myoelectric Complex
KSI	: Kilo Pounds Per Square Inch
DLI	: Donor Lymphocyte Infusion
ICCs	: Interstitial Cells of Cajal
CT	: Computed Tomography
MRI	: Magnetic Resonance Imaging
PET	: Positron Emission Tomography
TK	: Tyrosine Kinase
PDGF-R	: Platelet-Derived Growth Factor Receptor
NCC	: No Characteristic Change

μg/ml : Micro Gram per Mili Liter

Hcl : Hydro Chloric Acid

BP : British Pharmacopeia

USP : United States Pharmacopeia

Ph Eur : European Pharmacopoeia

JP : Japanese Pharmacopoeia

FTIR : Fourier Transform Infra Red

UV : Ultra Violet

INTRODUCTION

ORAL DRUG DELIVERY[1]

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for systemic effects. In addition oral medication is the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations mainly because of patient acceptance, convenience in administration and cost effective manufacturing process. For many drug substances, conventional immediate release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with an acceptable level of safety to the patient.

Based on desired therapeutic objectives, oral drug delivery systems may be assorted into three categories:

- Immediate- release preparations
- Controlled- release preparations
- Targeted- release preparations

Immediate release preparations

These preparations are primarily intended to achieve faster onset of action for drugs such as analgesics, antipyretics, and coronary vasodilators. Other advantages include enhanced oral bioavailability through transmucosal drug delivery and pregastric absorption, convenience in administration to dysphasic patients, especially the elderly and bedridden and new business opportunities.

Controlled release preparations

The currently employed CR technologies for oral drug delivery are diffusion- controlled systems; solvent activated systems and chemically controlled systems. Diffusion controlled systems include monolithic and reservoir devices in which diffusion of the drug is the rate limiting step through a polymer matrix or a polymeric membrane respectively. Solvent activated systems may be either osmotically controlled or controlled by polymer swelling. Chemically controlled systems release drugs via polymeric degradation (surface or bulk

matrix erosion) or cleavage of drug from polymer chain. It is worth mentioning here that so called programmed release (tailored release) profile of a final CR product is rarely the outcome of a single pharmaceutical principle. Depending upon physicochemical properties of the drug in question and desired therapeutic objectives different formulations and CR principles may be proportionally combined within the same dosage form. This task appears to be simpler when realized in terms of appropriate selection of polymers and excipients that incorporate different principles.

Targeted release preparations

Site specific oral drug delivery requires special placement of drug delivery device at a desired site within the GI tract. Although it is virtually possible to localize a device within each part of GI tract, the attainment of site specific delivery in the oral cavity and the rectum is relatively easier than in the stomach and the small and large intestines. The later requires consideration of both longitudinal and transverse aspects of GI constraints. Some of the potential CR and site specific DDSs will be described.

TABLETS[2]

Tablets are solid dosage forms consisting of one or more active ingredient were compressed into various shapes and sizes. Tablet is the most popular among all dosage forms existing today because of its convenience of self-administration, compactness and easy manufacturing; however in many cases immediate onset of action is required than conventional therapy. To overcome these drawbacks, immediate release pharmaceutical dosage form has emerged as alternative oral dosage forms. The immediate release tablets are prepared by using super disintigrants like Cross linked Carboxymethylcellulose (Croscarmellose), Sodium starch glycolate (Primogel, Explotab), Polyvinylpyrrolidone (Polyplasdone) etc. which provide instantaneous disintegration of tablet after administration**.**

Advantages of tablets

- They provide an accurately measured dose and low content variability of the unit dose.
- They are of low manufacturing cost.
- They are easy to package and ship.

- They are simple to identify.
- Manufacturing processes and techniques provide tablets certain special release products such as enteric and delayed release products

Disadvantages of tablets

- Some drugs may cause local irritation effect harmful to gastro intestinal mucosa.
- Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low-density character.
- Bitter tasting drugs, drug with obnoxious odor or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation / entrapment prior to compression.

TYPES OF TABLETS

Oral tablets for ingestion:

These tablets are meant to be swallowed intact along with a sufficient quantity of potable water. Exception is chewable tablet. Over 90% of the tablets manufactured today are ingested orally. This shows that this class of formulation is the most popular worldwide and the major attention of the researcher is towards this direction.

- Standard compressed tablets
- Multiple compressed tablets
- Compression coated tablet
- Layered tablet
- Inlay tablet
- Modified Release tablet
- Delayed action tablet
- Targeted tablet
- Floating tablet
- Colon targeting tablet
- Chewable tablet
- Dispersible tablet
- Immediate release tablet

Tablets used in the oral cavity

These tablets are aimed release API in oral cavity or to provide local action in this region. The tablets under this category avoids first-pass metabolism, decomposition in gastric environment, nauseatic sensations and gives rapid onset of action. The tablets formulated for this region are designed to fit in proper region of oral cavity.

- Lozenges and troches
- Sublingual tablet
- Buccal tablet
- Dental cones
- Mouth dissolved tablet

Tablets administered by other routes

These tablets are administered by other route except for the oral cavity and so the drugs are avoided from passing through gastro intestinal tract. These tablets may be inserted into other body cavities or directly placed below the skin to be absorbed into systemic circulation from the site of application.

- Vaginal tablet
- Implants

Tablets used to prepare solution

The tablets under this category are required to be dissolved first in water or other solvents before administration or application. This solution may be for ingestion or parenteral application or for topical use depending upon type of medicament used.

- Effervescent tablet
- Hypodermic tablet
- Soluble tablet

ADDITIVES[3]

DILUENTS:

Diluents are substances to increase bulk and convert in the compressible form, when drug material is potent or inadequate to provide a suitable shape and size to tablet.

A tablet diluent must be compatible, inert, economic, easily available and organoleptically acceptable, should not affect the bioavailability of a drug adversely.

Examples of tablet diluents include dibasic calcium phosphate, calcium sulphate, lactose, lactose anhydrous, lactose spray dried, mannitol, sorbitol, sucrose, dextrose etc.

Examples of directly compressible diluents include Sta-Rx-1500, Emdex (contains dextrose 90 to 92%, a maltose 3 to 5%), Celutab (dextrose & maltose), Avicel (Microcrystalline cellulose), Di-C (Dicalcium phosphate dihydrate), Cab-O-Sil (Colloidal silica).

BINDERS and ADHESIVE:

These materials are used in dry or liquid form to reduce the amorphous nature of substance and convert into compressible form (wet granulation). Example include acacia, tragacanth, gelatin, alginates, methylcellulose, hydroxypropyl- methylcellulose, hydroxypropylcellulose, PVP, Starch, sorbiol, ethylcellulose, pregelatinized starch, glucose, iris moss, ghatti gum, arabogalactan, waxes, etc.

DISINTEGRENT:

Most of the tablets contain disintegrating agent. Disintegrating agents facilitate the disintegration of the tablet in small particles in the gastrointestinal tract. Breaking of tablet' based on the swell ability, adsorption of water or chemical reaction.

Examples include soluble starch, pre-gelatinized starch (PGS), veegum HV, bentonite, microcrystalline cellulose, sodium carboxy methylcellulose, PVP, guar gum, Isapgul, primogel, explotab, aerosil, natural spon citrus pulp, Alginic acid and alginates, Ion exchange resin, magnesium aluminium silicat modified corn starch, sodium dodecyl sulphate, sodium starch glycollate, etc.

SUPER DISINTEGRENTS:

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 days pass, demand for faster disintegrating formulation is increased. So, pharmacist needs to formulate better disintegrants i.e. Superdisintegrants which are effective at low concentration and have greater disintegrating efficiency and they are more effective intragranularly. And these 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 types of commonly used superdisintegrants are

- Modified Starches- Sodium Carboxymethyl Starch (Sodium Starch Glycolate)
- Cross-linked Polyvinylpyrrolidone (Crospovidone)
- Modified Cellulose (Croscarmellose sodium)
- Soy polysaccharide
- Cross-linked alginic acid
- Gellan gum
- Xanthan gum
- Calcium Silicate

GLIDANTS:

Glidants act as a flow promoter and reduce the friction between particles. It improves the flow properties of granules or powder through hopper to die. It is not deformed compression pressure of the tablet machine. Examples include talc, starch, magnesium stearate, calcium stearate, boric acid, sugar, lycopodium and sodium chloride.

LUBRICANTS:

Lubricants reduce inter-particular friction. It improves the ejection of tablet from die wall and reduces the sticking problems and smooth tablets are produced. Examples include Talc, magnesium stearate, calcium stearate, stearic acid, polyethylene glycols, starch derivative

ANTI-ADHESIVES or ANTI-STICKING AGENTS:

These materials are used to reduce the adhesion of the tablet surface to dies and punches during the compression of tablets. The pressure of the machine deforms these materials. It reduces sticking, picking and chipping problems. Examples include paraffin, stearic acid, cocoa butter, soaps, starch derivatives.

COLORING AGENTS:

Colors are selected from 'permitted' list and are added to promote elegance and also to mask differences in color or speckling when either the drug or an additive is off white.

Pastel shades are commonly used as these shades help in achieving uniform color distribution. Coloring materials or dyes are used in tablet formulation mainly for three purposes; disguising of off color drugs, product identification and production of more elegant products. Colors may be added either to the vehicle used for granulation or to the mixture of powders prior to granulation.

The first approach is known to give better results provided migration of dye to the top of granules along with solvent during drying does not occur. When wet granulation is not to be employed, lake dyes (dyes adsorbed on alumina or aluminium hydroxide) are recommended.

Fading of the color on standing and exposure to light leading to mottling of tablets is the common problem with dyes. Examples include water soluble dyes and many other FD&C approved colors or dyes.

FLAVORING AGENTS:

These substances are not necessary for the formulation of compressed tablets. The proportion of flavors should generally be limited to 0.5% because excessive amounts may interfere with the free flow or cohesion of the granules. Special tablets require flavoring agents such as chewable tablet, lozenges, etc. Examples include flavoring oils like cinnamon, coriander, and caraway etc.

SWEETENERS:

Chewable tablets have sweetening agents because such tablets remain in the mouth and are not swallowed. Examples include saccharin sodium, aspartame, sugar, etc

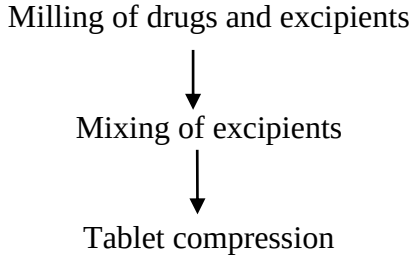
MANUFACTURING METHOD[4]

Pharmaceutical products are processed all over the world using the direct compressing, wet granulation or dry granulation methods. Method is chosen depend on the ingredients individual characteristics like flow property, compressibility. Choosing a method requires thorough investigation of each ingredient in the formula, the combination of ingredients, and how they work with each other. Then the proper granulation process can be applied.

DIRECT COMPRESSION

Direct compression name implies compressing tablets directly from powdered materials without modifying the physical nature of the materials itself. Direct compression is generally done for the crystalline materials having good physical properties required for formation of good tablets. Main advantage of direct compression is it saves time when compared to other methods of compression like wet granulation.

Main Steps Involved in the direct compression method



FACTORS TO BE CONSIDERED FOR DIRECTLY COMPRESSIBLE EXCIPIENTS

FLOWABILITY

Press speed requires powders to be very fluid, a property commonly referred to as product flowability. Good flow characteristics are necessary because the mechanical action of the tablet press requires a volume of fill and this volume of fill represents the actual tablet weight. Thus the powders in the formula must possess a consistent particle-size distribution and density to attain proper flow and achieve volume of fill.

COMPRESSIBILITY

Compressing a tablet of different powders that have varying physical characteristics can be difficult. If the formula has some of both characteristics large particles with high moisture content and small dry particles then the tablet may or may not compress well and probably will have difficulty holding together.

Directly compressible materials are pre-processed or are found naturally in the granular state. The reduced number of processing steps required by directly compressible materials allows for less equipment and shorter process times in comparison with wet- or dry-granulation processes.

WET GRANULATION

Most widely used and most general method of tablet preparation is by wet granulation method. Wet granulation forms the granules by binding the powders together with an adhesion instead of by compaction. The wet granulation technique is done by adding a solute, suspension or slurry containing binder this can be aqueous or non-aqueous which is added to the dry mix powder. In general the mass should be moist rather than wet or paste merely. The

surface tension forces and capillary pressure are primarily responsible for initial granules formation. The main advantage is it meets the all requirements for tablet formation and main disadvantage is it requires many steps in process, which is time consuming.

Main Steps Involved in the Wet granulation method

Sifting of Drugs and Excipients

↓

Mixing of Milled Powders

↓

Preparation of Binder Solution

↓

Mixing of Binder Solution with powder mixer to form wet mass

↓

Drying of Moist Granules

↓

Screening Dry Granules, Lubricant and Disintegrants

↓

Mixing of Screened Granules with Disintegrants and lubricant

↓

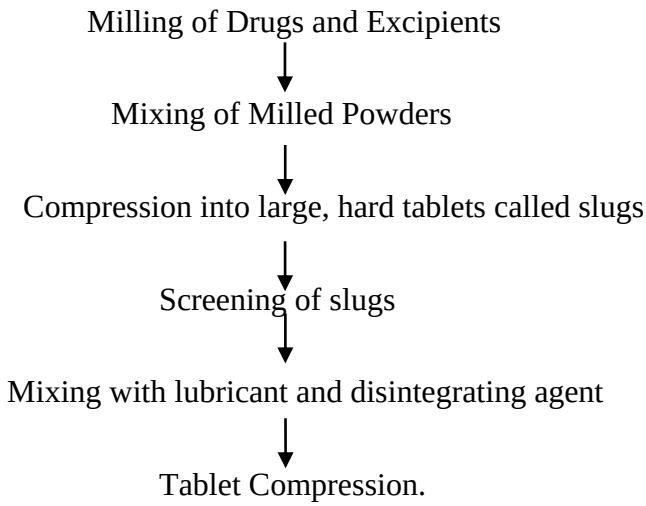
Tablet compression

DRY GRANULATION

The dry granulation process is used to form granules without using a liquid solution. This type of process is recommended for products, which are sensitive to moisture and heat. Forming granules without moisture requires compacting and densifying the powders. Dry granulation can be done on a tablet press using slugging tooling. On large-scale roller compactor commonly referred to as a chilsonator. The compacted mass is called slugs and the process is known as slugging. The slugs are then screened or milled to produce a granular form of tablet materials, which have the good flow properties than original powder mixture.

The main advantage of dry granulation is it requires less equipment and eliminates the addition of moisture and the application of heat, as found in wet massing and drying steps of the wet granulation method

Main Steps Involved in the Dry granulation method



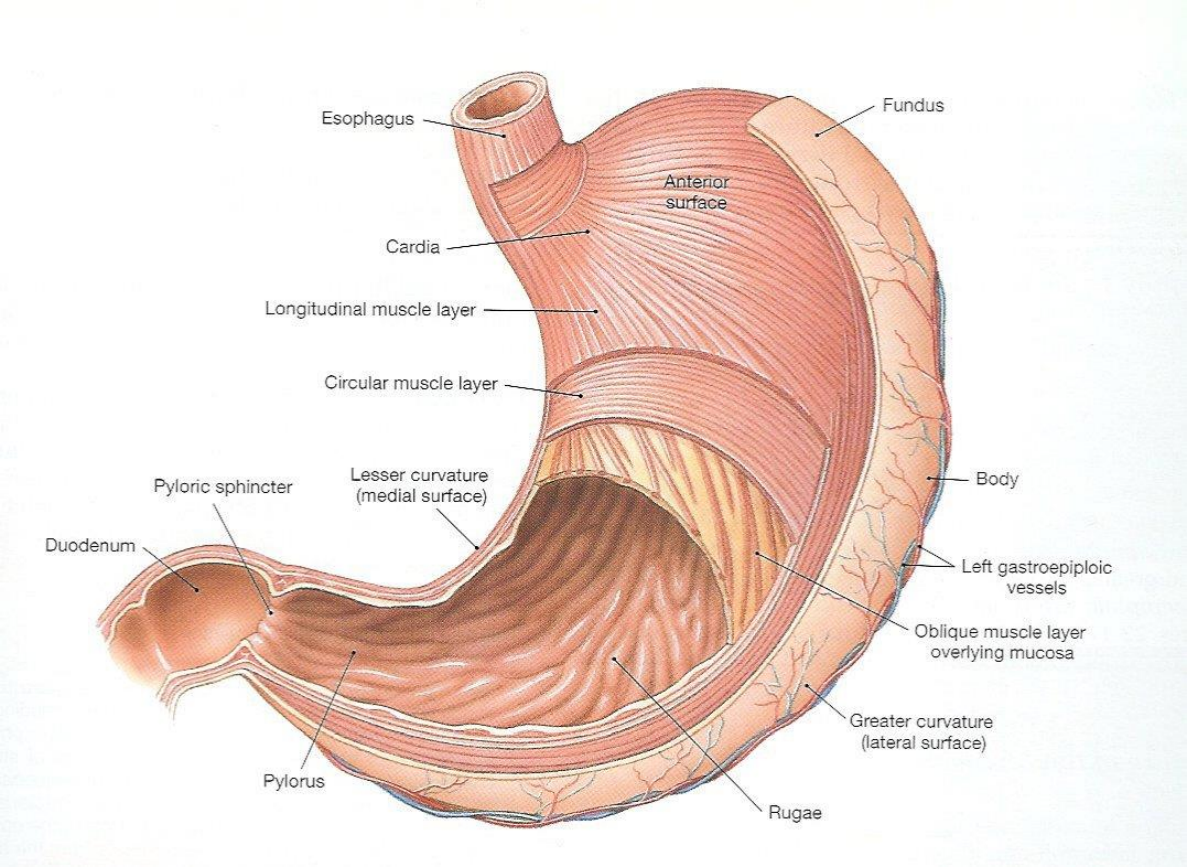
Gastroretentive drug delivery systems [5-14.]

Controlled release (CR) dosage forms have been extensively used to improve therapy with several important drugs. However, the development processes are faced with several physiological difficulties such as the inability to restrain and localize the system within the desired region of the gastrointestinal tract and the highly variable nature of the gastric emptying process. This variability may lead to unpredictable bioavailability and time to achieve peak plasma level. On the other hand, incorporation of the drug in a controlled release gastroretentive forms (CR-GRDF) which can remain in the gastric region for several hours would significantly prolong the gastric residence time of drugs and improve bioavailability, reduce drug waste, and enhance the solubility of drugs that are less soluble in high pH environment. Gastroretention would also facilitate local drug delivery to the stomach and proximal small intestine. Thus, gastroretention could help to provide greater availability of new products and consequently improved therapeutic activity and substantial benefits to patients

BASIC GASTROINTESTINAL TRACT PHYSIOLOGY

Stomach has mainly 4 main regions: The cardia, fundus, body and pylorus. The cardia surrounds the superior opening of the stomach. Pylorus has 2 main parts:- pyloric antrum which connects body of the stomach and the pyloric canal leads to duodenum. Body is the large central portion of the stomach which is inferior to the fundus. Body acts as reservoir for

Fig 1: Anatomy of stomach



undigested material, whereas the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions.

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states.The fasted state is associated with some cyclic contractile events commonly known as migrating myoelectric complex (MMC) which cycle both through stomach and intestine every 2 to 3hours. Apparently there are four consecutive phases of activity in the MMC.

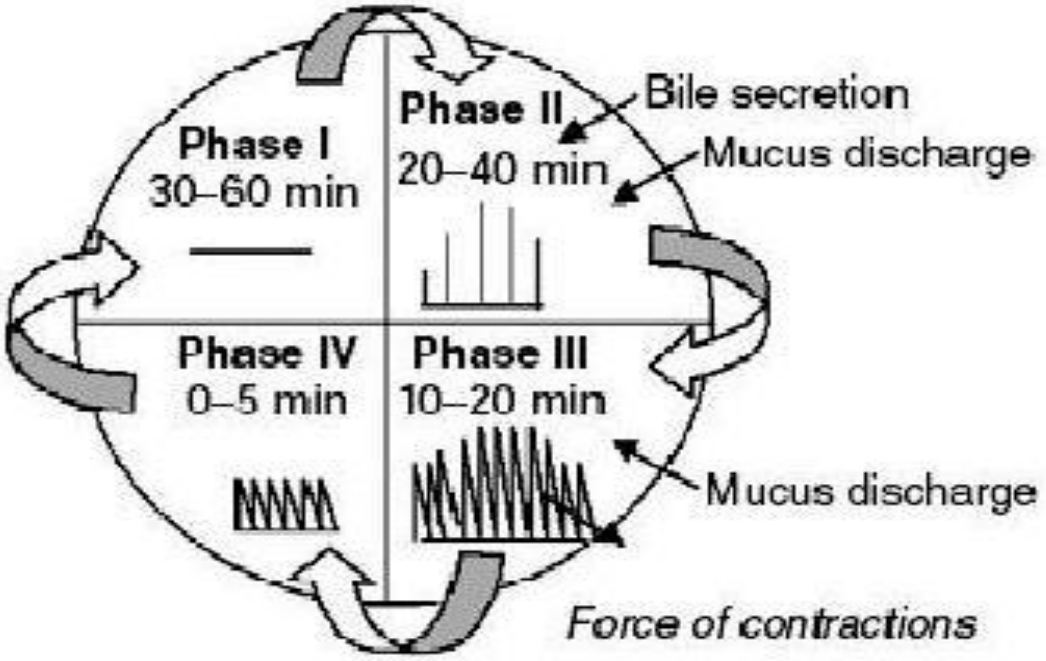
Phase-I (basal phase): It is a quiescent period lasting from 30 to 60min with no contractions.

Phase-II (preburst phase): It consists of intermittent contractions that gradually increase in intensity as the phase progresses, and lasts about 20-40min. Gastric discharge of fluid and very small particles begins later in this phase.

Phase-III (burst phase): This is a short period of intense distal and proximal gastric contractions (4-5 contractions per minute) lasting about 10-20minutes. These contractions also known as “house keeper waves” sweep gastric contents down the small intestine.

Phase-IV: This is a short transitory period of about 0-5minutes, and the contractions dissipate between the last part of phase-III and phase-I

Fig 2: Schematic representation of inter digestive motility pattern



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The different phases originating in the foregut continue to the terminal ileum, another begins in the stomach and duodenum. Liquid components easily pass through the partially constricted sphincter. On the contrary, the large undigested materials are retained by an "antral-seieving" process and are retropulsed into the body of stomach and remain in the fed state. In the fed state, gastric contractions move the contents towards the antrum and the pyloric sphincter.

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in the phase-II of fasted state. These contractions results in reducing the size of food particles (to less than 1mm) which are propelled towards the pylorus in a suspension form. During the fed, state onset of MMC is delayed resulting in slow down of gastric emptying rate.

APPROACHES TO PROLONG GASTRIC RESIDENCE TIME

The need for gastroretentive dosage forms (GRDFs) has led to extensive efforts in both academia and industry towards the development of such drug delivery systems.

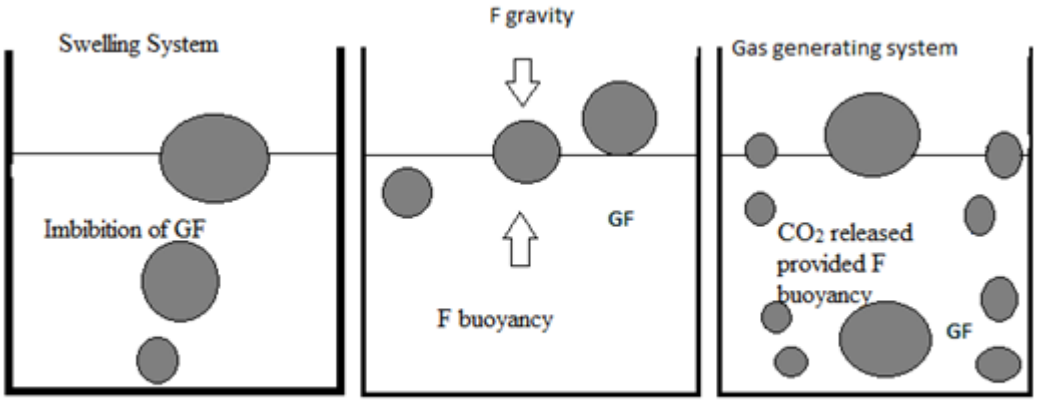
These efforts resulted in GRDFs that were designed in large part, based on the following approaches.

1. Floating drug delivery systems
2. High density systems
3. Bioadhesion to stomach mucosa
4. Slowed motility of gastrointestinal tract by concomitant administration of drugs or pharmaceutical excipients
5. Expansion by swelling or unfolding to a large size which limits emptying of dosage form through the pyloric sphincter

FLOATING DRUG DELIVERY SYSTEMS

Floating drug delivery systems have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time while the system is floating on the gastric contents the drug is released slowly at the desired rate from the system. This results in increased GRT and better control of fluctuations in plasma drug concentration.

Fig 3: Mechanism of Floating System



Mechanism of floating system, GF = Gastric fluid

1. SINGLE UNIT FLOATING DOSAGE FORM

a. Non-effervescent systems: The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene., which swells in contact with gastric fluids after oral administration and maintains a relatve integrity of shape, bulk density of less than unity. The air entrapped by the swollen polymer confers buoyancy to these dosage forms.

i. Colloidal gel barrier system: This system incorporates a high level (20-75%w/w) of one or more gel-forming, highly swellable, cellulose type hydrocolloids (e.g. Hydroxy ethyl cellulose, hydroxy propyl cellulose, hydroxy propyl methyl cellulose , sodium carboxymethyl cellulose) polysaccharides and matrix forming polymers such as polycarbophil, polyacrylates and polystyrene, incorporated either in tablets or in capsules. When coming in contact with gastric fluid, the hydrocolloid in the system hydrates and form colloidal gel barrier around its surface. This gel-barrier control the rate of fluid penetration into the device and consequent release of the drug. As the exterior surface of the dosage form goes into the solution, the gel layer is maintained by the adjacent hydrocolloid layer becoming hydrated. The air trapped in by the swollen polymer maintains a density less than unity and confers buoyancy to these dosage forms.

The HBS must comply with 3 major criteria:

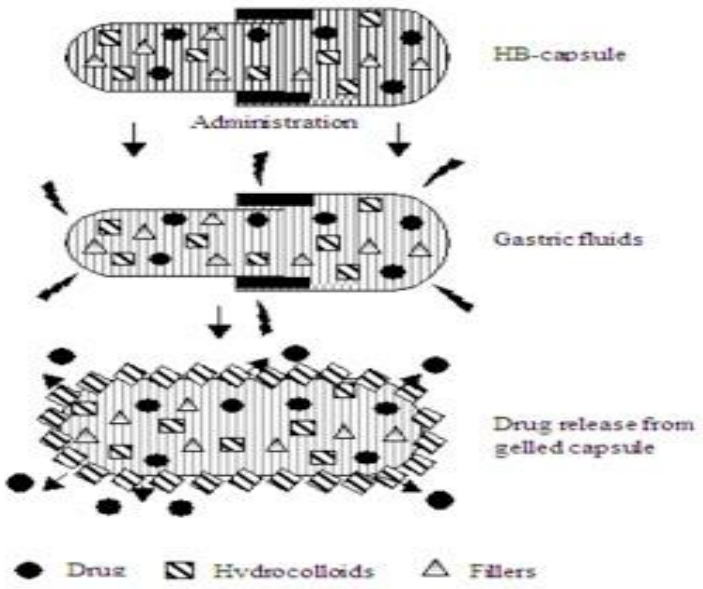
1) It must have sufficient structure to form a cohesive gel barrier

2) It must maintain an overall specific density lower than that of gastric contents

3) It should dissolve slowly enough to serve as a reservoir for the delivery system.

A bilayer tablet can also be prepared to contain one immediate-release and sustained release layer. Immediate-release layer delivers the initial dose, whereas SR layer absorbs gastric fluid and forms a colloidal gel barrier on its surface. This results in a system with bulk density lesser than that of the gastric fluid, and allows it to remain buoyant in stomach for an extended period of time.

Fig 4: Working principle of hydro dynamically balanced systems

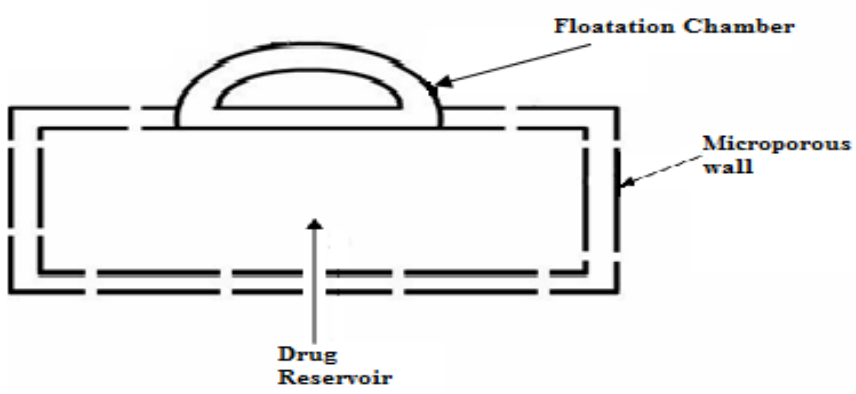


ii. Microporous compartment system: This technology is based on the encapsulation of a drug reservoir inside a microporous compartment with apertures along its top and bottom walls. The peripheral wall of the drug reservoir compartment is completely sealed to prevent any direct contact of gastric mucosal surface with the un-dissolved drug. In stomach, the floatation chamber containing entrapped air causes the delivery system to float over the apertures, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

b. Effervescent systems: A drug delivery system can be made to float in the stomach by incorporating a floating chamber, which may be filled with vaccum, air or inert gas. The gas in the floating chamber can be introduced either by the volatilization of an organic solvent or by the effervescent reaction between organic acids and bicarbonate salts.

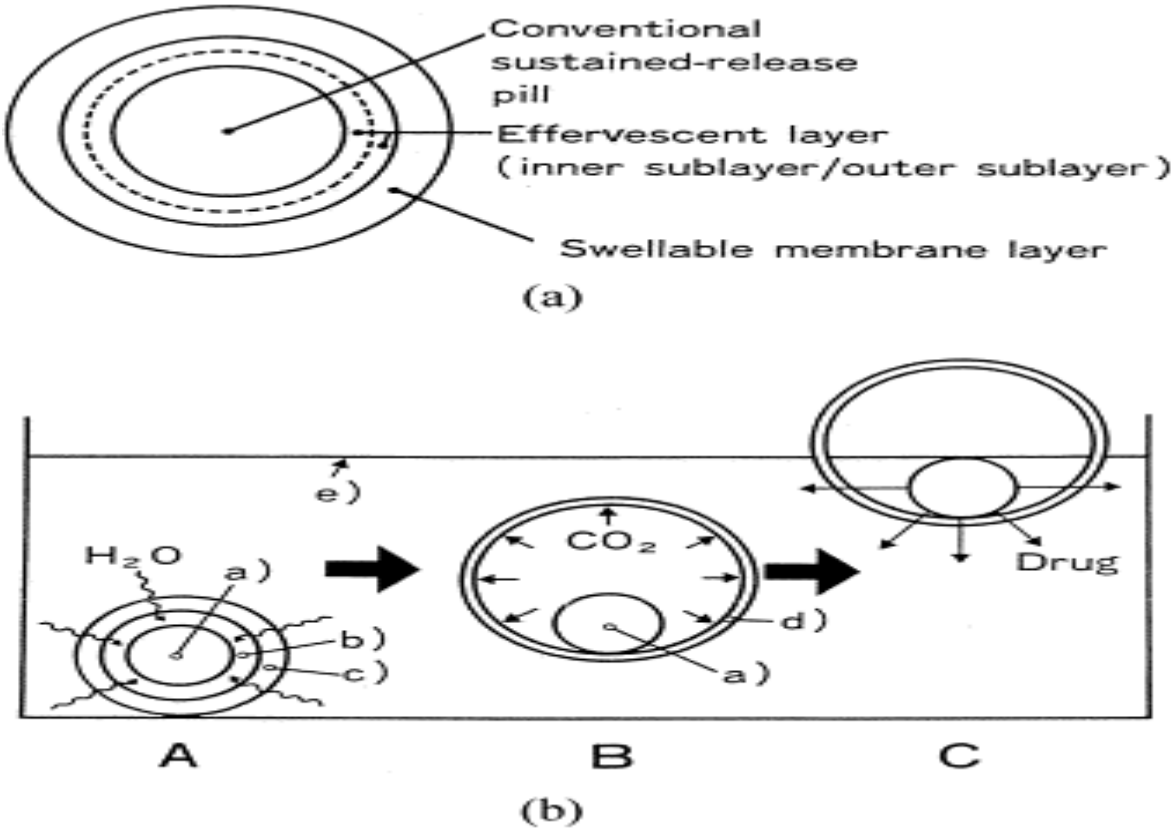
i. Volatile liquid containing systems: The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber which contains a liquid e.g. ether, cyclopentane that gasifies at body temperature to cause the inflatation of the chamber in the stomach. These devices are osmotically controlled floating systems containing a hollow deformable unit that can convert from a collapsed to an expanded position and returns to collapsed position after an extended period. The deformable system consists of two chambers separated by an impermeable, pressure-responsive, movable bladder. The first chamber contains the volatile liquid. The device inflates and the drug is continuously released from the reservoir into the gastric fluid. The device may also consists of a bioerodible plug made up of PVA, polyethylene etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit spontaneous ejection of the inflatable system from the stomach

Fig 5: Intra gastric floating gastrointestinal drug delivery device



ii. Gas-generating systems : These buoyant systems use matrices prepared with swellable polymers like HPMC, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid, tartaric acid, Di-sodium glycine carbonate, citroglycine etc. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. Effervescent reaction between bicarbonate salts and citric acid/tartaric acid liberates CO2,which gets entrapped in the gellified hydrocolloid layer of the system, thus decreasing its specific gravity and making it to float over chyme. These tablets may be either single layered wherein the carbondioxide generating components are intimately mixed within the tablet matrix, or they may be bilayered in which the gas generating components are compressed in hydrocolloid containing layer and the drug in other layer formulated for a SR effect.

Fig 6: Schematic representation of floating pill, (a) The penetration of water into effervescent layer leads to a Co_2 generation and makes the system to float. (b)
A)Penetration of water into the device; B) generation of carbon dioxide and floating; C) dissolution of the drug. Where, a) Conventional sustained release core; b) effervescent layer; c) swellable layer; d) expanded swellable membrane layer; e) water surface in the beaker



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2. MULTIPLE UNIT FLOATING DOSAGE FORM

a. Non-effervescent system

i. Alginate beads: Spherical beads of approximately 2.5mm in diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium alginate. The beads are then separated, snap frozen in liquid nitrogen and freeze-dried at -400C for 24 hours, leading to the formation of a porous system, which can maintain a floating force for 12 hours.

ii. **Hollow microspheres:** Hollow microspheres are considered as one of the most promising buoyant systems as they possess the unique advantages of multiple unit systems as well as better floating properties, because of the central hollow space inside the microsphere. The general techniques involved in their preparation include simple solvent evaporation and solvent diffusion and evaporation. Polymers such as polycarbonate, eudragit S and cellulose acetate are used in the preparation of hollow microspheres and the drug release can be modified by optimizing the amount of polymer-plasticizer ratio. Hollow microspheres floated with drug in their outer polymer shelf can also be prepared by a novel emulsion solvent-diffusion method. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of poly vinyl alcohol that was thermally controlled at 400C. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed an internal cavity in the microsphere of the polymer with drug. The micro balloon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12 hours.

b. Gas-generating systems: Multi unit types of floating pills, which generate CO2 have also been developed. The system consists of a SR pill as seed, surrounded by double layers. The inner layer is an effervescent layer containing sodium bicarbonate and tartaric acid. When the system is immersed in buffer solution at 37^0**C** swollen pills, like balloons are formed having density less than 1g/ml. This occurs due to CO2 neutralization of the inner effervescent layer with the diffusion of water through the outer swellable membrane layer. These kinds of systems float completely within 10min and remain floating over extended periods of 5-6 hours.

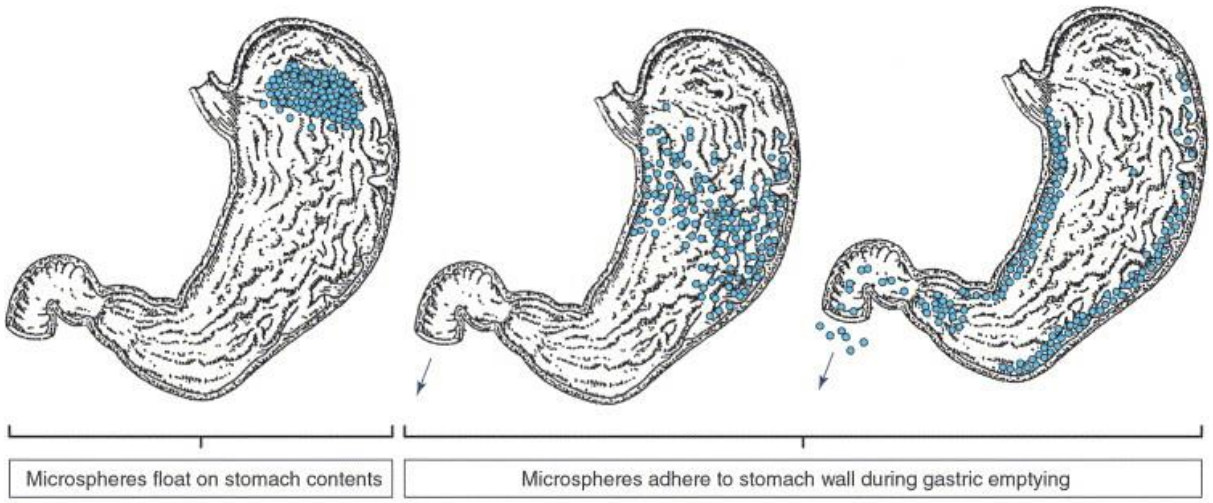
c. Ion-exchange resin system: The system consisted of resin beads, which were loaded with the bicarbonate and a negatively charged drug that was bound to the resin. The resultant beads were then encapsulated in a semipermeable membrane to overcome rapid loss of CO2. Upon arrival in the acidic environment of stomach, an exchange of chloride and bicarbonate ions took place. As a result of this reaction, carbon dioxide was released and trapped in the

membrane, thereby carrying beads towards the top of gastric contents and producing a floating layer of resin beads.

Bio/Mucoadhesive systems:

Bioadhesive drug delivery systems (BDDS) are useful as a delivery device within the lumen to enhance drug absorption in a site-specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. Gastric mucoadhesion does not tend to be strong enough to impart the dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production of mucous that is lost through peristaltic contractions and the dilution of the stomach contents also seem to limit the potential of mucoadhesion as a gastroretentive force. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan and gliadin etc. The adhesion of the polymers with the mucous membrane may be mediated by hydration, bonding or receptor mediated.

Fig 7: Bio- Adhesion of microspheres.



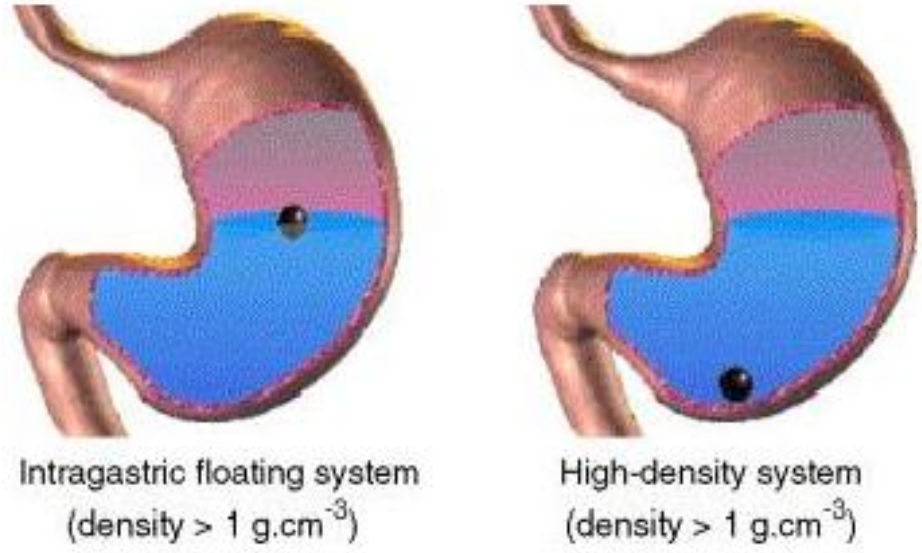
Swelling systems:

Swelling systems are also referred to as plug type systems. The presence of polymers in the systems promotes their swelling to a size that prevents their passage through pyloric sphincter resulting in prolonged GRT. However, a balance between the rate and extent of swelling and the rate of erosion of the polymer is crucial to achieve optimum benefits and to avoid unwanted side effect

High density system:

This approach involves formulation of dosage forms with the density that must exceed density of normal stomach content (1.004g/cm3). These formulations are prepared by coating drug on a heavy core or mixed with heavy inert materials such as iron powder, zinc oxide, titanium dioxide or barium sulphate. These resultant pellets can be coated with diffusion controlled membrane. These systems with a density of about 3g/cm3 are retained in the rugae of the stomach and are capable of withstanding its peristalitic movements. 2.6-2.8g/cm3 acts as a threshold density after which such systems can be retained in the lower part of the stomach.

Fig 8: High density and Low density systems



Expansive gastroretentive dosage form

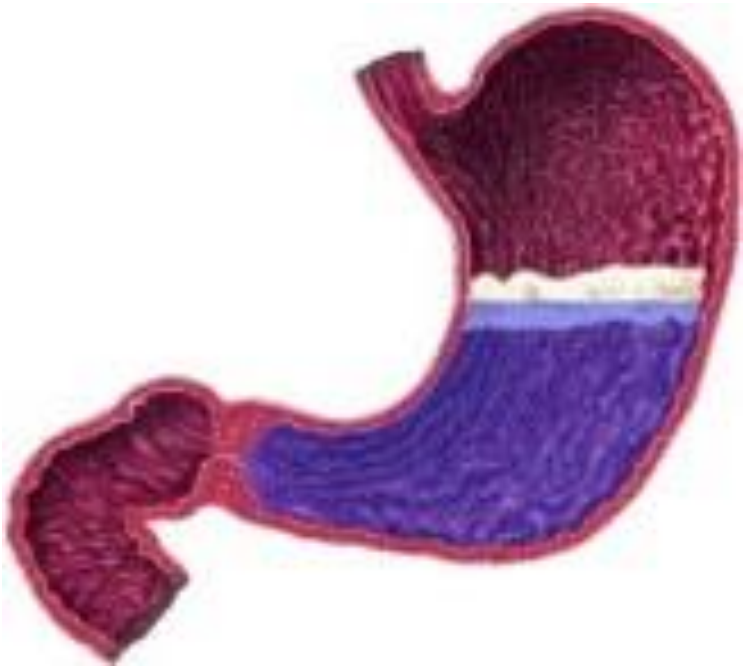
This is a class of gastroretentive systems capable of expanding in stomach. The expanded structure is trapped in stomach for prolonged period leading to sustained drug release and subsequent controlled absorption in stomach and intestine. These systems are administered perorally in the form of capsule bearing the dosage form in folded and compact configuration. When exposed to gastric environment capsule shell breaks and the dosage form attains its expanded structure, which is retained in stomach for longer time. The serous drawback of this system is clogging of pylorus end of stomach.

Raft forming systems:

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections a

nd other disorders. The mechanism involved in the raft formation includes the formation of a viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of the low bulk density created by the formation of CO_2. Usually, the system contains a gel forming agents and alkaline bicarbonates or carbonates responsible for the formation of CO_2 to make the system less dense and able to float on the gastric fluids. This floating rafts impedes the reflux of acids and food by acting as a physical barrier. The raft has a pH value higher than that of the stomach contents so that in the event of gastric reflux, the wall of the esophagus is not subjected to irritation by Hcl.

Fig 9: Schematic Illustration of the barrier formed by raft forming system



SUITABLE CANDIDATE FOR GASTRIC RETENTION

In general, appropriate candidates for CR-GRDF are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT:

- Narrow absorption window in GI tract, e.g. Riboflavin and levodopa
- Primarily absorbed from stomach and upper part of GI tract e.g. calcium supplements, chlorodiazepoxide and cinnarazine.

- Drugs that act locally in the stomach e.g. antacids and misoprostol
- Drugs that degrade in the colon e.g. ranitidine Hcl and metronidazole
- Drugs that disturb normal colonic bacteria, e.g. amoxicillin trihydrate

FACTORS AFFECTING FLOATING DRUG DELIVERY SYSTEM

1. Density of dosage form: Dosage forms having a density lower than that of gastric fluid experience floating behavior and hence gastric retention. Density <1.0g/cm3 is required to exhibit floating property.

2. Size of dosage form: The size of the dosage form is another factor that influences gastric retention .The mean gastric residence times of non-floating dosage forms are highly variable and greatly dependent on their size, which may be small, medium and large units. In fed conditions, the smaller units get emptied from the stomach during the digestive phase and the larger units during the house keeping waves. In most cases, the larger the size of the dosage form the greater will be the gastric retention time because the larger size would not allow the dosage form to quickly pass through the pyloric sphincter into the intestine. Dosage form units with a diameter more than 7.5mm are reported to increase GRT compared with those with diameter of 9.9mm.

3. Food intake and nature of food: Food intake, the nature of the food, caloric content and frequency of feeding has a profound effect on the gastric retention of dosage forms. The presence or absence of food in the stomach influences the GRT of the dosage forms. Usually, the presence of food increases the GRT of the dosage form and increases drug absorption by allowing it to stay at the absorption site for a longer time. Usually fats tend to form an oily layer on the other gastric contents. As such, fatty substances are emptied later than other. Also, increased acidity and osmolality slow down gastric emptying.

4. Stress: stress appears to cause an increase in gastric emptying rate, while depression slows it down.

5. Sex: women and elderly have a slower gastric emptying rate than men and young people respectively.

6. Posture: In a comparative study in humans by Gansbeke et al; the floating and non-floating systems behaved differently. In the upright position, the floating systems floated to the top of the gastric contents and remained for a longer time, showing prolonged GRT. But the non-floating units settled to the lower part of the stomach and underwent faster emptying as a result of peristaltic contractions and the floating units remained away from the pylorus. However, in supine position, the floating units are emptied faster than non-floating units of

similar size. A study by Mojaverian et al showed that effect of posture on GRT found no significant difference in mean GRT for individuals in upright, ambulatory and supine state.

7. **Shape:** Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to exhibit a better GRT and 90%-100% retention at 24hour compared with other shapes

8.**Concomitant drug administration:** Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride affect the FDDS.

9. **Biological factors:** Diabetes and crohn‟s disease also affect the FDDS.

Advantages of gastro retentive drug delivery system:

1. Enhanced bioavailability: The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulation.

2. Enhanced first-pass biotransformation: In a similar fashion to the increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enymes (Cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input.

3. Sustained drug delivery/ reduced frequency of dosing: For drug with relatively short biological half-life, sustained and slow input from CR-GRDF may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance and thereby improves therapy.

4. Targeted therapy for local ailments in the upper GIT: The prolonged and sustained administration of the drug from GRDF to the stomach may be advantageous for local therapy in the stomach and small intestine as in the case of case of H.pylori induced peptic ulcer.

5. Reduced fluctuations of drug concentration: Continuous input of the drug following CR-GRDF administration produces blood drug concentrations within a narrow range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.

6. Extended time over critical (effective) concentration: The sustained mode of administration enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.

7. Site specific drug delivery: A floating dosage form is a feasible approach for drugs which have limited absorption sites in upper small intestine

8. Minimized adverse activity at the colon: Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of drug in the colon may be prevented as in the case of β-lactam antibiotics.

9. Administration of a prolonged release floating dosage form tablets or capsules will result in dissolution of the drug in gastric fluid. After emptying of the stomach contents, the dissolved drug available is for absorption in the small intestine. It is therefore expected that a drug will be fully absorbed from the floating dosage form if it remains in solution form even at alkaline pH of the intestine.

10. When there is vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected under such circumstances and it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

11. Many drugs categorized as once-a-day delivery have been demonstrated to have suboptimal absorption due to dependence on the transit time of the dosage form making traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extend the time within which drug absorption can occur in small intestine.

LIMITATIONS OF FLOATING DRUG DELIVERY SYSTEMS

1. They require a sufficiently high level of fluids in the stomach, for enabling the system to float and to work efficiently. This limitation can be overwhelmed by coating the dosage form with bioadhesive polymer or alternatively by prescribing the dosage form to be taken up with a glass full of water (200-250ml).

2. FDDS are not suitable candidates for drugs with stability or solubility problem in stomach.

3. Some drugs like nifedipine, which is well absorbed along the entire GI tract and undergoes extensive first pass metabolism may not be suitable for FDDS as the slow gastric emptying limits the systemic bioavailability.

4. Drugs with irritant effect on gastric mucosa also limit the applicability of FDDS.

5. In case of bioadhesive systems, which form electrostatic and hydrogen bonds with the mucus, the acidic environment and the thick mucus prevent the bond formation at the mucus polymer interface. High turnover rate of the mucus may further aggravate the problem

6. For swellable systems, the maintenance of their size larger than the aperture of resting pylorus for required period of time is the major rate limiting factor.

7. Above all, any dosage form designed to stay in stomach during the fasting state should be capable of resisting the house keeper waves of phase-III contractions of MMC.

APPLICATIONS OF FDDS

1. Sustained drug delivery: HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of less than1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited. Recently sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo. The formulation compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8hours).

2. **Site-specific drug delivery**: These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine e.g. riboflavin and furosemide. A bilayer-floating capsule was developed for local delivery of misoprostol, which is a synthetic analog of prostaglandin E1 used as a protectant of gastric ulcers caused by administration of NSAIDs. By targeting slow delivery of misoprostol to the stomach, desired therapeutic levels could be achieved and drug waste could be reduced.

3. Absorption enhancement: Drugs that have poor bioavailability because of site-specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. A significant increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric coated LASIX-long product (29.5%).

4. Medopar HBS – containing L-dopa and benserazide-here drug was released and absorbed over a period of 6-8 hour and maintain substantial plasma concentration in parkinson‟s patients

5. Cytotech- containing misoprostol, a synthetic prostaglandin-E1 analog, for prevention of gastric ulcers caused by NSAIDs. As it provides high concentration of drug within gastric mucosa, it is used to eradicate pylori.

6. 5-Flurouracil has been successfully evaluated in patients with stomach neoplasm.

7. Developing HBS dosage form for Tacrine provides a better delivery system and reduces its GI side effects in Alzheimer‟s patients.

IN-VITRO RELEASE MEHANISMS OF FLOATING SYSTEMS[15, 16]

The *in vitro* release mechanisms have been performed for the floating tablets and

Depending upon R^2 and slope values obtained from different models, the best-fit model was selected.

ZERO ORDER RELEASE

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented as

$$\mathbf{Q = Q_0 + K_0 t}$$

Where Q is the amount of drug released or dissolved (assuming that release occurs rapidly after the drug dissolves), Q_0 is the initial amount of drug in solution (it is usually zero), and K_0 is the zero order release constant. The plot made: cumulative % drug release Vs time (zero order kinetic model).

Zero order drug release mechanism is mainly applicable to dosage forms like transdermal systems, coated forms, osmotic systems as well as matrix tablets with low soluble drugs.

FIRST ORDER RELEASE

To study the first order release rate kinetics the release rate data were fitted into the following equation,

$$\mathbf{LogC = LogC_o - K_1 t / 2.303}$$

where: C is the amount of drug released at time t,

C_o is the initial amount of drug in the solution and

K_1 is the first order release constant.

This model is applicable to study of hydrolysis kinetics and to study the release profiles of pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices.

HIGUCHI MODEL

This model is based on the hypotheses that (i) initial drug concentration in the matrix is much higher than drug solubility; (ii) drug diffusion takes place only in one dimension (edge effect must be negligible); (iii) drug particles are much smaller than system thickness; (iv) matrix swelling and dissolution are negligible; (v) drug diffusivity is constant and (vi) perfect sink conditions are always attained in the release environment.

Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion

$$\mathbf{Q = K_t^{1/2}}$$

Where, K is the rate constant reflecting the design variables of the system.

This model is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water soluble drug.

KORSMEYER-PEPPAS Model

Korsmeyer et al (1983) derived a simple relationship which described drug release from a polymeric system. To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer-Peppas model:

$$\mathbf{M_t/M_\infty = Kt^n}$$

Where M_t / M_∞ is fraction of drug released at time t, k is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms as given in following table for cylindrical shaped matrices

Table No 1: Diffusion exponent and release mechanism

Diffusion exponent (n)	Diffusion mechanism
< 0.5	Fickian diffusion
0.5-1	Non- Fickian Transport
1	Case-II transport
> 1	Super Case-II transport

Table No 2: Drugs Used in the floating drug delivery systems[17]

SI.NO	Dosage form	Drug
1	Floating microspheres	Aspirin, griseofulvin, p-nitroaniline, ibuprofen, terfinadine and Tranilast
2	Floating Granules	Diclofenac sodium, indomethacin and prednisolone
3	Films	Cinnarazine
4	Floating capsules	Chlordiazepoxide hydrogen chloride, diazepam, furosemide, misoprostol, L-dopa, benserazide, Urosdeoxycholic acid and pepstatin
5	Floating tablets and pills	Acetaminophen, acetylsalicylic acid, ampicillin, amoxicillin trihydrate, atenolol, diltiazem, flurouracil, isosorbide mononitrate, p-amion benzoic acid, theophylline and verapamil

Table No 3: Marketed products of floating drug delivery systems[18]

SI.NO	Brand name	Drug(dose)	Company	Remarks
1	Madopar	Levodopa(100mg), Benserazide(25mg)	Roche products	Floating,CR capsule
2	Valrelese	Diazepam(15mg)	Hoffmann-LaRoche	Floating capsule
3	Liquid Gaviscon	Al-hydroxide(95mg),Mg Carbonate(385mg)	Glaxo smith Kline,India	Effervescent floating liquid alginate preparation
4	Topalkan	Al-Mg antacid	Pierre fabre drug	Floating liquid alginate
5	Amalgate	Al-mg antacid		Floating liquid form
6	Conviron	Ferrous sulphate	Ranbaxy,India	Colloidalgel forming FEDS
7	Cifran OD	Ciprofloxacin(1g)	Ranbaxy,India	Gas-generating floating form
8	Cytotec	Misoprostal (100mcg/200mcg)	Pharmaacia	Bilayer floating capsule

Leukaemia[19]

Leukaemias are a group of cancers of the blood-forming cells. They start in the bone marrow, which is spongy tissue that is found in the middle of some of our bigger bones. The abnormal cells spread from there into the bloodstream and to other parts of the body. The leukaemia is described as lymphoid or myeloid, depending on which type of blood-forming cell in the bone marrow the abnormal leukaemia cells develop from

Types

Types of leukaemia Leukaemia that develops quickly is called acute leukaemia and leukaemia that develops slowly is called chronic leukaemia. The main types are named according to whether they are acute or chronic and also according to which type of blood-forming cell has become cancerous.

There are four main types of leukaemia:

● Acute lymphoblastic leukaemia (ALL)

● Acute myeloid leukaemia (AML)

● Chronic lymphocytic leukaemia (CLL), Chronic myeloid leukaemia (CML).

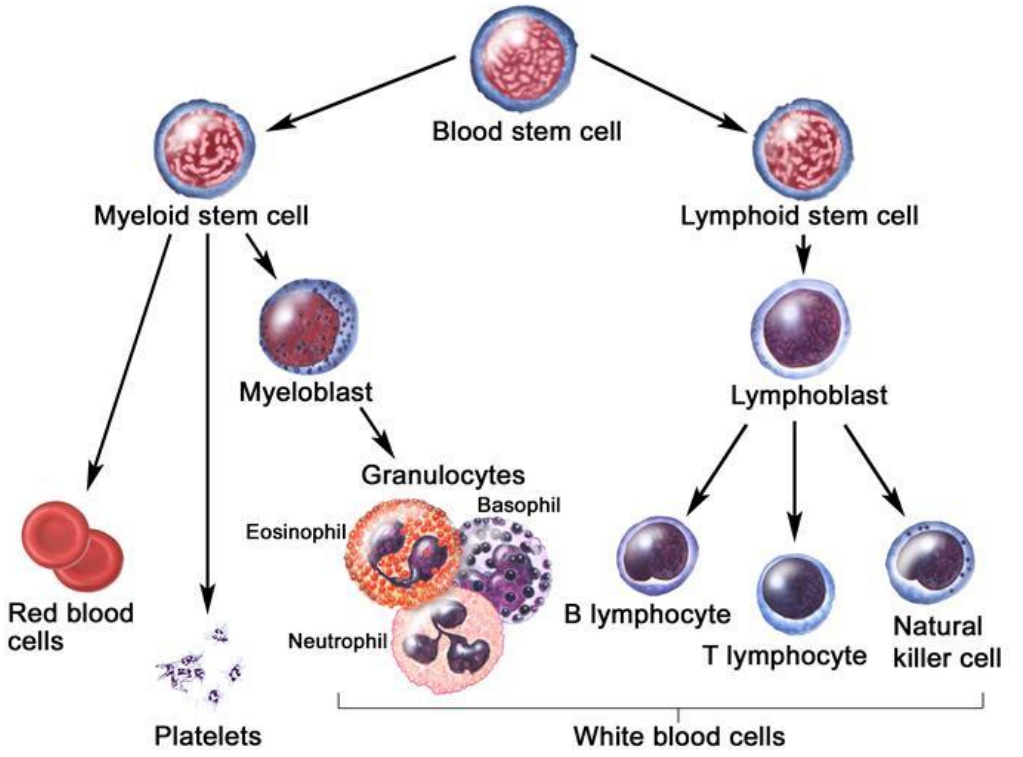
Chronic myelogenous (or myeloid) leukemia(CML)[20]

Chronic myelogenous leukemia (also called CML or chronic granulocytic leukemia) is a slowly progressing blood and bone marrow disease that usually occurs during or after middle age, and rarely occurs in children.

Normally, the bone marrow makes blood stem cells (immature cells) that become mature blood cells over time. A blood stem cell may become a myeloid stem cell or a lymphoid stem cell. A lymphoid stem cell becomes a white blood cell. A myeloid stem cell becomes one of three types of mature blood cells:

- Red blood cells that carry oxygen and other substances to all tissues of the body.
- Platelets that form blood clots to stop bleeding.
- Granulocytes (white blood cells) that fight infection and disease.

Fig 10: The process And several steps involved in the formation of red blood cell, platelet, or white blood cell.



CLASSIFICATION

CML is often divided into three phases based on clinical characteristics and laboratory findings. In the absence of intervention, CML typically begins in the *chronic* phase, and over the course of several years progresses to an *accelerated* phase and ultimately to a *blast crisis*. Blast crisis is the terminal phase of CML and clinically behaves like an acute leukemia.

CHRONIC PHASE

The first stage of CML is chronic phase. During this phase, patients are usually asymptomatic or have only mild symptoms of fatigue, left side pain, joint and/or hip pain, or abdominal fullness. The duration of chronic phase is variable and depends on how early the disease was diagnosed as well as the therapies used. In the absence of treatment, the disease progresses to an accelerated phase.

ACCELERATED PHASE

Second stage of CML is considered to be in the accelerated phase, it can be identified by the below conditions. The accelerated phase is significant because it signals that the disease is progressing and transformation to next phase. Drug treatment often becomes less effective in the advanced stages.

- 10–19% myeloblasts in the blood or bone marrow

- >20% basophils in the blood or bone marrow
- Platelet count <100,000, unrelated to therapy
- Platelet count >1,000,000, unresponsive to therapy
- Cytogenetic evolution with new abnormalities in addition to the Philadelphia chromosome
- Increasing splenomegaly or white blood cell count, unresponsive to therapy

BLAST CRISIS

Blast crisis is the final phase in the evolution of CML, and behaves like an acute leukemia, with rapid progression and short survival. Blast crisis is diagnosed if any of the following are present in a patient with CML

- >20% myeloblasts or lymphoblasts in the blood or bone marrow
- Large clusters of blasts in the bone marrow on biopsy
- Development of a chloroma (solid focus of leukemia outside the bone marrow

SYMPTOMS

- enlarged spleen causing pain on the left side,
- malaise,
- joint and/or hip pain,
- low-grade fever,
- increased susceptibility to infections,
- anemia, and thrombocytopenia with easy bruising

DIAGNOSIS

CML is often Diagnosed on the basis of a complete blood count, which shows increased granulocytes of all types, typically including mature myeloid cells. Basophils and eosinophils are almost universally increased; this feature may help differentiate CML from a leukemoid reaction. A bone marrow biopsy is often performed as part of the evaluation for CML, and CML is diagnosed by detecting the Philadelphia chromosome. This characteristic chromosomal abnormality can be detected by routine cytogenetics, by fluorescent in situ hybridization, or by PCR for the bcr-abl fusion

gene. Controversy exists over so-called *Ph-negative* CML, or cases of suspected CML in which the Philadelphia chromosome cannot be detected. Many such patients in fact have complex chromosomal abnormalities that mask the (9;22) translocation, or have evidence of the translocation by FISH or RT-PCR in spite of normal routine karyotyping. The small subset of patients without detectable molecular evidence of bcr-abl fusion may be better classified as having an undifferentiated myelodysplastic/myeloproliferative disorder, as their clinical course tends to be different from patients with CML.

TREATMENT

Different types of treatment are available for patients with chronic myelogenous leukemia (CML). Some treatments are standard (the currently used treatment), and some are being tested in clinical trials. There are six types of standard treatments are available. Which are as follows.

TARGETED THERAPY

Targeted therapy is a type of treatment that uses drugs or other substances to identify and attack specific cancer cells without harming normal cells. Tyrosine kinase inhibitors are targeted therapy drugs used to treat chronic myelogenous leukemia.

CHEMOTHERAPY

Chemotherapy is a cancer treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. When chemotherapy is taken by mouth or injected into a vein or muscle, the drugs enter the bloodstream and can reach cancer cells throughout the body (systemic chemotherapy). When chemotherapy is placed directly into the cerebrospinal fluid, an organ, or a body cavity such as the abdomen, the drugs mainly affect cancer cells in those areas (regional chemotherapy). The way the chemotherapy is given depends on the type and stage of the cancer being treated.

BIOLOGIC THERAPY

Biologic therapy is a treatment that uses the patient's immune system to fight cancer. Substances made by the body or made in a laboratory are used to boost, direct, or restore the body's natural defenses against cancer. This type of cancer treatment is also called biotherapy or immunotherapy.

HIGH-DOSE CHEMOTHERAPY WITH STEM CELL TRANSPLANT

High-dose chemotherapy with stem cell transplant is a method of giving high doses of chemotherapy and replacing blood-forming cells destroyed by the cancer treatment. Stem

cells (immature blood cells) are removed from the blood or bone marrow of the patient or a donor and are frozen and stored. After the chemotherapy is completed, the stored stem cells are thawed and given back to the patient through an infusion. These reinfused stem cells grow into (and restore) the body's blood cells.

DONOR LYMPHOCYTE INFUSION (DLI)

Donor lymphocyte infusion (DLI) is a cancer treatment that may be used after stem cell transplant. Lymphocytes (a type of white blood cell) from the stem cell transplant donor are removed from the donor's blood and may be frozen for storage. The donor's lymphocytes are thawed if they were frozen and then given to the patient through one or more infusions. The lymphocytes see the patient's cancer cells as not belonging to the body and attack them

SURGERY

Splenectomy is surgery to remove the spleen.

New types of treatment are being tested in clinical trials.

SIDE EFFECTS:

Chemotherapy drugs work by attacking cells that are dividing quickly, which is why they work against cancer cells. But other cells in the body, such as those in the bone marrow, the lining of the mouth and intestines, and the hair follicles, also divide quickly. These cells are also likely to be affected by chemotherapy, which can lead to side effects.

Possible side effects depend on the type and dose of drugs given and the length of time they are taken. Some common side effects of chemotherapy include:

- Hair loss
- Mouth sores
- Loss of appetite
- Nausea and vomiting
- Increased risk of infection (from low white blood cell counts)
- Easy bruising or bleeding (from low blood platelet counts)
- Fatigue (from low red blood cell counts)

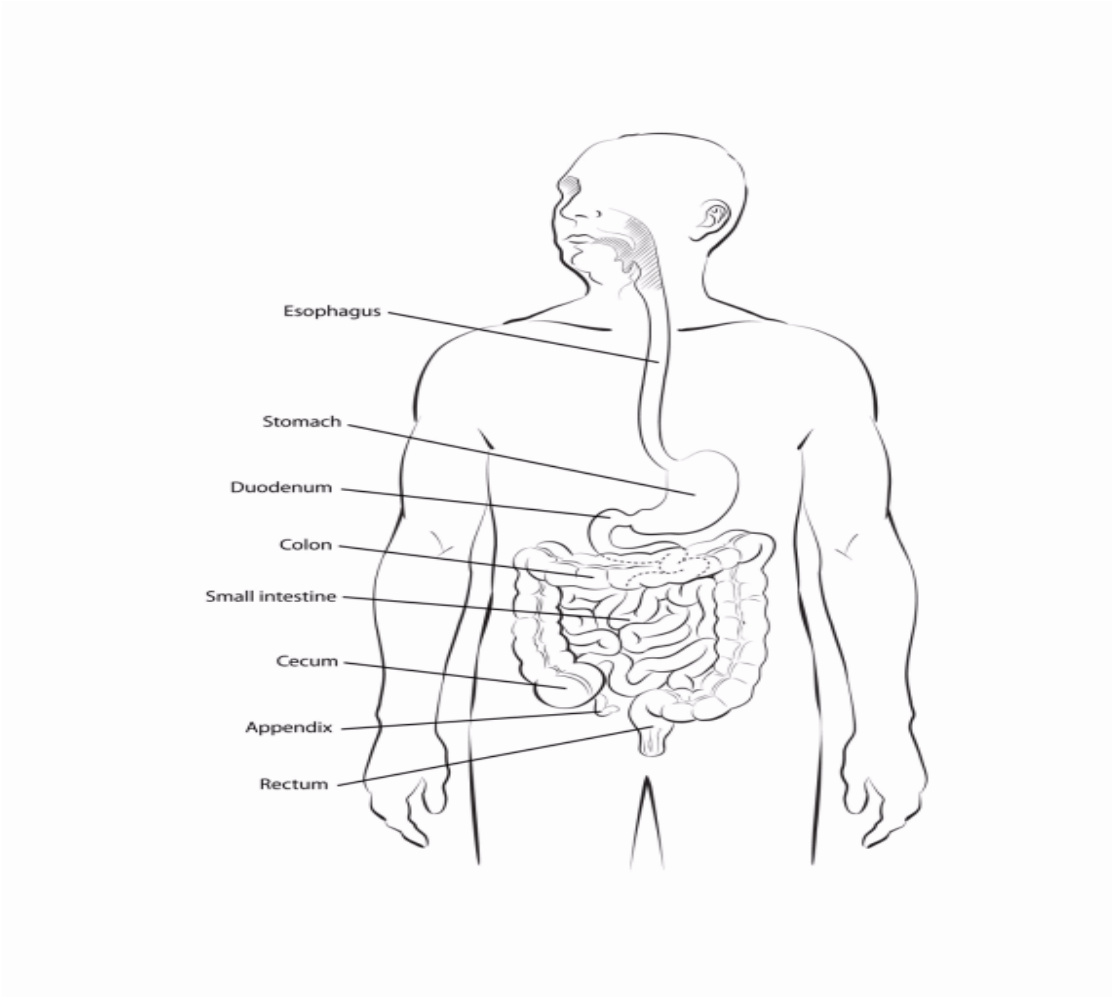
Still, different drugs can have different side effects. For example, vincristine can cause nerve damage (*neuropathy*) leading to numbness, tingling, or even pain or weakness in the hands or feet. Lung damage from busulfan is rare, but can be severe.

Gastrointestinal stromal tumors (GISTs) [21]

GASTROINTESTIINAL SYSTEM

The gastrointestinal (GI) system (or digestive system) processes food for energy and rids the body of solid waste. After food is chewed and swallowed, it enters the oesophagus, a tube that carries food through the neck and chest to the stomach. The oesophagus joins the stomach just beneath the diaphragm (the thin band of muscle below the lungs)

Fig 11: The gastrointestinal system



The stomach is a sac-like organ that holds food and helps the digestive process by secreting gastric juice. The food and gastric juices are mixed into a thick fluid called *chyme* that is then emptied into the small intestine. The small intestine continues breaking down the food and absorbs most of the nutrients into the bloodstream. This is the longest section of the GI tract, measuring more than 20 feet.

The small intestine joins the large intestine, the first part of which is the colon, a muscular tube about 5 feet long. The colon absorbs water and mineral nutrients from the remaining

food matter. The waste left after this process goes into the rectum as stool (feces), where it is stored until it passes out of the body through the anus.

GISTs:

Gastrointestinal stromal tumors (GISTs) are uncommon tumors of the GI tract. These tumors start in very early forms of special cells found in the wall of the GI tract, called the *interstitial cells of Cajal* (ICCs). ICCs are cells of the autonomic nervous system, the part of the nervous system that regulates body processes such as digesting food. ICCs are sometimes called the "pacemakers" of the GI tract because they signal the muscles in the digestive system to contract to move food and liquid through the GI tract.

More than half of GISTs start in the stomach. Most of the others start in the small intestine, but GISTs can start anywhere along the GI tract. A small number of GISTs start outside the GI tract in nearby areas such as the omentum (an apron-like layer of fatty tissue that hangs over the organs in the abdomen) or the peritoneum (the layer of tissue that lines the organs and walls of the abdomen).

SIGNS AND SYMPTOMS

Most GISTs occur in the stomach or small intestine. These tumors might not cause any symptoms unless they are in a certain location or grow to a certain size. Small tumors might not cause any symptoms and may be found accidentally when the doctor is looking for some other problem. These tumors are often benign.

GISTs are often found because they cause bleeding into the gastrointestinal (GI) tract. Bleeding into the intestines can make bowel movements black and tarry. If the tumor bleeds into the stomach or esophagus, a person might vomit blood. Slower bleeding might not cause these problems, but over time it can lead to anemia (low red blood cell counts), making a person feel tired and weak.

Other possible symptoms of GISTs are:

- Abdominal (belly) discomfort or pain
- A mass or swelling in the abdomen
- Nausea, vomiting
- Feeling full after eating only a small amount of food
- Loss of appetite
- Weight loss

- Problems swallowing (for tumors in the esophagus)

Sometimes the tumor grows large enough to block the passage of food through the stomach or intestine. This is called an *obstruction*, and it causes severe abdominal pain and vomiting. Emergency surgery is often needed to treat the blockage.

DIAGNOSIS

Although these tumors are easily detected, there are several methods which are used to confirm the GISTs which are as follows

Imaging tests

Barium x-rays

Computed tomography (CT) scan

Magnetic resonance imaging (MRI) scans

Positron emission tomography (PET) scan

Endoscopy

Biopsy

TREATMENT

Once a gastrointestinal stromal tumor (GIST) is found and staged, tumors are treated by considering their tumor characteristics (such as its size, location, growth rate, and whether it has spread) and overall health of a patient.

The main types of treatment used for GISTs include:

- Surgery
- Targeted therapy drugs

Other treatments, such as chemotherapy and radiation therapy, are used much less often.

LITERATURE REVIEW

Literature review

N Anjali Devi et al[22] 2013 developed a Floating controlled release tablets of Imatinib using hydrophilic matrix system by wet granulation technique and found that all the formulations were showing good drug release around 98.25- 98.91 where as the best formulation released the maximum amount of drug around 99.46% by zero-order release kinetics in 12 hours.

Mudgal Vinod Kumar et al[23] 2012 developed a sustained release floating system of Ciprofloxacin by direct compression method and coated with polymeric material Eduragit 30D and ATEC are used as film formers and plasticizers and reported that the optimized formulation was floating within 20 min and remained buoyant for 13hours and the drug action was sustained for 20 hours.

E Sathish Reddy et al[24] 2012 developed a sustained release floating tablets of Ciprofloxacin. Sodium bicarbonate was used in the formulations as a source of Carbondioxide. The matrix type of system was prepared with the help of swell-able polymer hydroxypropylmethylcellulose k15M and was formulated in such a way that when in contact with the acidic gastric contents, CO_2 was liberated and got entrapped in swollen hydrocolloid, which provides buoyancy to the dosage forms. More over DL-methionine was added as a hepato- protective agent that makes the formulation a unique one.

Madhusudan Rao et al[25] 2012 developed Gastro retentive formulation of Cefuroximeaxetil by using hydrophilic polymers such as HPMC K15M, HPMC K4M and observed that all the formulations followed fickian diffusion. And have a gastric residence time of 6 hours in fed state.

Sonia dhiman et al[26] 2012 formulated controlled release floating type gastro retentive tablets of famotidine using HPMC K15M as a polymer and reported that targeted delivery of the drug provides an effective and safe therapy with reduced dose and duration of therapy. The floating drug delivery system was developed by effervescent approach.

K. Karuna Kar et al[27] 2011 developed floating matrix tablets of Lamivudine to prolong the gastric residence time and to increase its bio availability, tablets were prepared by using HPMC E15 and xanthan gum, and found that the drug release is Korsmeyer Peppas model. And found that the tablet hardness has little or no effect on drug release kinetics.

Pramod Patil et al[28] 2011 developed and desigined Floating tablets of Olfloxacin to prolong gastric residence time after oral administration by using wet granulation method by incorporating natural polymers like guar gum, locust beam gum along with HPMC K100M

and found that the drug release from the best formulation was uniform throughout the study and follows Higuchi kinetic model.

Gada et al[29] 2011 designed and developed floating tablets by direct compression technique using polymers like HPMC K4M, HPMC K15M and HPMC K100M as gel forming polymers , and concluded that the floating tablets are the systems which are retained in the body for a longer period of time and there by increases the drug bio availability.

Kurnal patel M et al[30] 2011 Formulated and evaluated a gastro retentive drug delivery system of Mebendazole by wet granulation technique with several additives like chitosan, HPMC and stearic acid and studied the effect of citric acid and stearic acid on drug release profiles and floating properties and concluded that the addition stearic acid decreases the dissolution properties due to its hydro phobic nature.

Afsar c.shaikh et al[31] 2011 formulated floating bio-adhesive tablets of Tramadol by Direct compression method using various amounts of Carbopol, HPMC, and concluded that the muco adhesion and hydrodynamic balance are playing an important role in the controlled release of drug.

Burpute S.S et al[32] 2011 developed floating tablets of Nizatidine employing two different grades of HPMC, and other polymers incuding carbopol and also the gas forming agents and reported that the tablets swelled axially and radially during the study.

Singh L. P et al[33] 2011 developed a dosage form to prolong the release of the drug from the dosage form and improve drug absorption in upper GIT and stomach, using effverscent technique and concluded that the gastric retention increases the absorption of the drug with narrow therapeutic index.

N. Damadoran et al[34] 2011 developed bi-layered floating tablets of Theophylline using wet granulation technique, using polymers like HPMC and Sodium carboxy methyl cellulose and found that the combination of HPMC and methyl Cellulose can sustain the release of the drug and the drug release followed first order kinetics.

Anilkumar Jet et al[35] 2010 formulated an oral floating tablet of Cephlaxin using the hydrophilic polymer HPMC and gas generating agents, by means of wet granulation method and concluded that the drug action is controlled for a period of 12 hours.

ChandraShekar B et al[36] 2010 designed and developed a gastro retentive drug delivery system of Ketoconazole by direct compression technology, by incorporating several hydrophilic polymers and found out that the drug release was around 24 hours and obeying mixed order kinetics.

Sharada Shinde et al[37] 2010 developed a floating matrix tablets of Salbutamol Sulphate by wet granulation method by using HPMC K100M and gas generating agents such as sodium bi carbonate and citric acid and concluded that the initial burst effect can't be retarded by using high level of HPMC.

Vinod. K. R et al[38] developed controlled release Imatinib mesylate oral dosage form which can retain the drug in the stomach for prolonged duration and to achieve therapeutic levels over an extended period of time, by direct compression method. The tablets were also evaluated for in vitro drug release in 0.1N Hcl for 12 hrs in USP Type II dissolution apparatus. In order to determine the mode of release, the data was fitted into various kinetic models and the optimized formulation followed Korsmeyer peppas model and the 'n' value was greater than one indicated super case II mechanism of drug release. The radiographic pictures of the rabbits confirm the in vivo mucoadhesion in the stomach for 6h.

AIM AND OBJECTIVE

AIM

To design and formulate a gastro-retentive drug delivery system of Imatinib.

OBJECTIVES

The objectives of the present work include:

1. Drug-polymer interaction studies
2. Preparation of Gastro-retentive tablets of IMATINIB by direct compression technique.
3. Evaluation of blends for pre and tablets for post compression parameters.
4. Physical parameters like hardness, friability, weight variation, drug content uniformity.
5. *In-Vitro* evaluation of matrix tablets for the release characteristics.
6. To study the release kinetics of developed formulations.

PLAN OF WORK

PLAN OF WORK

The Plan of research work has been scheduled as:

1. Preformulation studies:

- Compatability studies
- Solubility
- Angle of repose
- Bulk density
- Tapped density
- Compressibility index
- Hausners ratio

2. Development of gastroretentive dosage form of Imatinib
3. Evaluation of Formulated dosage form

- Hardness
- Friability
- Weight variation
- Content uniformity
- In-Vitro buoyancy studies
- Swelling index
- In-Vitro dissolution studies
- Pharmacokinetic modelling
- Stability studies of optimized formulation

MATERIALS AND EQUIPMENTS

MATERIALS AND EQUIPMENTS

Table 4: Materials used in the study

Name of chemical	Source
Imatinib	Hetero drugs pvt Ltd, Hyderabad.
HPMCK15	Lara drugs pvt Ltd, Hyderabad.
Carbapol	Lara drugs pvt Ltd, Hyderabad.
Chitosan	Lara drugs pvt Ltd, Hyderabad.
Sodium bi carbonate	Lara drugs pvt Ltd, Hyderabad.
Citric acid	Lara drugs pvt Ltd, Hyderabad.
Magnesium stearate	Lara drugs pvt Ltd, Hyderabad.
MCC	Lara drugs pvt Ltd, Hyderabad.

Table 5 : Equipments used in the study

SI.NO	Equipments	Manufacturer
1	Weighing balance	Sartorius
2	UV – visible spectrophotometer	Labindia – 3200, Double beam Spectrophotometer
3	FT – IR spectrophotometer MB 104	Shimadzu corporation,japan
4	Dissolution test apparatus	Labindia Dissolution tester, DISSO 14000
5	Tablets Punching machine	Cadmach, Ahmedabad.
6	Humidity chamber	Sigma instruments, Mumbai
7	Friabilator	Labindia Friability tester, FT 1020.
8	Tapped density tester	Labindia Tap density tester, TD 1025.

DRUG PROFILE

DRUG PROFILE

IMATINIB: [39]

AVAILABLE FORMS:

Imatinib mesylate,

Imatinib methasulfonate.

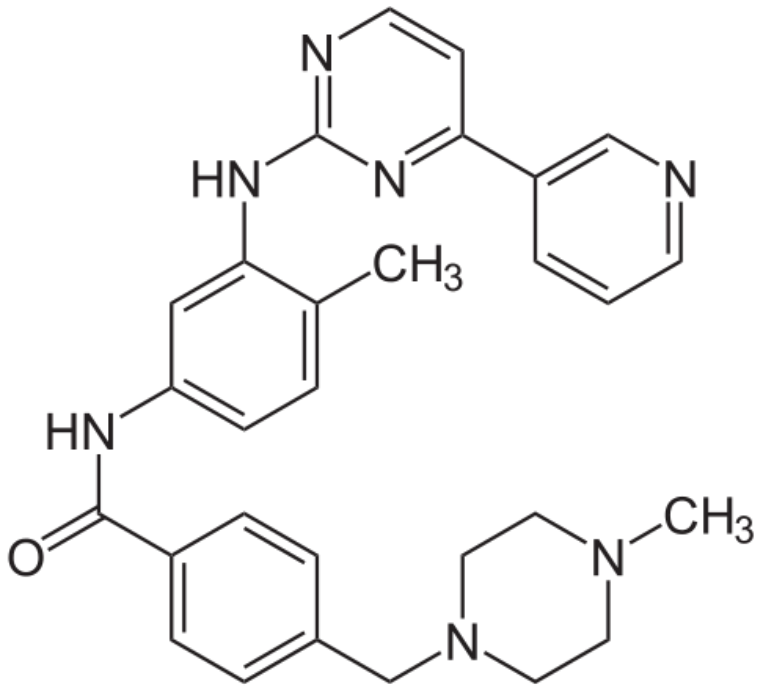
THERAPEUTIC CATEGORY:

Antineoplastic Agent,

Protein Kinase Inhibitor.

STRUCTURE

Fig 12: Molecular structure of Imatinib



CHEMICAL NAME

4-[(4-methylpiperazin-1-yl)methyl]-*N*-(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)benzamide

MOLECULAR WEIGHT:

493.60274[g/mol]

MOLECULAR FORMULA:

$C_{29}H_{31}N_7$ O

DESCRIPTION:

It is a white to off-white amorphous solid.

APPEREANCE:

White amorphous

SOLUBILITY:

It is soluble in 0.1N HCL, DMSO and Water.

MELTING POINT:

Melting point is around 226^0C

MECHANISM OF ACTION: [40]

Imatinib is a 2-phenylaminopyrimidine derivative that functions as a specific inhibitor of a number of tyrosine kinase enzymes. It occupies the *TK* active site, leading to a decrease in activity.

There are a large number of *TK* enzymes in the body, including the insulin receptor. Imatinib is specific for the *TK* domain in *abl* (the Abelson proto-oncogene), c-kit and PDGF-R (platelet-derived growth factor receptor).

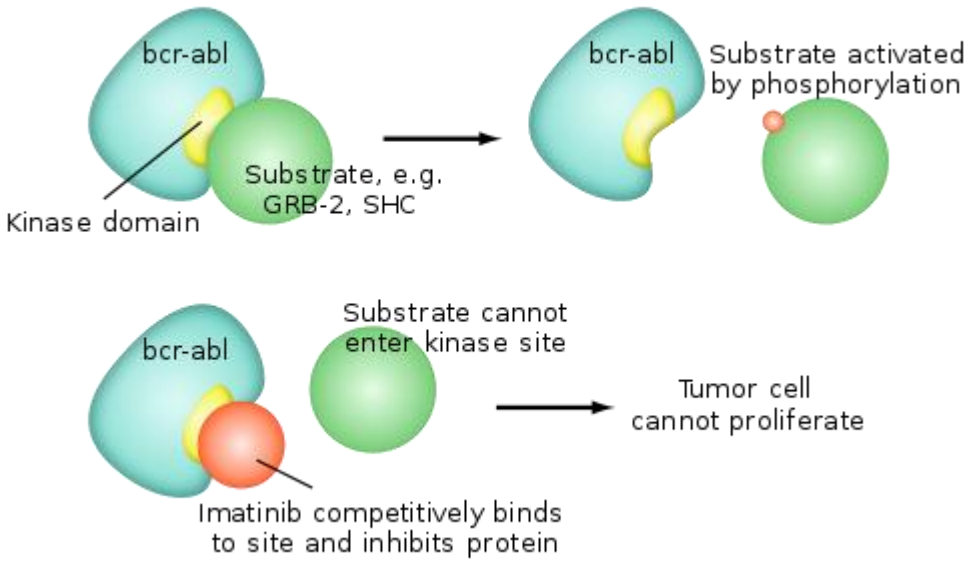
In chronic myelogenous leukemia, the Philadelphia chromosome leads to a fusion protein of *abl* with *bcr*(*breakpoint cluster region*), termed *bcr-abl*. As this is now a constitutively active tyrosine kinase, imatinib is used to decrease *bcr-abl* activity.

The active sites of tyrosine kinases each have a binding site for ATP. The enzymatic activity catalyzed by a tyrosine kinase is the transfer of the terminal phosphate from ATP to tyrosine residues on its substrates, a process known as protein tyrosine phosphorylation. Imatinib works by binding close to the ATP binding site of *bcr-abl*, locking it in a closed or self-inhibited conformation, and therefore inhibiting the enzyme activity of the protein semi-competitively. This is fact explains why many BCR-ABL mutations can cause resistance to imatinib by shifting its equilibrium toward the open or active conformation.

Imatinib is quite selective for *bcr-abl* – it does also inhibit other targets mentioned above (c-kit and PDGF-R), but no other known tyrosine kinases. Imatinib also inhibits the *abl* protein of non-cancer cells but cells normally have additional redundant tyrosine kinases which allow them to continue to function even if *abl* tyrosine kinase is inhibited. Some tumor cells, however, have a dependence on *bcr-abl*. Inhibition of the *bcr-abl* tyrosine kinase also stimulates its entry in to the nucleus, where it is unable to perform any of its normal anti-apoptopic functions.

The Bcr-Abl pathway has many downstream pathways including the Ras/MapK pathway, which leads to increased proliferation due to increased growth factor-independent cell growth. It also affects the Src/Pax/Fak/Rac pathway. This affects the cytoskeleton, which leads to increased cell motility and decreased adhesion. The PI/PI3K/AKT/BCL-2 pathway is also affected. BCL-2 is responsible for keeping the mitochondria stable; this suppresses cell death by apoptosis and increases survival. The last pathway that Bcr-Abl affects is the JAK/STAT pathway, which is responsible for proliferation.

Fig 13: Mechanism of action of Imatinib



PHARMACOKINETIC PROPERTIES[41]

ABSORPTION

After oral intake, imatinib is rapidly absorbed from the gut, because of its rapid dissolution at acidic pH. Imatinib should be taken with a meal and water to reduce gastrointestinal side effects. However, a high fat meal can prolong the uptake and therefore the time to reach a maximum plasma concentration (t_{max}). Under normal conditions, the maximal plasma concentration of approximately 1.9 μg/ml is reached after 2–4 hours. After repeated administration of 400 mg of imatinib per day, the mean plasma concentration in steady state is ≥1 μmol/l after 24 hours.

Absolute bioavailability is estimated to be almost complete, but can be significantly lower in some cases as a result of limited absorption. Bioavailability is unaffected by Normal meal.

PROTEIN BINDING

Imatinib is highly protein bound. It binds mostly to albumin. Protein binding is approximately 95% . Imatinib also binds to α1-acid-glycoprotein in vitro and in vivo. But binding to α1-acid-glycoprotein binding does not influence the activity of imatinib.

METABOLISM

Imatinib is metabolized by the cytochrome P450 (CYP) isoenzymes in the gut wall and liver. The metabolism is mainly mediated by CYP3A4 and CYP3A5, but other CYP isoenzymes such as CYP1A2, CYP2D6, CYP2C9, and CYP2C19 also play minor roles. The main metabolite is the N-demethylated piperazine derivate. Based on in vitro studies, this metabolite has potency comparable to that of the parent compound. The exposure measured as a percentage of the area under the concentration–time curve in plasma of the N-demethylated piperazine derivate is approximately 10%–15% of that of imatinib. In addition, imatinib and its N-demethylated piperazine derivate are N-oxidized in the liver.

ELIMINATION

On average, 75% of the dose of imatinib undergoes biotransformation. Imatinib has a terminal half-life of 19 hours (range, 14–23 hours), while its main metabolite has a terminal half-life of 40 hours (range, 30–50 hours) . Excretion takes place mainly via the bile, 68% as metabolites and 20% as parent compound. Renal excretion is low, as only 13% of the metabolites and 5% of the parent compound are excreted via the kidneys

PHARMACODYNAMIC PROPERTIES

The pharmacokinetic–pharmacodynamic relationships of imatinib have not been extensively studied. However, there seems to be a relationship between dose and likelihood of tumor response. In CML, patients treated at a dose <400 mg/day showed a significantly lower cytogenic response than patients treated with a higher dose . Early trials showed no significant positive effect of a starting dose >400 mg/day in most patients if adverse effects are considered. Therefore, it was concluded that a 400-mg/day dose would be optimal in most patients . However, in patients with an unsatisfactory response to the 400-mg/day dose, dose

escalation to 600 mg/day or 800 mg/day can be effective without resulting in greater adverse effects. At a dose >800 mg/day, toxic effects are significantly greater without greater activity.

In patients with CML, the overall survival rate after 60 months is estimated to be approximately 89% after treatment with imatinib. The progression-free survival rate at 60 months was approximately 83% (95% confidence interval, 79%–87%) in the same study .

In patients with GISTs, the progression-free survival duration after treatment with imatinib is estimated to be approximately 2 years. A European trial in GIST patients showed that the progression-free survival rate was significantly higher in patients who started on 400 mg twice daily than in patients treated with 400 mg daily (56% versus 50%) .

DOSE

100 to 400 mg daily, in divided doses.

SIDE EFFECTS

The most common side effects include: feeling sick (nausea), diarrhoea, headaches, leg aches/cramps, fluid retention, visual disturbances, itchy rash, lowered resistance to infection, bruising or bleeding, loss of appetite; weight gain, reduced number of blood cells (neutropenia, thrombocytopenia, anemia), headache, and edema.

Severe congestive cardiac failure is an uncommon but recognized side effect of imatinib and mice treated with large doses of imatinib show toxic damage to their myocardium.

If imatinib is used in prepubescent children, it can delay normal growth, although a proportion will experience catch-up growth during puberty.

PRECAUTIONS[42]

There are several tips advised for a person during the Administration of Imatinib, which are as follows.

- Take this medication after a meal with a large glass of water to reduce upset stomach. Take this medication at about the same time each day.
- If you miss a dose of this medication, do not take the missed dose at all and do not double the next one. Instead, go back to your regular dosing schedule and check with your health care provider.
- You may be at risk of infection so try to avoid crowds or people with colds and those not feeling well, and report fever or any other signs of infection immediately to your health care provider.
- Wash your hands often.
- Drink at least two to three quarts of fluid every 24 hours, unless you are instructed otherwise.
- Use an electric razor and a soft toothbrush to minimize bleeding.
- Avoid contact sports or activities that could cause injury.
- In general, drinking alcoholic beverages should be kept to a minimum or avoided completely. You should discuss this with your doctor.
- Get plenty of rest.
- Maintain good nutrition.
- If you experience symptoms or side effects, be sure to discuss them with your health care team. They can prescribe medications and/or offer other suggestions that are effective in managing such problems.

INTERACTIONS

There are several no of drug interactions detected for Imatinib, in some cases both drugs action will get increased and may leads to toxicity where as in some cases the drug action will get reduced, the detailed drug interactions were classified in the tables below.

Table 6: Drug Interactions with Increased Drug action.

SI.NO	DRUG	INTERACTION
1	Acenocoumarol	Imatinib may increase the anticoagulant effect of acenocoumarol.
2	Acetaminophen	Increased hepatic toxicity of both agents
3	Anisindione	Imatinib may increase the anticoagulant effect of anisindione.
4	Atorvastatin	Imatinib, a strong CYP3A4 inhibitor, may increase the effect and toxicity of atorvastatin by decreasing its metabolism.
5	Bromazepam	Imatinib, a strong CYP3A4 inhibitor, may increase the serum concentration of bromazepam by decreasing its metabolism.
6	Cerivastatin	Imatinib, a strong CYP3A4 inhibitor, may increase the serum concentration of cerivastatin by decreasing its metabolism.
7	Clarithromycin	The macrolide, clarithromycin, may increase the serum concentration of imatinib.
8	Cyclosporine	Imatinib increases the effect and toxicity of cyclosporine.
9	Dicumarol	Imatinib may increase the anticoagulant effect of dicumarol.
10	Erythromycin	The macrolide, erythromycin, may increase the serum concentration of Imatinib.
11	Itraconazole	Itraconazole may increase the levels of imatinib.

12	Josamycin	The macrolide, josamycin, may increase the serum concentration of imatinib.
13	Ketoconazole	Ketoconazole may increase the levels of imatinib.
14	Lovastatin	Imatinib, a strong CYP3A4 inhibitor, may increase the effect and toxicity of lovastatin by decreasing its metabolism.
15	Nifedipine	Imatinib increases the effect and toxicity of nifedipine
16	Simvastatin	Imatinib, a strong CYP3A4 inhibitor, may increase the effect and toxicity of simvastatin by decreasing its metabolism.
17	Tamoxifen	Imatinib may increase the serum concentration of Tamoxifen by decreasing its metabolism and clearance.
18	Topotecan	Imatinib, may increase the bioavailability and serum concentration of oral Topotecan
19	Tramadol	Imatinib may increase Tramadol toxicity by decreasing Tramadol metabolism and clearance
20	Trastuzumab	Trastuzumab may increase the risk of neutropenia and anemia.
21	Trazodone	The CYP3A4 inhibitor, Imatinib, may increase Trazodone efficacy/toxicity by decreasing Trazodone metabolism and clearance.
22	Vardenafil	Imatinib, a strong CYP3A4 inhibitor, may reduce the metabolism and clearance of Vardenafil
23	Verapamil	Imatinib, a strong CYP3A4 inhibitor, may increase the serum concentration of Veramapil, a CYP3A4 substrate, by decreasing its metabolism and clearance.

24	Vincristine	Imatinib, a strong CYP3A4 inhibitor, may increase the serum concentration of Vincristine by decreasing its metabolism.
25	Vinorelbine	Imatinib, a strong CYP3A4 inhibitor, may increase the serum concentration of Vinorelbine by decreasing its metabolism.
26	Voriconazole	Voriconazole, a strong CYP3A4 inhibitor, may increase the serum concentration of imatinib by decreasing its metabolism.
27	Warfarin	Imatinib may increase the anticoagulant effect of warfarin increasing the risk of bleeding.
28	Zonisamide	Imatinib, a strong CYP3A4 inhibitor, may increase the serum concentration of zonisamide by decreasing its metabolism.
29	Zopiclone	Imatinib, a strong CYP3A4 inhibitor, may increase the serum concentration of zopiclone by decreasing its metabolism.
30	Dantrolene	Imatinib may increase the serum concentration of dantrolene by decreasing its metabolism.
31	Pimozide	Pimozide may increase the effect and toxicity of imatinib.
32	Tamsulosin	Imatinib increases its action

Table 7: Drug Interactions with Decreased drug action.

SI.NO	DRUG	INTERACTION
1	Aprepitant	Aprepitant may change levels of the chemotherapy agent, imatinib.
2	Carbamazepine	Carbamazepine, a strong CYP3A4 inducer, may increase the metabolism of imatinib.
3	Dexamethasone	Dexamethasone may decrease levels of imatinib.
4	Ethotoin	The hydantoin decreases the levels of imatinib.
5	Fosphenytoin	The hydantoin decreases the levels of imatinib.
6	Mephenytoin	The hydantoin decreases the levels of imatinib.
7	Phenobarbital	The Phenobarbital decreases the level of imatinib.
8	Phenytoin	The hydantoin decreases the levels of imatinib
9	Rifampin	Rifampin decreases levels of imatinib
10	St. John's Wort	St. John's Wort decreases levels of imatinib
11	Tacrolimus	The strong CYP3A4 inhibitor, Imatinib, may decrease the metabolism and clearance of Tacrolimus,
12	Tadalafil	Imatinib may reduce the metabolism of Tadalafil. Concomitant therapy should be avoided if possible due to high risk of Tadalafil toxicity.
13	Telithromycin	Co-administration may result in altered plasma concentrations of Imatinib and/or Telithromycin.
14	Temsirolimus	Imatinib may inhibit the metabolism and clearance of

		Temsirolimus.
15	Tramadol	Imatinib may decrease the effect of Tramadol by decreasing active metabolite production
16	Tolterodine	Imatinib may decrease the metabolism and clearance of Tolterodine

EXCIPIENT PROFILE

EXCIPIENT PROFILE[43]

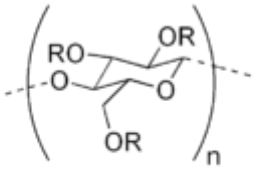
A.HYPERMELLOSE

SYNONYMS

Benecel MHPC; E464; hydroxyl-pro-pyl methylcellulose; HPMC; Hypro-mellosum; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; MHPC; Pharmacoat; Tylopur; Tylose MO.

STRUCTURAL FORMULA

Fig 14: Structure of Hypermellose



R = H or CH_3 or $CH_2CH(OH)CH_3$

NONPROPRIETARY NAMES

BP: Hypromellose

JP: Hypromellose

PhEur: Hypromellose

USP: Hypromellose

CHEMICAL NAME

Cellulose hydroxyl-pro-pyl methyl ether.

DESCRIPTION

Hypromellose is an odorless and tasteless, white or creamy-white

fibrous or granular powder.

FUNCTIONAL CATEGORY

Bio-adhesive material; coating agent; controlled-release agent; dispersing agent; dissolution enhancer; emulsifying agent; emulsion stabilizer; extended-release agent; film-forming agent; foaming agent; granulation aid; modified-release agent; mucoadhesive; release-modifying agent; solubilizing agent; stabilizing agent; suspending agent; sustained-release agent; tablet binder; thickening agent; viscosity-increasing agent.

APPLICATIONS

Hypromellose is widely used in oral, ophthalmic, nasal, and topical Pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating and as a matrix for use in extended release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.2.5% to 5.0%. Hypromellose is also used as a suspending and thickening agent in topical formulations. Compared with methylcellulose, hypromellose produces aqueous solutions of greater clarity, with fewer undissolved fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions. It is also used commercially in liquid nasal formulations at a concentration of 0.1%. Hypromellose is used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.

STABILITY AND STORAGE CONDITIONS

Hypromellose powder is a stable material, although it is hygroscopic After drying. Solutions are stable at pH 3–11. Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively. The gelation temperature is 50–908C, depending upon the grade and concentration of material. For temperatures below the gelation temperature, viscosity of the solution decreases as temperature is increased. Beyond the gelation temperature, viscosity increases as temperature is increased. Aqueous solutions are

comparatively enzyme-resistant, providing good viscosity stability during long-term storage. However, aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative: when hypromellose is used as a viscosity-increasing agent in ophthalmic solutions, benzalkonium chloride is commonly used as the preservative. Aqueous solutions may also be sterilized by autoclaving; the coagulated polymer must be redispersed on cooling by shaking. Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

INCOMPATABILITIES

Hypromellose is incompatible with some oxidizing agents. Since it is Nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

B. CARBOMER

NONPROPRIETARY NAMES

BP: Carbomers

PhEur:Carbomers

USP-NF:Carbomers

SYNONYMS

Acropyl; Acritamer; Acrylic acid Polymer; Carbomera; Carbopol; Carboxy Polymethylene; Polyacrylic acid; Carboxyvinyl Polymer; Pemulen; Tego Carbomer.

CHEMICAL NAME

CARBOMER [9003-01-4]

Note that alternative CAS registry numbers have been used for carbomer 934([9007-16-3]),940 (9007-17-4]) and 941([9062-04-08]). The CAS registry number [9007-17-4] has also been used for carbomer.

EMPIRICAL FORMULA AND MOLECULAR WEIGHT

Carbomers are synthetic high molecular weight polymers of acrylic acid that are cross linked with either allyl sucrose or allyl ethers of pentaerythritol. They contain between 52% and 68% of carboxylic acid(COOH) groups calculated on the dry basis. The BP2009 and PhEur 6.4 have a single monograph describing individual carbomer grades that vary in aqueous viscousity, polymer type, and polymerization solvent. The molecular weight of carbomer is theriotically estimated as $7*10^5$ to $4*10^9$. In an effort to measure the molecular weight between cross-links ,M_c,reserchers have extended the network theory of elasticity to swollen gels and have utilized the inverse relationship between the elastic modulus and M_c [1-3] .Estimated M_c values of 237600g/mol for carbomol 941 and of 104 400g/mol for carbopol 940 have been reported . In general ,carbomer polymers with lower viscousity and lower rigidity will have higher M_c values.Conversily ,high-viscousity,more rigid carbomer polymers will have lower M_c values.

STRUCTURAL FORMULA

Carbomer polymers are formed from repeating units of acrylic acid. The polymer chains are crosslinked with allyl pentaerythritol.

FUNCTIONAL CATEGORY

Bioadhesive material; controlled-release agent

Emulsifying agent;

Emulsion stabilizer;

Rheology modifier;

Stablizer;

Suspending agent and tablet binder

APPLICATIONS

Carbomers are used in liquid or semisolid pharmaceutical formulation as rheology modifiers. Formulations include creams, gels, lotions and ointments for use in ophthalmic, rectal, topical and vaginal preparations. carbomer grades with residual benzene content greater than 2ppm do not meet the specifications of the PhEur 6.4 monograph. However, carbomer having low residual of other solvent than the ICH-defined class IOVI solvents may be used in europe. Carbomer having low resuidals of ethl acetate, such as carbopol 971 P NF or carbopol 974PNF may be used in oral preparations, in suspensions, capsules or tablets. In tablet formulations, carbomer are used as controlled release agents and/or as blinders. In contrast to linear polymers, higher viscosity does not results in slower drug release with carbomers . Lightly cross linked carbomers are generally more efficient in controlling drug release than highly cross linked carbomers. In wet granulation processes, water, solvents or their mixtures can be used as the granulating fluid. The tackiness of wet mass may be reduced by including talc in the formulation or by adding certain cationic species to the granulating field. However the presence of cationic salts may accelerate the drug release rates and release rates and reduce bioadhesive properties. carbomer polymers have also been investigated in the preparation of sustained –release matrix beads, an enzime inhibitors of intestinal proteass in peptide –containing dosage forms as a bioadhesive for a cervical patch and for intranasally administered microspheres in magnetic granules for site-specific drug delivery to the esophagus, and in oral mucoadhesive controlled drug delivery systems. Carbomer copolymers are employed as emulasifying agents in the preparation of the oil-in water emulsion for external administrarion. carbomer 951 has been investigated as a viscosity increasing aid in the preparation of multiple emulsion microspheres. Carbomers are also used in cosmetics. Therapeutically carbomer formulation have been provided efficacious in improving symptoms of moderate to severe dry eye syndrome

Table 8: Use of carbomers

Use	Concentration
Emulsifying agent	0.1-0.5
Gelling agent	0.5-2.0
Suspending agent	0.5-1.0
Table blinder	0.75-3.0
Rate Controlling agent	5.0-30.0

DESCRIPTION

Carbomers are white-colored,'fluffy',acidic, hygroscopic powders with a characteristics slight oder.a granular carbomer is also available.

PHARMACOPEIAL SPECIFICATIONS

The USP32-NF27 has several monographs for different carbomer grades, while the BP 2009 and PhEur 6.4 have only a single monograph.

The USP32-NF27 lists three umberlla monographs carbomer copolymer, carbomer homopolymer and carbomer interpolymer, which separates carbomer products, based on polymer structure and apply to prodycts not polymerized in benzene. The differentiation within each umberlla monograph is based on viscousity characterastics.

The USP32-NF27 also lists monographs for carbomer 934,934p,940 and 941,which are manufactured usuing benzene. Currently these monographs can apply to products manufactured both with and without the use of benzene. Effectively from january 1 ,2011 products manufactured without the use of benzene will be officially tilted carbomer homopolymer provided they comply with the carbomer 1342,which applies to carbomer copolymers manufactured using benzene.

Carbomer polymers are also covered either individually or together in other pharmacopeias.

Note that unless otherwise indicated ,the test limits shown above apply to all grades of carbomer.

TYPICAL PROPERTIES

Acidity/alkalinity

pH=2.5-4.0 for 0.2% w/v aqueous dispersion;

pH=2.5-3.0 for acrypol 1% w/v aqueous dispersion;

Density (bulk) 0.2g/cm^3(powder);0.4g/cm^3(granular)

Density (tapped) 0.3g/cm^3(powder);0.4g/cm^3(granular)

Dissociation constant pK_a =6.0+0.5

Glass transition temperature 100-105^{0}c

Melting point :decomposition occurs within 30 minutes at 260^{0}c.

moisture content typical water content is upto 2% w/w. however ,carbomers are hygroscopic and a typical equlibrium moisture content at 25^{0}c and 50% relative humidity is 8-10% w/w. the moisture content of carbomer does not affect its thickness efficiency ,but an increase in the moisture content makes the carbomer more difficultto handle because it is less readily dispersed.

STABILITY AND STORAGE CONDITIONS

Carbomers are stable, hygroscopic material that may be heated at temperature below 104^{0}c and 2 hours without affecting their thickening efficiency. However exposure to excessive temperatures can result in discoloration and reduced stability. Complete decomposition occurs with hearing for ong fungi. In contrast microorganisms grow well in unpreserved aqueous dispersion and therefore an antimicrobial preservative such as 0.1% w/v thimerosal should be added. The w/v propylene Or 0.1%w/v thimerosal the addition of certain antimicrobials such as benzalkonium chloride or sodiam benzonite in high concentration can

cause cloudiness And a reduction in viscosity of carbomer dispersions. Aqueous gels may be sterilized by autoclaving with minimal changes in viscosity pH ,provided care is taken to exclude oxygen from the system or by gamma radiations although this technique may increase the viscosity of formulation. At room temperature carbomer disperse maintain their viscosity during storage for prolonged periods. Similarly dispersion viscosity is maintained or only slightly reduced at elevated storage temperature if an antioxidant is include in the formulation or if the dispersion is stored protected from the light . exposture to light causes oxidation that is reflected in a decrease in dispersion viscosity stability to light may be improved by the addition of 0.05-0.1% w/v edetic acid.

Carbomer powder should be stored in an alright corrosion resistant container and protected from moisture. The use of glass plastic or resin-lined container is recommended for the storage of formulation containing carbomer.

INCOMPATIBILITIES

Carbomers are discolored by resorcinol and are incompatible with phenol, cationic polymers,

Strong acids and high levels of electrolytes. Certain antimicrobial adjuvants should also be avoided or

Used at low levels, see section 11. Trace levels of iron and other transition metals can catalytically degrade carbomers dispersions.

Certain amino-functional actives from complexes with carbomers; often this can be prevented by adjusting the pH of the dispersion and/or te solubility perameter by using appropriate alcohols and polyols.

Carbomers also form pH- dependent complexes with certain polymeric excipients.Adjustment of pH and/or solubility perameter can also work in this sitation.

SAFTEY

Carbomers are used extensively in nonparenteral products, particularly topical liquid and semisolid preparations. Grades polymerized in ethyl acetate may also be used in oral formulations; see section 18. There is no evidence of systemic absorption of carbomer

polymers following oral administration. [56] Acute oral toxicity studies in animals indicate that carbomer934p has a low oral toxicity, with doses up to 8g/Kg being administered to dogs without fatalities occurring. Carbomers are generally regarded as essentially nontoxic and nonirritant materials there is no evidence in humans of hypersensitivity reactions to carbomers used topically

HANDLING PRECAUTIONS

Observe normal precautions appropriate to the circumstances and quantity of material handled. Excessive dust generation should be minimized to avoid the risk of explosion (lowest explosive concentration is 130 g/m^3). Carbomers dust is irritating to the eyes mucous membranes, and respiratory tract. In the event of eye contact with caroler dust. Saline should be used for eye irrigation purpose. Gloves, eye protection, and a dust respirator are recommended during handling. A solution of electrolytes (sodium chloride) is recommended for cleaning equipment after processing carbomers.

C. CHITOSAN

NONPROPRIETARY NAMES

BP: Chitosan hydrochloride

phEur: Chitosan hydrochloride

SYNONYMS

2-Amino2-deoxy(1,4)-β-D-glucopyranan;chitosanihydrochloridum;deacetylated chitin;deacetylchitin;β-1,4-poly-D-glucosamine;poly-D-glucosamine;poly-(1,4-β-D-glucopyranosamine).

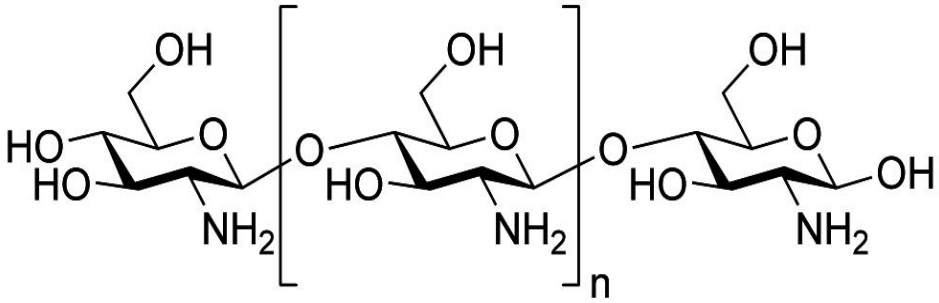
EMPERICAL FORMULA AND MOLECULAR WEIGHT

Partial deacetylation of chitin results in the production of chitosan, which is a polysaccharide comprising copolymers of glucosamine and N-acetylglucosamine. Chitosan is the ter4m applied to deacetylated chitins in various stages of deacetylation and depolymerization and it is therefore not easily defined in terms of its exact chemical composition. A clear

nomenclature with respect to the degrees of N-deacetylation between chitin and chitosan has not been defined, and as such chitosan is not one chemical entity but vadries in composition depending on the manufacturer. In essence, chitosan is chitin is chitin sufficiently deacetylated to form soluble amine salts. The degree of deacetylation necessary to obtain a soluble product must be greater than 80-85%. Chitosan is commercially available in several types and grades that vary in molecular weight by 10 000-1 000 000, and vary in degree of deacetylation and viscosity

STRUCTURAL FORMULA

Fig 15: Structure of Chitosan



FUNCTIONAL CATEGORY

Coating agent; disintegrant; film-forming agent; mucoadhesive; tablet binder; viscosity increasing agent.

APPLICATIONS

Chitosan is used in cosmetics and is under investigation for use in a number of pharmaceutical formulations. The suitability and performance of chitosan as a component of pharmaceutical drug formulations for drug delivery applications has been investigated in numerous studies. These include controlled drug delivery applications, use as a component of mucosaadhesive dosage forms rapid release dosage forms, improved peptide delivery colonic drug delivery systems, and use for gene delivery. chitosan has been processed into several pharmaceutical forms including gels films, beads, microspheres, tablets and coating for liposomes. Furthermore, chitosan may be processed into drug delivery systems using several

techniques including spray-drying, coatcervation, direct compression, and conventional granulation processes.

DESCRIPTION

Chitosan occurs as odorless, white or creamy-white powder or flakes. Fiber formation is quite common during precipitation and the chitosan may look ‘cottonlike

PHARMACOEPIAL SPECIFICATIONS

Table 9: Pharmacopeial Specifications for chitosan

TEST	PhEur
Identification	+
Characters	+
Appearance of solution	+
Matter insoluble in water	<=0.5
pH(1%w/v solution)	4.0-6.0
Viscosity	+
Degree of deacetylation	+
Chlorides	+10.0-20.0%
Heavy metals	<=40ppm
Loss of drying	<=10%
Sulfated ash	<=1.0%

TYPICAL PROPERTIES

Chitosan is cationic polyamine with a high charge density at pH<6.5, and so adheres to negatively charged surface and chelates metal ions. It is a linear polyelectrolyte with reactive hydroxyl and amino groups available in for chemical reaction and salt formation the properties of chitosan relate to its polyelectrolyte polymeric carbohydrate character. The presence of a number of amino groups allows chitosan to react chemically with anionic systems, which results in alteration of physiochemical characteristics of such combinations. The nitrogen in chitosan is mostly in the form of primary aliphatic amino groups. Chitosan therefore undergoes reaction typical of amines: for example N-acylation and Schiff reactions.(3) Almost all functional properties of chitosan depend on chain length, chain density , and chain charge distribution.(8) Numerous studies have demonstrated that the salt form, molecular weight, and degree of deacetylation as well as pH at which the chitosan is used all influence how this polymer is utilizes in pharmaceutical applications.(7)

Acidity/alkalinity pH= 4.0-6.0(1 % w/v aqueous solution)

Density 1.35-1.40 g/cm^3

Glass transition temperature 203^{o}C

Moisture content chitosan adsorbs moisture from the atmosphere, the amount of water adsorbed depending upon the initial moisture content and the temperature and relative humidity of the surrounding air.

PARTICLE SIZE DISTRIBUTION

Solubility sparingly soluble in water ; practically insoluble in ethanol(95%), other organic solvents, and neutral or alkali solutions at pH above approximately 6.5. chitosan dissolves readily in dilute and concentrated of most organic acids and to some extent in mineral inorganic acids(except phosphoric and sulfuric acids). Upon dissolution, amine groups of the polymer become protonated, resulting in a positively charged polysaccharide(RNH3) and chitosan salts (chloride,glutamate,etc.) that are soluble in water; the solubility is affected by the degree of deacetylation. Solubility is also greatly influenced by the addition of salts to the solution. The higher the ionic strength, the lower the solubility as a result of salting out effect, which leads to precipitation of chitosan solution. When chitosan is in solutions, the repulsions

between the deacetylated units and their neighboring glucosamine units cause it to exist in an extended conformation. Addition of an electrolyte reduces this effect and the molecule possesses a more random, coli-like conformation.

VISCOSITY (DYNAMIC)

A wide range of viscosity types is commercially available. Owing to its high molecular weight and linear un-branched structure, chitosan is an excellent viscosity-enhancing agent in an acid environment. It acts as pseudo-plastic material, exhibiting a decrease in viscosity with increasing rate of sheer. The viscosity of chitosan solutions increases with increasing chitosan concentration, decreasing temperature, and increasing degree of deacetylation.

Table 10: Typical viscosity(dynamic) values for chitosan in different acids

Acid	**1% acid concentration**		**5% acid concentration**		**10% acid concentration**	
	Viscosity	pH	Viscosity	pH	viscosity	Ph
Acetic	260	4.1	260	3.3	260	2.9
Adipic	190	4.1	-	-	-	-
Citric	35	3.0	195	2.3	215	2.0
Formic	240	2.6	185	2.0	185	1.7
Lactic	235	3.3	235	2.7	270	2.1
Malic	180	3.3	205	2.3	220	2.1
Malonic	195	2.5	-	-	-	-
Oxalic	12	1.8	100	1.1	100	0.8
Tartaric	52	2.8	135	2.o	160	1.7

STABILITY AND STORAGE CONDITIONS

Chitosan powder is a stable material at room temperature, although it is a hygroscopic after drying. Chitosan should be stored in a tightly closed container in a cool, dry place. The PhEur 6.5 specifies that chitosan should be stored at a temperature of 2-8^{o}C

INCOMPATABILITIES

Chitosan is incompatible with strong oxidizing agents

SAFTEY

Chitosan is being investigated widely for use as an excipient in oral and other pharmaceutical formulations. It is also used in cosmetics. Chitosan is generally as a nontoxic and nonirritant material. It is biocompatible [41] with both healthy and infected skin. Chitosan has been shown to be biodegradable. LD_{50}(mouse, oral):>16g/Kg

HANDLING PRECAUTIONS

Observe normal precautions appropriate to the circumstances and quantity of material handled. Chitosan is combustile; open flames should be avoided. Chitosan is temperature sensitive and should not be heated above 200^{o}C. Airborne chitosan dust may explode in the presence of a source of ignition, depending on its moisture content and particle size. Water, dry chemicals, carbon dioxide, sand, or, foam fire fighting media should be used.

Chitosan may cause skin or eye irritation. It may be harmful if absorbed through the skin or if inhaled, and may be irritating to mucous membranes and the reparatory tract. Eye and skin protection and protective clothing are recommended; wash thoroughly after handling. Prolonged or repeated exposure (inhalation) should be avoided by handling in a well-ventilated area and wearing a respirator.

D. SODIUM BICARBONATE

NONPROPRIETARY NAMES

• BP : Sodium bicarbonate

• JP : Sodium bicarbonate

• PhEur : Natrii hydrogenocarbonas

• USP : Sodium bicarbonate

SYNONYMS

Baking soda; E500; Effer-Soda; monosodium carbonate; Sal de Vichy; sodium acid carbonate; sodium hydrogen carbonate.

CHEMICAL NAME

Carbonic acid monosodium salt

EMPIRICAL FORMULA AND MOLECULAR WEIGHT

NaHCO3 84.01

FUNCTIONAL CATEGORY

Alkalizing agent; therapeutic agent.

APPLICATIONS

Sodium bicarbonate is generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules. It is also widely used to produce or maintain an alkaline pH in a preparation.

Tablets may also be prepared with Sodium bicarbonate alone since the acid of gastric fluid is sufficient to cause effervescence and disintegration. Sodium bicarbonate is also used in tablet formulations to buffer drug molecules that are weak acids, thereby increasing the rate of

tablet dissolution and reducing gastric irritation. The effects of tablet binders, such as polyethylene glycols, Microcrystalline cellulose, silicified Microcrystalline cellulose, pregelatinized starch, and povidone, on the physical and mechanical properties of Sodium bicarbonate tablets have also been investigated. Additionally, Sodium bicarbonate is used in solutions as a buffering agent for Erythromycin, Lidocaine, local anesthetic solutions, and total parenteral nutrition solutions. In some parenteral formulations, e.g., in Niacin parenteral formulation, Sodium bicarbonate is used to produce a sodium salt of the active ingredient that has enhanced solubility. Sodium bicarbonate has also been used as a freeze-drying stabilizer and in toothpastes. Recently, Sodium bicarbonate has been used as a gas-forming agent in alginate raft system and in floating, controlled-release oral dosage forms of Furosemide and Cisapride. Tablet formulations containing Sodium bicarbonate have been shown to increase the absorption of Paracetamol, and improve the stability of Levothyroxine.

Sodium bicarbonate is used in food products as an alkali or as a leavening agent, e.g. baking soda.

Table 11: Uses of sodium bicarbonate

Use	Concentration (%)
Buffer in tablets	10-40
Effervescent tablets	25-50
Isotonic injection/infusion	1.39

Use Concentration (%) Buffer in tablets 10–40 Effervescent tablets 25–50 Isotonic injection/infusion 1.39

Description:

Sodium bicarbonate occurs as an odorless, white, crystalline powder with a saline, slightly alkaline taste. The crystal structure is monoclinic prisms. Grades with different particle sizes, from a fine powder to free-flowing uniform granules, are commercially available.

Typical Properties:

Acidity/alkalinity: pH = 8.3 for a freshly prepared 0.1 M aqueous solution at 25°C; alkalinity increases on standing, agitation, or heating.

Density (bulk): 0.869 g/cm3

Density (tapped): 1.369 g/cm3

Density (true): 2.173 g/cm3

Freezing point depression: 0.381°C (1% w/v solution)

Melting point: 270°C (with decomposition)

Moisture content: below 80% relative humidity, the moisture content is less than 1% w/w. Above 85% relative humidity, sodium bicarbonate rapidly absorbs excessive amounts of water and may start to decompose with loss of carbon dioxide.

Osmolarity: a 1.39% w/v aqueous solution is isoosmotic with serum.

Refractive index: n20 D = 1.3344 (1% w/v aqueous solution

Solubility: Solvent Solubility at 20°C unless otherwise stated Ethanol (95%) Practically insoluble Ether Practically insoluble 1 in 11 1 in 4 at 100°Ca 1 in 10 at 25°C Water 1 in 12 at 18°C

Table 12: Solubility of Sodium bi carbonate

SOLVENT	SOLUBILITY
Ethanol(95%)	Practically insoluble
Ether	Practically insoluble
Water	1 in 4 at 100^0C, 1 in 10 at 25^0C, 1 in 12 at 18^0C

STABILITY AND STORAGE CONDITIONS

When heated to about 50°C, Sodium bicarbonate begins to dissociate into carbon dioxide, sodium carbonate, and water; on heating to 250–300°C, for a short time, Sodium bicarbonate is completely converted into anhydrous sodium carbonate. The effects of relative humidity and temperature on the moisture sorption and stability of Sodium bicarbonate powder have been investigated. Sodium bicarbonate powder is stable below 76% relative humidity at 25°C and below 48% relative humidity at 40°C.At 54% relative humidity, the degree of pyrolytic decarboxylation of Sodium bicarbonate should not exceed 4.5% in order to avoid detrimental effects on stability.

At ambient temperatures, aqueous solutions slowly decompose with partial conversion into the carbonate; the decomposition is accelerated by agitation or heat. Aqueous solutions of Sodium bicarbonate may be sterilized by filtration or autoclaving. To minimize decomposition of Sodium bicarbonate by decarboxylation on autoclaving, carbon dioxide is passed through the solution in its final container, which is then hermetically sealed and autoclaved. The sealed container should not be opened for at least 2 hours after it has returned to ambient temperature, to allow time for the complete reformation of the bicarbonate from the carbonate produced during the heating process.

Sodium bicarbonate is stable in dry air but slowly decomposes in moist air and should therefore be stored in a well-closed container in a cool, dry place.

INCOMPATIBILITIES

Sodium bicarbonate reacts with acids, acidic salts, and many alkaloidal salts, with the evolution of carbon dioxide. Sodium bicarbonate can also intensify the darkening of salicylates. In powder mixtures, atmospheric moisture or water of crystallization from another ingredient is sufficient for Sodium bicarbonate to react with compounds such as boric acid or alum. In liquid mixtures containing bismuth subnitrate, Sodium bicarbonate reacts with the acid formed by hydrolysis of the bismuth salt. In solution, Sodium bicarbonate has been reported to be incompatible with many drug substances such as Ciprofloxacin, Amiodarone, Nicardipine, and Levofloxacin.

SAFTEY

Sodium bicarbonate is used in a number of pharmaceutical formulations including injections and ophthalmic, otic, topical, and oral preparations. Sodium bicarbonate is metabolized to the sodium cation, which is eliminated from the body by renal excretion, and the bicarbonate anion, which becomes part of the body's bicarbonate store. Any carbon dioxide formed is eliminated via the lungs. Administration of excessive amounts of Sodium bicarbonate may thus disturb the body's electrolyte balance, leading to metabolic alkalosis. When used as an excipient, Sodium bicarbonate is generally regarded as an essentially nontoxic and nonirritant material. LD50 (mouse, oral) : 3.36 g/kg LD50 (rat, oral) : 4.22 g/kg Handling Precautions Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

REGULATORY STATUS

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (injections; ophthalmic preparations; oral capsules, solutions, and tablets). Included in parenteral (intravenous infusions and injections) and nonparenteral medicines (ear drops, eye lotions, oral capsules, chewable tablets, effervescent powders, effervescent tablets, granules, tablets, suppositories and suspensions) licensed in the UK.

E.CITRIC ACID

Nonproprietary Names

BP: Citric Acid Monohydrate

JP: Citric Acid Hydrate

PhEur: Citric Acid Monohydrate

USP: Citric Acid Monohydra

SYNONYMS

Acidum citricum monohydricum; E330; 2-hydroxypropane-1,2,3-

tricarboxylic acid monohydrate.

CHEMICAL NAME

2-Hydroxy-1,2,3-propanetricarboxylic acid

4 Empirical Formula and Molecular Weight

C6H8O7_H2O 210.14

FUNCTIONAL CATEGORY

Acidifying agent; antioxidant; buffering agent; chelating agent;

flavor enhancer; preservative.

APPLICATIONS

Citric acid (as either the monohydrate or anhydrous material) is widely used in pharmaceutical formulations and food products, primarily to adjust the pH of solutions. It has also been used experimentally to adjust the pH of tablet matrices in enteric-coated formulations for colon-specific drug delivery.(1) Citric acid monohydrate is used in the preparation of effervescent granules, while anhydrous citric acid is widely used in the preparation of effervescent tablets.(2–4) Citric acid has also been shown to improve the stability of spray-dried insulin powder in inhalation formulations. In food products, citric acid is used as a flavor enhancer for itstart, acidic taste. Citric acid monohydrate is used as a sequestering agent and antioxidant synergist; see Table I. It is also a componentof anticoagulant citrate solutions. Therapeutically, preparations containing citric acid have been used to dissolve renal calculi.

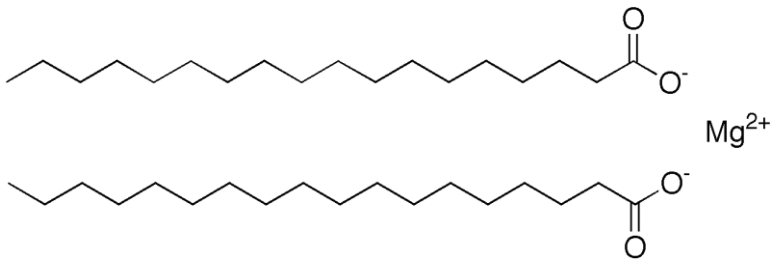
F.MAGNESIUM STEARATE

SYNONYMS

Dibasic magnesium stearate; magnesium distearate; magnesia stearate; magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt;

STRUCTURE

Fig 16: Structure of Magnesium stearate



CHEMICAL NAME

Octadecanoic acid magnesium salt.

STRUCTURAL FORMULA

[CH3 (CH2)16COO] 2Mg

FUNCTIONAL CATEGORY

Tablet and capsule lubricant.

DESCRIPTION

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

APPLICATIONS

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

STABILITY AND STORAGE CONDITIONS

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

INCOMPATIBILITIES

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloid salts.

G.CELLULOSE, MICROCRYSTALLINE (Avicel PH-101)

NONPROPRIETARY NAMES

BP : Microcrystalline cellulose

JP : Microcrystalline cellulose

PhEur : Cellulosum microcristallinum

USPNF : Microcrystalline cellulose

SYNONYMS

Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres ; Fibrocel; Pharmacel; Tabulose; Vivapur.

Chemical Name and CAS Registry Number: Cellulose [9004-34-6]

Empirical Formula and Molecular Weight: (C6HO105)n = 36 000,where n =220.

FUNCTIONAL CATEGORY

Adsorbent; suspendin agent; tablet and capsule diluent; tablet disintegrant.

STRUCTURAL FORMULA

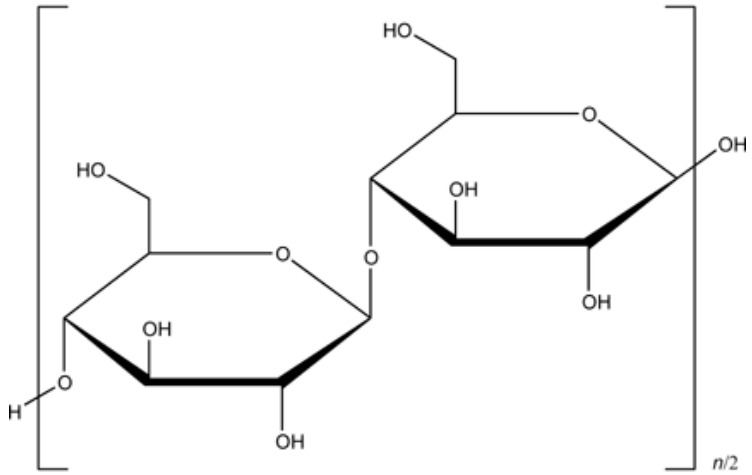


Fig 17: Structure of MCC

APPLICATIONS

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and directcompression processes. In addition to its use as a binder/diluent, Microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting. Microcrystalline cellulose is also used in cosmetics and food products.

Table 13: Uses of Microcrystalline cellulose.

Si.No	Use	Concentration
1	Adsorbent	20-90
2	Antiadherent	5-20
3	Capsule binder/diluents	20-90

4	Tablet disintegrent	5-15
5	Tablet binder/diluent	20-90

DESCRIPTION

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

TYPICAL PROPERTIES

Density (bulk): 0.32 g/cm for Avicel PH-101

Density (tapped): 0.45 g/cm for Avicel PH-101;

Density (true): 1 .512–1.668 g/cm

Melting point: C hars at 260–270°C.

MOISTURE CONTENT

Typically less than 5% w/w. However, different grades may contain varying amounts of water. Microcrystalline cellulose is hygroscopic.

PARTICLE SIZE DISTRIBUTION

Typical mean particle size is 20–200 µm. Different grades may have a different nominal mean particle size.

SOLUBILITY

Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

STABILITY AND STORAGE CONDITIONS

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

INCOMPATIBILITIES

Microcrystalline cellulose is incompatible with strong oxidizing agents.

SAFTEY

Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a relatively nontoxic and nonirritant material.Microcrystalline cellulose is not absorbed systemically following oral administrationand thus has little toxic potential. Consumption of large quantities of cellulose may have a laxative effect, although this is unlikely to be a problem when cellulose is used as an excipient in pharmaceutical formulations. Deliberate abuse of formulations containing cellulose, either by inhalation or by injection, has resulted in the formation of cellulose granulomas.

REGULATORY STATUS

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (inhalations; oral capsules, powders, suspensions, syrups, and tablets; topical and vaginal preparations). Included in non-parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

MTHODOLOGY

EXPEREMENTAL METHODS

PREFORMULATION STUDIES

Preformulation may be described as a stage of development during which the physicochemical and biopharmaceutical properties of a drug substance are characterized. It is important part of the drug development process. The information relating to drug development acquired during this phase is used for making critical decisions in subsequent stages of development. A wide variety of information must be generated to develop formulations rationally. Characterization of the drug is a very important step at the preformulation phase of product development followed by studying the properties of the excipients and their compatibility.

The API was tested for the following properties:

1.Physical characteristics

- Solubility

2. Drug excipients compatibility

SOLUBILITY STUDY[44]

The solubility study was used to identify the suitable solvent that possess good solubilizing capacity for Imatinib. Solubility of imatinib in various solvents was determined by adding excess of drug in each of selected solvents in each conical flask containing 20 ml and is shaken for 24 hours using Rotary shaking apparatus. Then the solubility of drug in each solvent is observed visually and by UV spectrophotometrically at maximum wave length of 236 nm after relevant dilutions.

COMPATIBILITY STUDIES

PHYSICAL COMPATIBILITY STUDIES[45]

Drug Excipient compatibility study by Stability studies

The drug-excipient compatibility studies were determined in 1:1 ratios under Humidity chamber at different temperature and humidity conditions for the period of four weeks.

Table 14 : Drug and Excipients Compatibility by Stability Studies

S. No.	Drug and Excipients	Ratio
1	Imatinib	
2	Imatinib+ HPMC K15M	1:1
3	Imatinib+ Carbopol	1:1
4	Imatinib+ Chitosan	1:1
6	Imatinib+ SBC	1:1
7	Imatinib+ Citric acid	1:1
8	Imatinib+ Magnesium sterate	1:1
9	Imatinib+ MCC	1:1

1. Drug and excipients ratios were accurately weighed and sifted
2. Physical mixtures were blended in mortar with pestle to get uniformity
3. The above mixtures were sieved through # 40 sieve. The blends were filled in glass vials with suitable stoppers
4. Label the vials and charged at accelerated conditions.
5. The drug-excipient blends were prepared and charged for accelerated conditions at40^{o}C / 75%RH for a period of 1 month. The samples are analysed for related substances.
6. FTIR studies were done to verify if there was any interaction between the pure drug and excipients employed. The various FTIR graphs of pure drug, excipients are mixed and the blend was formulated into IR pellet and scanned.

CHMICAL COMPATIBILITY STUDIES[46]

FTIR (Fourier transform infra-red spectroscopy) studies:

Infra-red spectroscopy is widely used in pharmaceutical research. IR spectroscopy is routinely used for compound identification as a fingerprinting tool. IR spectroscopy also has its application in studies of drug – excipient interaction, contaminant analysis etc. IR spectrum with high quality is acquired with the FTIR method. Fourier transformation

mathematical operation can resolve the signal captured by detector as a summation of all these signals and in connection with the contribution of each wavelength. Several sampling methods are available for IR spectrum acquisition, such as alkali halide pellet, mineral-oil mull, diffuse reflectance technique and attenuated total reflectance. Each has its advantages and disadvantages.

IR spectrum with high quality is acquired with KBr pellet method. Compatibility study of drug with the excipients was determined by using FTIR. The sample powder of drugs, excipients and mixture of both were subjected to FTIR study. The mixture spectra were compared with that of the original spectra

STANDARD CURVE OF IMATINIB[47]

Preparation of 0.1N Hydrochloric acid:

8.5 ml of concentrated hydrochloric acid was diluted with distilled water and the volume was made upto 1000ml with distilled water.

Preparation of Imatinib Standard Stock Solution In 0.1N HCl:

A Standard Solution of Imatinib was prepared by dissolving accurately weighed 100 mg of Imatinib with little quantity of 0.1N HCl solution, in a 100 ml volumetric flask. The volume was made up to 100 ml with 0.1N HCl, to obtain a stock solution of 1000µg/ml.

From the above solution several dilutions are made to obtain 50, 75, 100, 125, 150 mcg/ml solutions. The absorbencies of these drug solutions were estimated at λ_{max} 236 nm.

FORMULATION DEVELOPMENT OF GASTRO-RETENTIVE TABLETS

The active ingredient i.e. Imatinib and each single polymer (HPMC K15M, Carbopol, Chitosen) and also mixture of three polymers, filler (MCC), lubricant (Magnesium stearate), Gas forming ingredients (SBC, Citric acid mono-hydrate) were blended together by dry mixing in a laboratory mixer (polybag) for 10 mins. The mixture was compressed by using 12mm standard flat round punch and die set at compression force 4-6 kg.

Table 15: Formulation development of Imatinib Gastro-retentive tablets:

SI.NO	Quantity for each tablet(mg)					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
API	100	100	100	100	100	100
HPMC K15	100	200	300	-	-	100
Carbopol	-	-	-	300	-	100
Chitosan	-	-	-	-	300	100
SBC	30	30	30	30	30	30
Citric acid	5	5	5	5	5	5
Magnesium sterate	10	10	10	10	10	10
MCC	355	255	155	155	155	155
Avg. Wt	600	600	600	600	600	600

Before going for the compression the drug and excipients blend is supposed to be evaluated for several pre-compression parameters which are given as follows.

PRE-COMPRESSION EVALUATION PARAMETERS

Angle of repose[48]

The angle of repose of powder blend was determined by the funnel method. The accurately weighed powder blends were taken in the funnel. The height of the funnel was maintained approximately 2-4 cm from the top of the powder pile in order to minimize the impact of falling powder on the tip of the cone. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

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

Where, h and r are the height and radius of the powder cone.

Table 16: Comparison between angle of repose and flow properties

Angle of repose (θ)	Flow
< 25	Excellent
25 – 30	Good
30 – 40	Moderate (addition of 0.2% glidant required)
> 40	Poor

Bulk Density[49]

About 20gms of material was passed through a sieve #40 to break up agglomerates and introduced into a dry 50 ml cylinder. Without compacting the powder carefully leveled and the un-settled apparent volume, Vo, was recorded. The bulk density was calculated in grams per mL, using the following formula

$$\textbf{Bulk density} = M/V_0$$

Where, M = total mass of the material.

Tapped Density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a mechanical tapped density tester. The cylinder was tapped until no change in volume and then tapped volume V_f was measured to the nearest graduated unit. The tapped density was calculated, in grams per mL, using the formula:

$$\textbf{Tapped density} = M/V_f$$

Hausner's Ratio

It indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density.

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Table 17: Scale of Flowability according to Hausner's ratio

Hausner's ratio	Flow character
1.0-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.59	Very poor
> 1.60	Very, very poor

Compressibility index (Carr's Index): CI

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. A material having values of less than 20% has good flow property

$$\text{CI} = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped Density}} \times 100$$

Table 18: Scale of Flowability according to Compressibility index

% Comp. Index	Properties
<12	Free flowing
12-16	Good
18-21	Fair
23-35	Poor
33-38	Very poor
>40	Extremely poor

Post compression evaluation parameters

The tablets were evaluated for in process and finished product quality control tests i.e. appearance, dimensions (diameter and thickness), weight variation, hardness, friability, assay, and drug content.

Weight variation[50]

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit. USP official limits of percentage deviation of tablet are presented in the table.

Table 19: Weight variation limits

Maximum % of weight difference allowed	Average weight of tablet (mg)	
	USP	**IP**
10	<130	<80
7.5	130- 324	80 – 250
5	>324	>250

Tablet hardness[51]

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. 3 tablets were chosen randomly and tested for hardness. The average hardness of 3 determinations was recorded.

Friability

Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients.

Method

10 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator, dusted off the fines and again weighed and the weight was recorded.

$$\text{friability} = \frac{(w_1 - w_2)}{w_1} \times 100$$

Where:w_1= weight of the tablet before test.

. w_2 = weight of the tablet after test

Content Uniformity[52]

The tablets were tested for their drug content uniformity. At random 10 tablets were weighed and powdered. The powder equivalent to 100 mg of drug was weighed accurately and dissolved in 100ml of 0.1N HCl solution. The solution was shaken thoroughly. The un-dissolved matter was removed by filtration through Whatman No.1 filter paper. Then transfer 1mL of the above solution into 100mL volumetric flask and make up the volume with 0.1N HCl solution. The absorbance of the diluted solutions was measured at 236nm. By using UV spectrophotometer taking 0.1N HCl as blank

***In-Vitro* Buoyancy studies**[53]

In vitro buoyancy was determined by floating lag time. The tablets were placed in a 100 mL beaker containing 0.1N HCL. The time required for the tablet to rise to the surface and to float was determined as **floating lag time.** The duration of time for which the dosage constantly remained on the surface of medium was determined as the **total floating time.**

Swelling studies

The extent of swelling was measured in terms of % of weight gained by the tablet. One tablet from each formulation was introduced into Basket type dissolution apparatus containing 900 ml 0.1N HCl (37^0C) at 50 RPM, the tablets were removed at different time intervals and the weight of the swollen tablet is noted.

Finally the swelling index of the tablet was calculated by using the formula below

$$\text{Swelling index (\%)} = \frac{M_t - M_0}{M_0} \text{ X } 100$$

Where, M_t – weight of tablets at time‘t’;

M_0 –initial weight of tablets

***In-Vitro* Dissolution studies[54]**

The *in vitro* drug release study was performed for all the tablets using USP type II dissolution apparatus under the following conditions.

Dissolution test parameters:

Medium	900 mL of 0.1N HCl
Temperature	37ºC±0.5ºC
RPM	50
Sampling Volume	5 ml
Sampling time	1, 4, 8, 16, 20 hours

Preparation 0.1 N HCl:

Take 8.5 ml of concentrated hydrochloric acid in a 1000 ml volumetric flask and make up the volume.

Procedure

Tablet was introduced into dissolution test apparatus and the apparatus was set at 50rpm. 5 ml of sample was withdrawn at the predetermined time intervals. Samples were analyzed by UV spectrophotometer at 236nm using 0.1N HCl solution as blank.

Stability studies[55]

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications. Stability studies were conducted for the optimized gastroretentive formulation of Imatinib. The stabilitystudy was performed as per following.

Preliminary stability of the optimized batch

The optimized batch (F4) was charged for accelerated stability studies as per ICH guidelines.

RESULTS AND DISCUSION

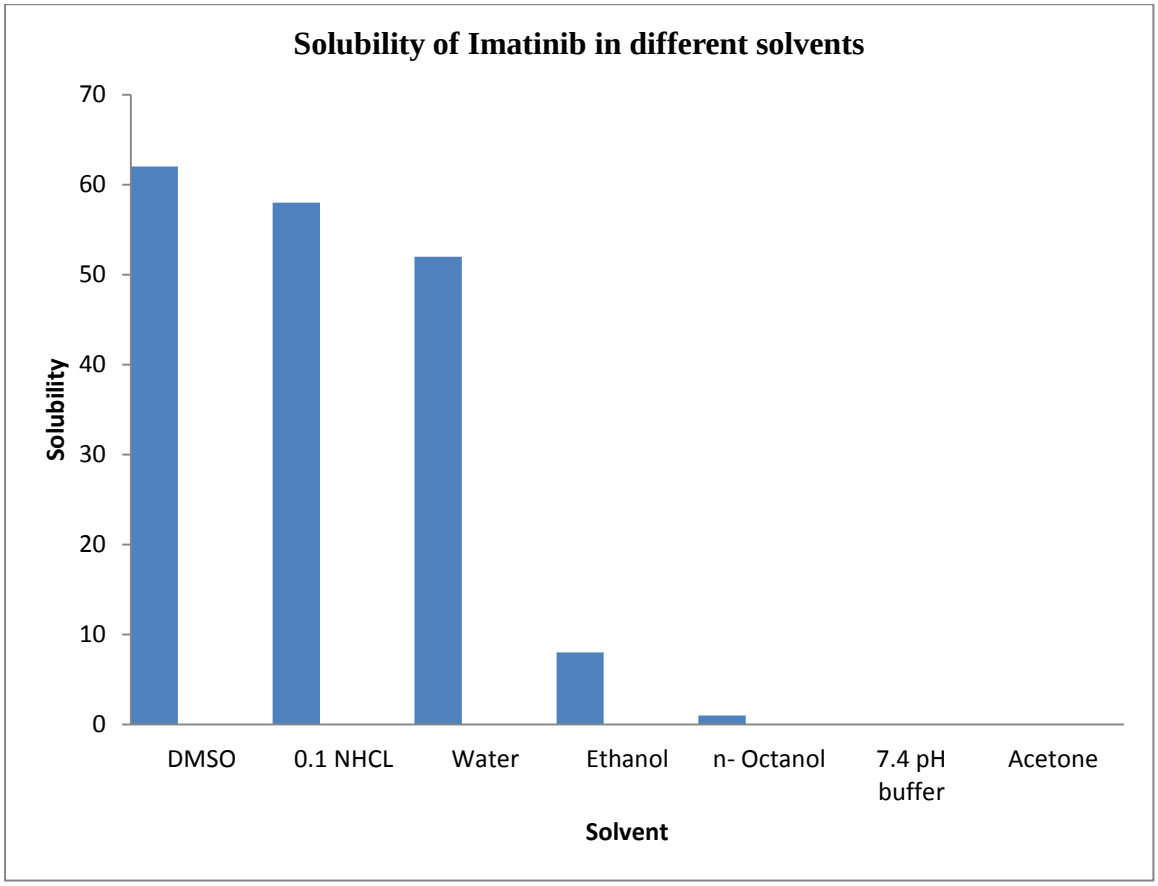
Results

In the present work tablet dosage form containing Imatinib were prepared by using direct compression method. The prepared dosage forms were evaluated by different methods which are as follows.

SOLUBILITY STUDIES

The solubility of Imatinib is evaluated in different solvents.

Fig 18: Comparison of solubility profile of Imatinib in different solvents



COMPATIBILITY STUDIES

PHYSICAL COMPATIBILITY

Table 20: Results of Excipients Compatibility by Stability Studies

S. No.	Drug and Excipients	Initial Physical Description	40°C / 75% RH (Closed)		
			1st Week	2nd Week	4th Week
1	Imatinib	White powder	NCC	NCC	NCC
2	Imatinib+ HPMC K15M	Off-white powder	NCC	NCC	NCC
3	Imatinib+ Carbopol	Off-white powder	NCC	NCC	NCC
4	Imatinib+ Chitosan	Off white powder	NCC	NCC	NCC
6	Imatinib+ SBC	white powder	NCC	NCC	NCC
7	Imatinib+ Citric acid	Off-white powder	NCC	NCC	NCC
8	Imatinib+ Magnesium sterate	Off-white powder	NCC	NCC	NCC
9	Imatinib+ MCC	Off-white powder	NCC	NCC	NCC

NCC indicates that there is no interaction between drug and excipients at 40°C/75% RH.

CHEMICAL COMPATIBILITY

Compatability study of active pharmaceutical ingredient and excipients:

The drug and excipient mixtures are evaluated for chemical compatibility by means of FTIR and the results are given in the following figures

Fig 19: Spectra of Pure Drug

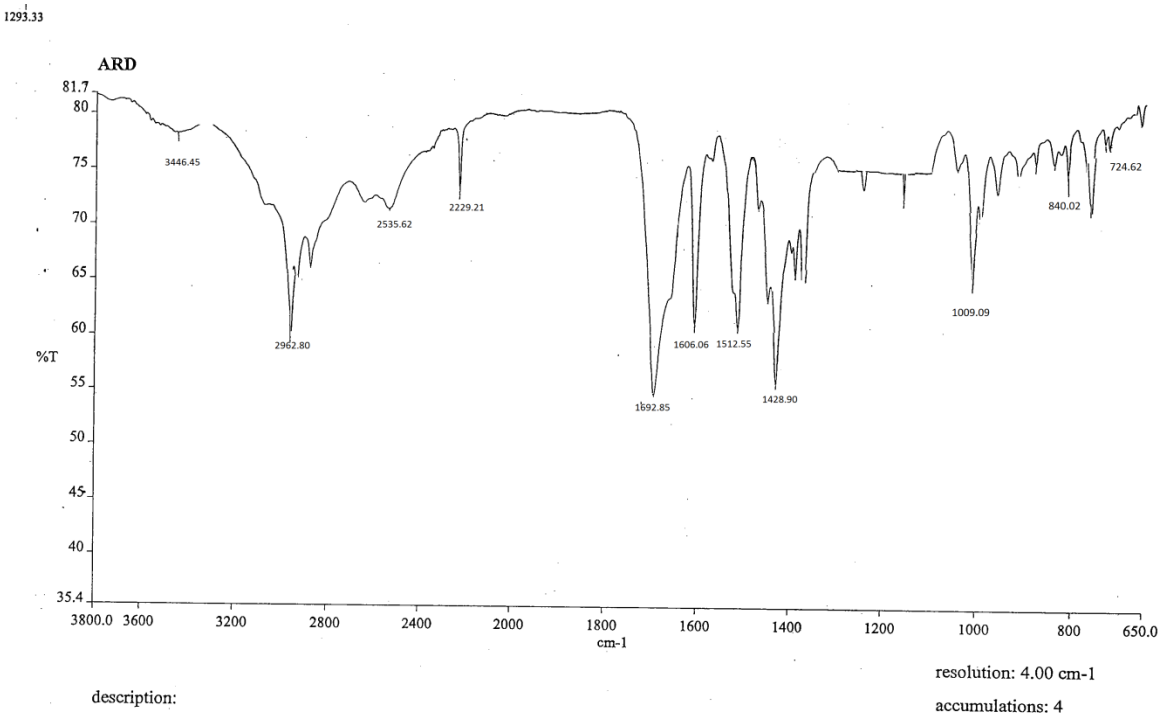


Fig 20: Spectra of Pure Drug and HPMC K15M

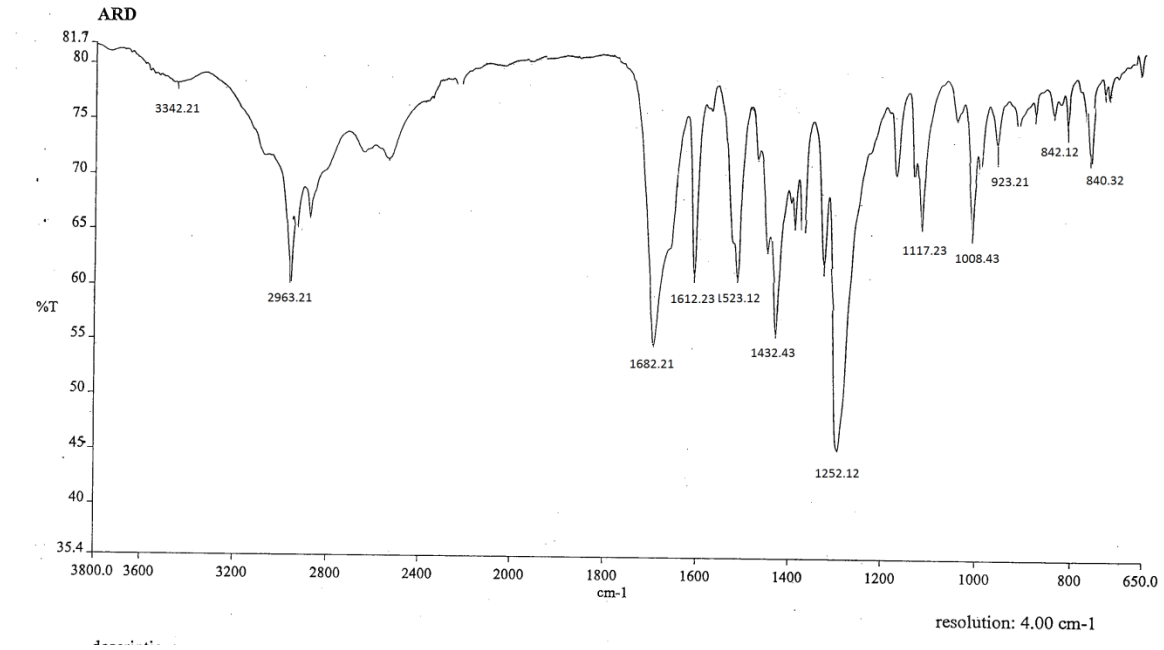


Fig 21: Spectra of Pure Drug and Carbopol

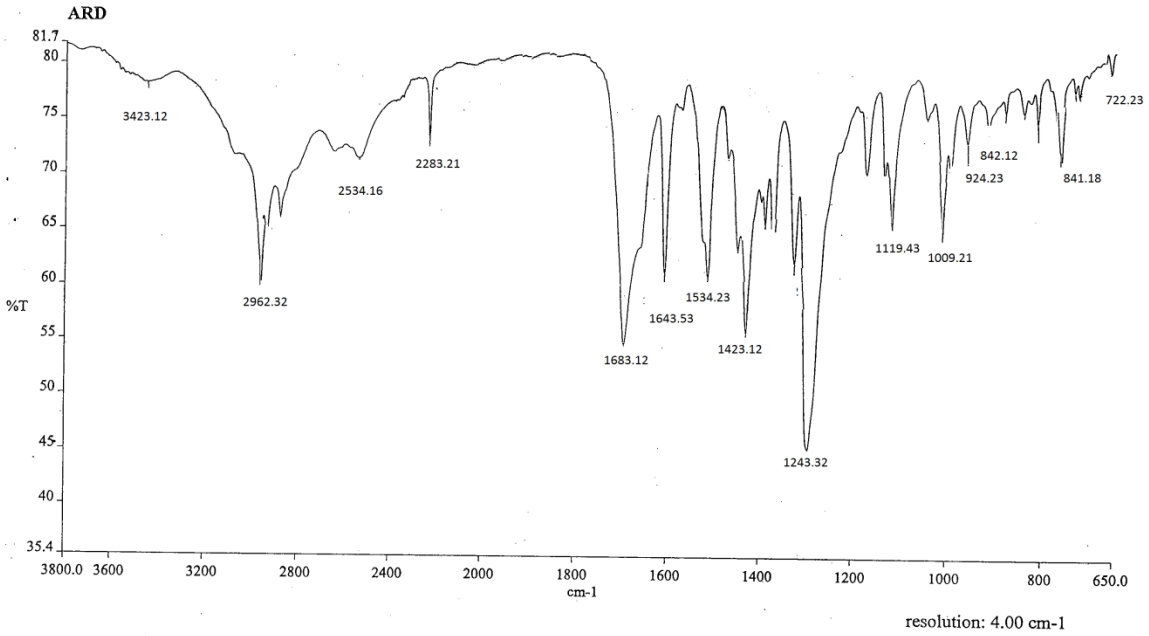


Fig 22: Spectra of Pure Drug and Chitosan

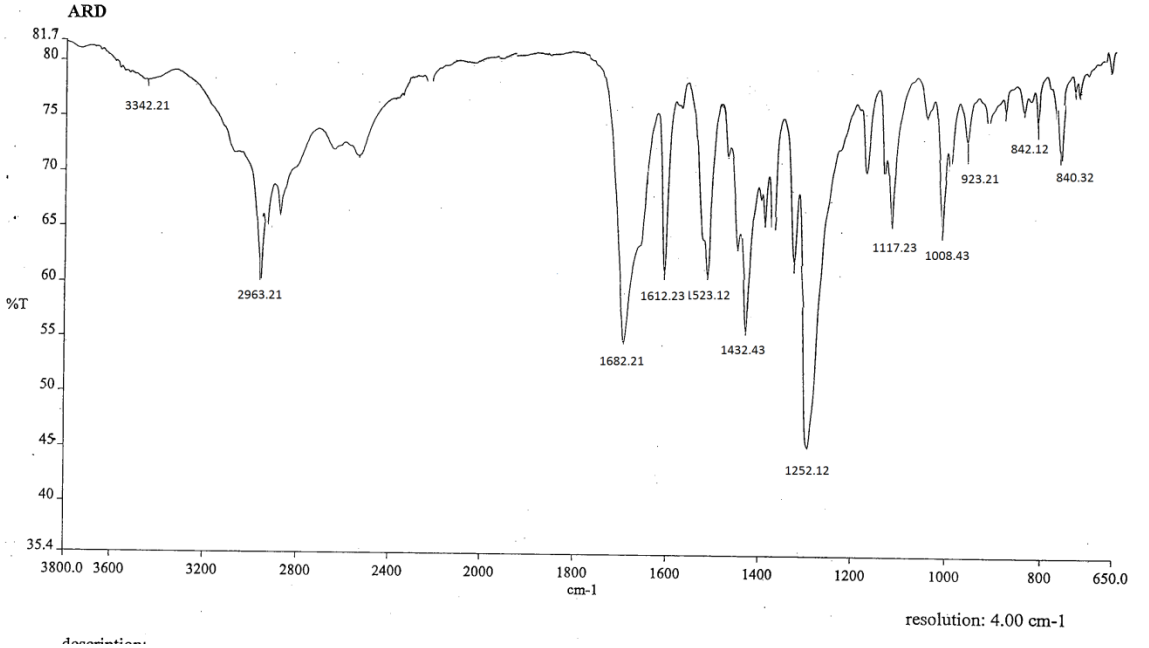


Fig 23: Spectra of Pure Drug and Citric Acid

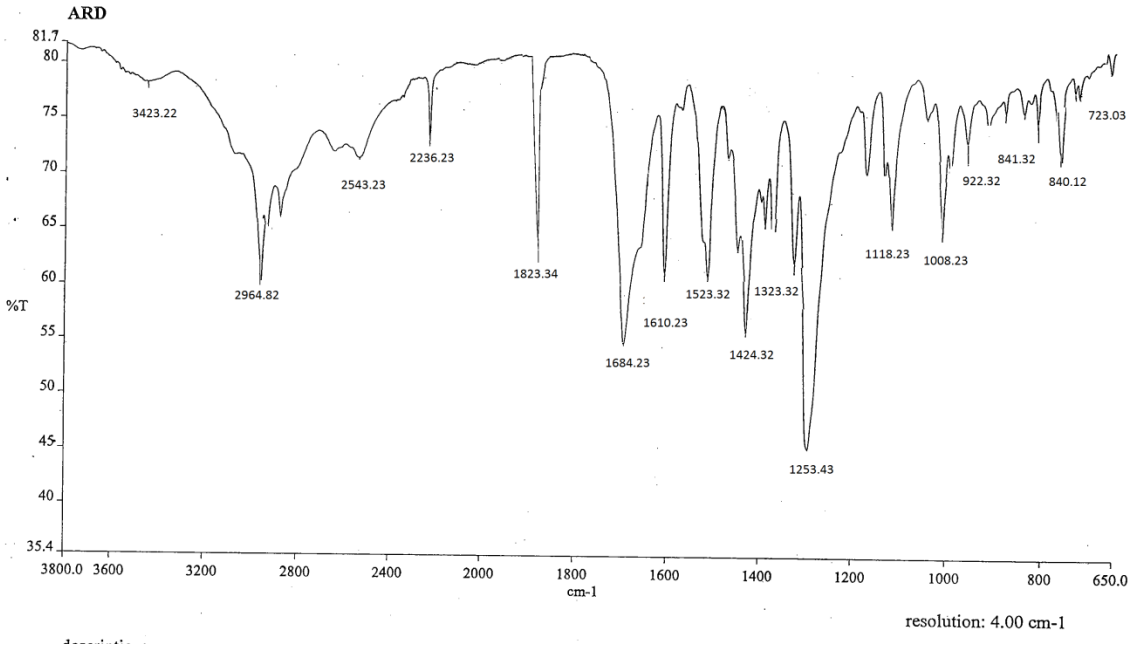


Fig24: Spectra of Pure Drug and MCC

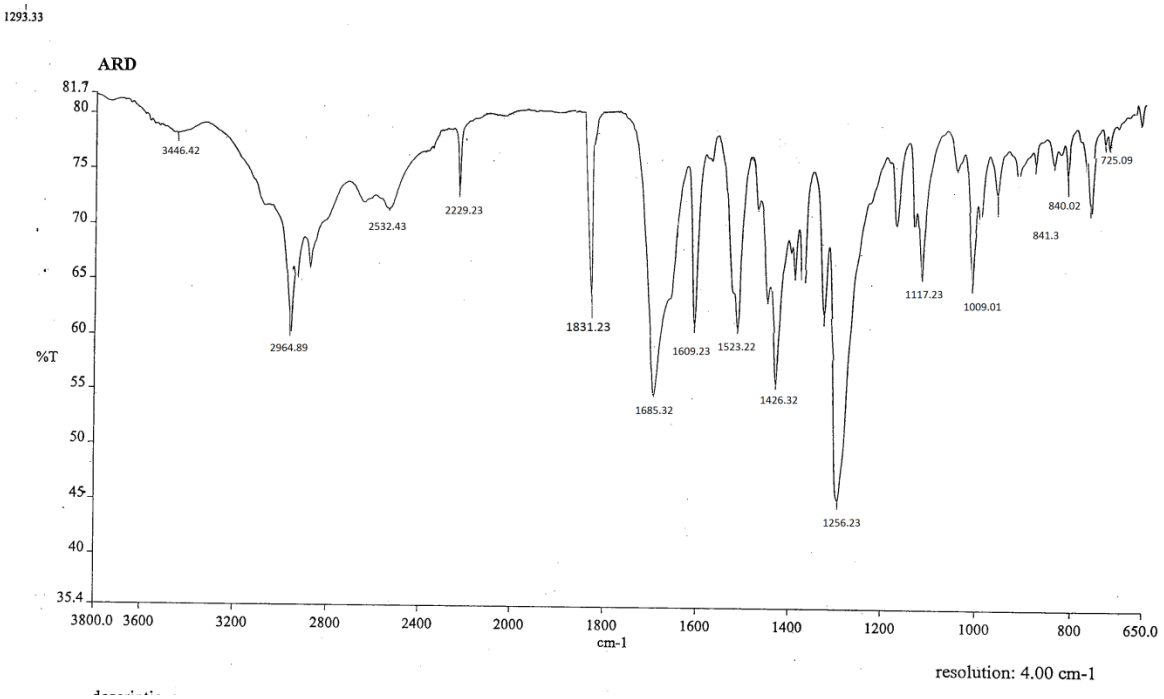
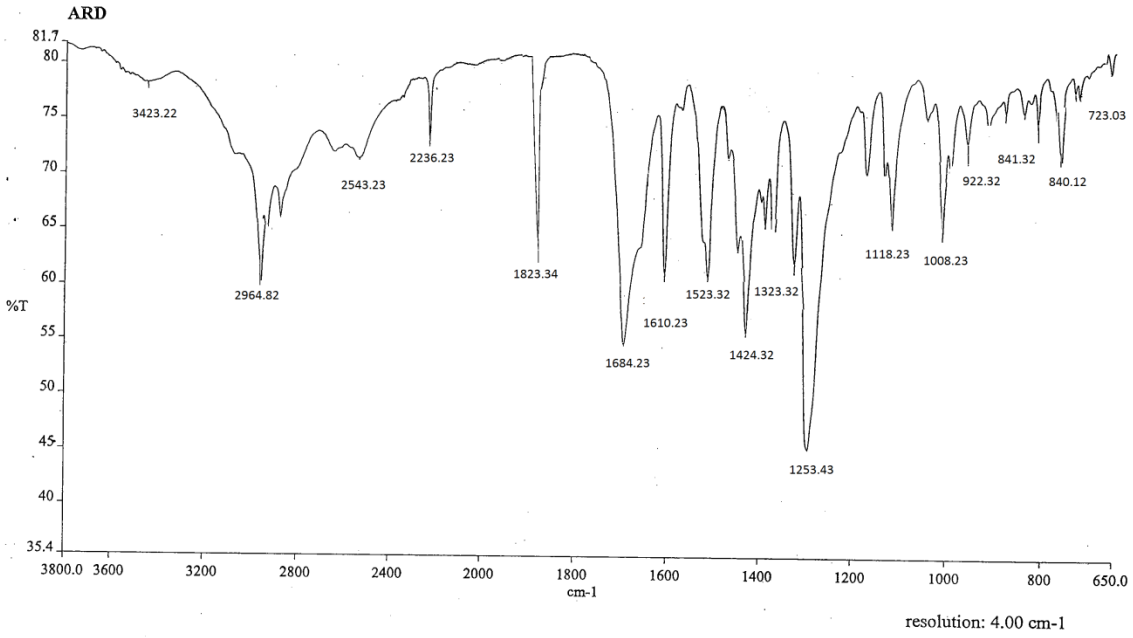


Fig 25: Spectra of Pure drug and Sodium Bi Carbonate

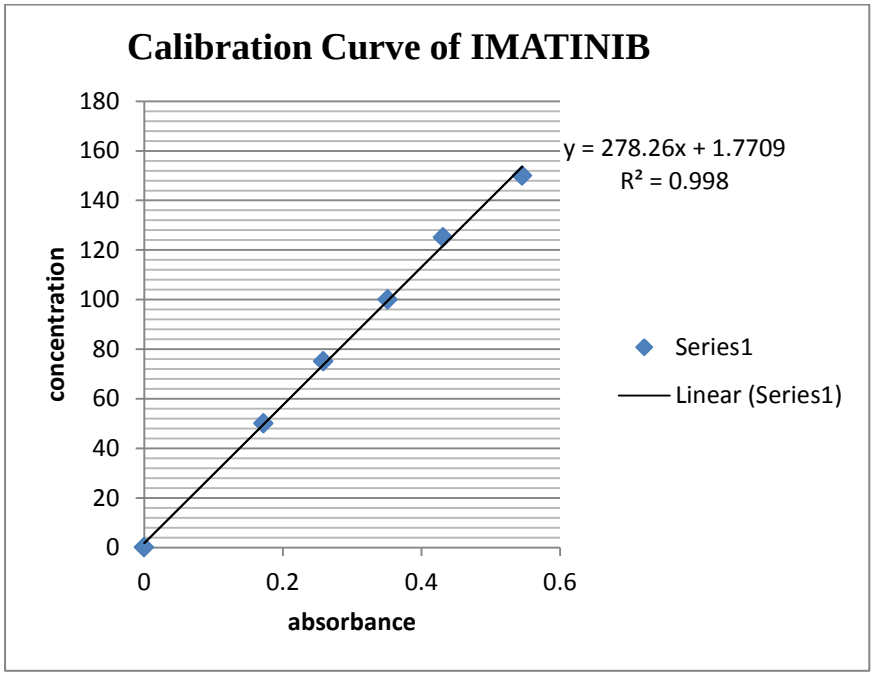


Standard curve of Imatinib

Table 21: Absorbance of Imatinib with different concentrations at 236nm

SI.NO	Concentration(mcg/ml)	Absorbance
1	0	0
2	50	0.1722
3	75	0.2583
4	100	0.3513
5	125	0.4313
6	150	0.5456

Fig 26: Calibration curve of Imatinib in 0.1N HCl solution, at 236 nm.



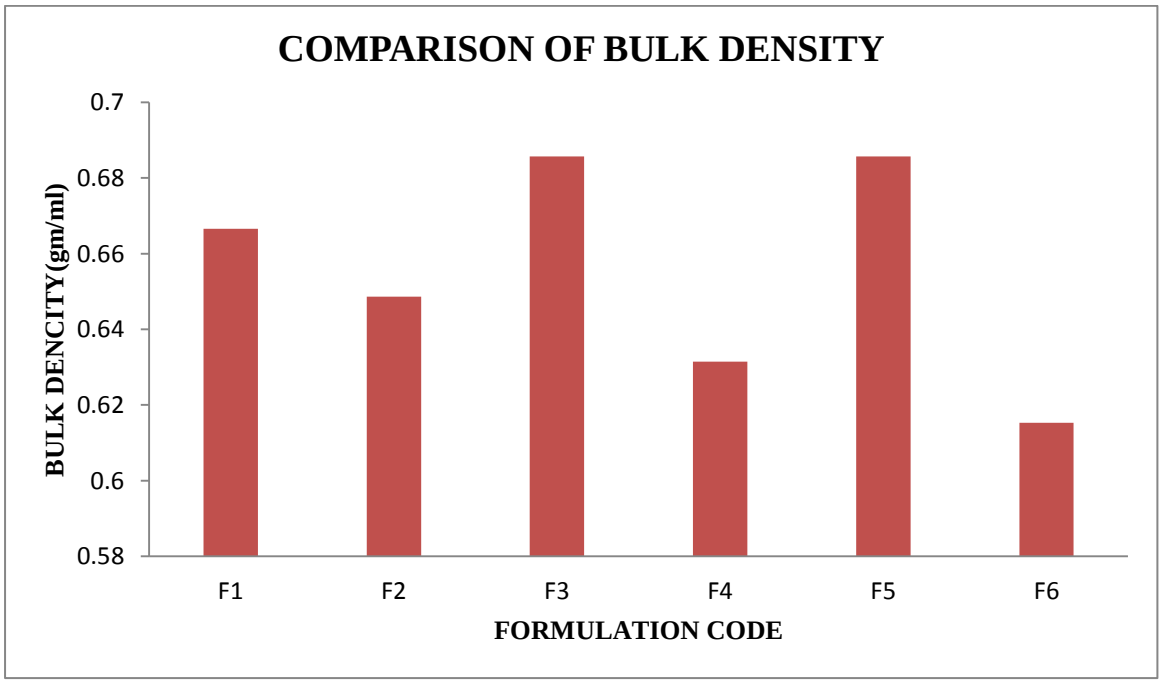
PRE-COMPRESSION RESULTS

Bulk density:

Table 22: Data for bulk density

SI.NO	FORMULATION CODE	BULK DENSITY (gm/ml)
1	F-1	0.6666±0.005
2	F-2	0.6486±0.003
3	F-3	0.6857±0.006
4	F-4	0.6315±0.002
5	F-5	0.6857±0.004
6	F-6	0.6153±0.003

Fig 27: COMPARISON OF BULK DENSITY OF THE FORMULATIONS F1-F6



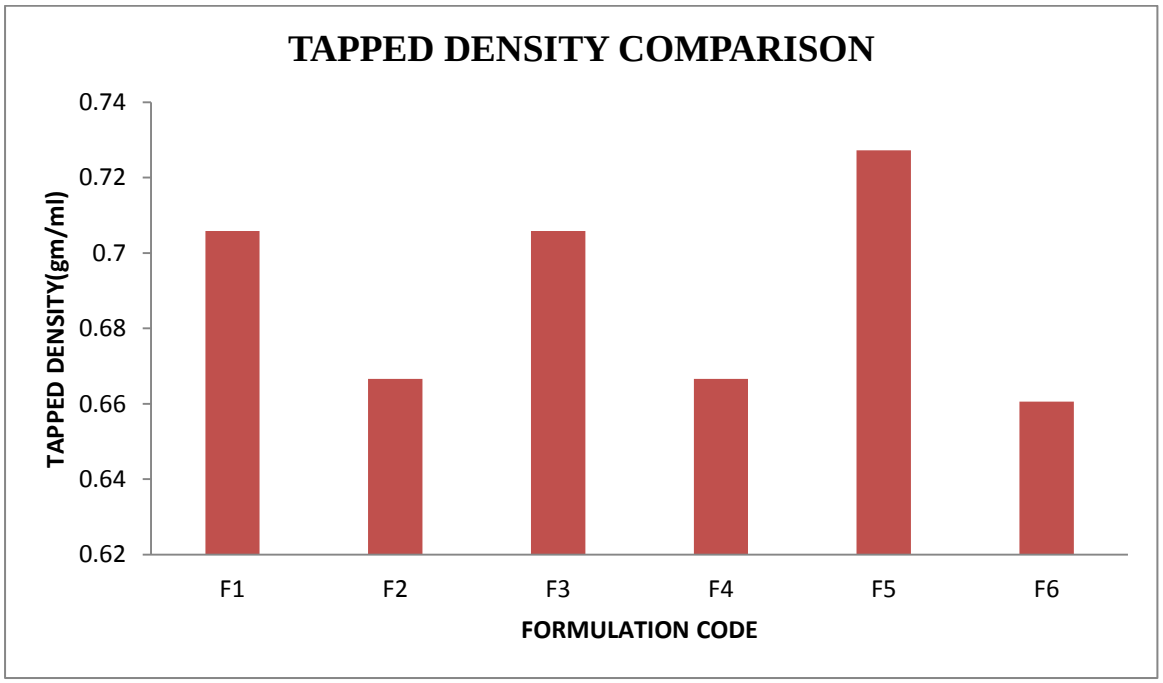
Tapped Density:

The tapped density results are been found to be as following

Table 23: Data for tapped density

SI.NO	FORMULATION CODE	TAPPED DENSITY(gm/ml)
1	F1	0.7058±0.008
2	F2	0.6666±0.004
3	F3	0.7058±0.009
4	F4	0.6666±0.003
5	F5	0.7272±0.004
6	F6	0.6606±0.006

Fig 28: Comparison of Tapped density of formulations F1-F6



Hausner's ratio and Compressability index:

Table 24: Data for Hausner's ratio and Compressability index

Formulation code	Hausner's Ratio	Compressibility Index (%)
F-1	1.0585±0.005	5.5319±0.381
F-2	1.026±0.003	2.6126±0.214
F-3	1.029±0.003	2.8478±0.271
F-4	1.0555±0.002	7.764±0.179
F-5	1.0605±0.006	5.7608±0.004
F-6	1.0829±0.004	7.6957±0.285

Fig 29: Comparison of Hausner's ratio of formulations F1-F6

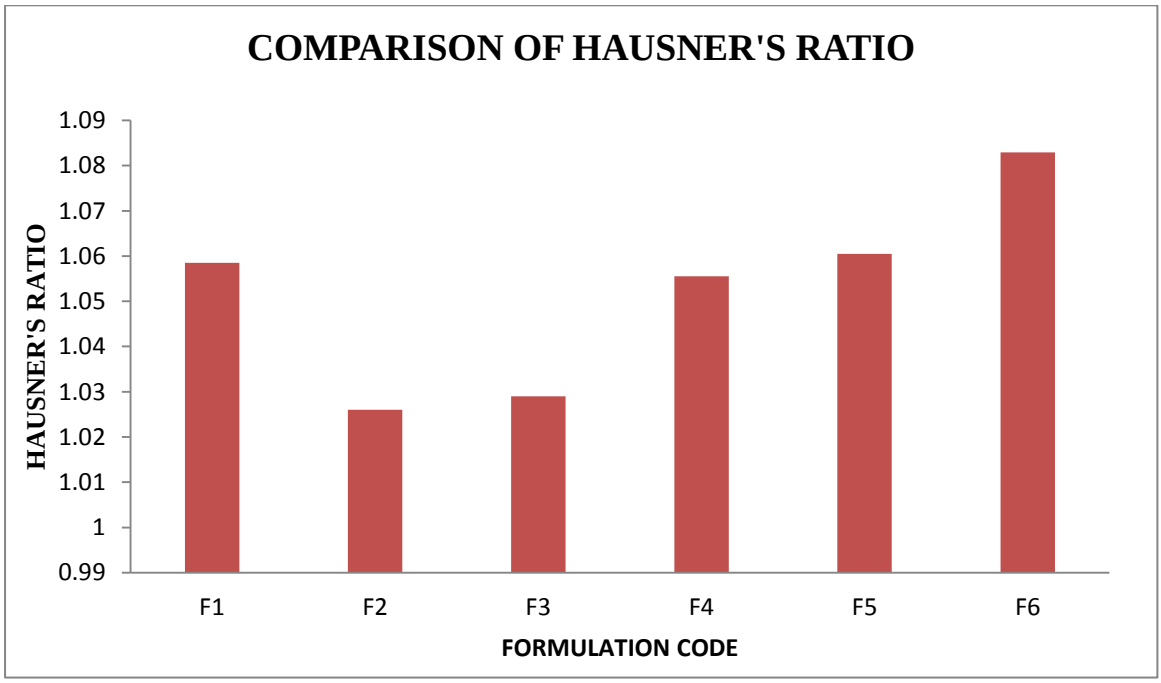
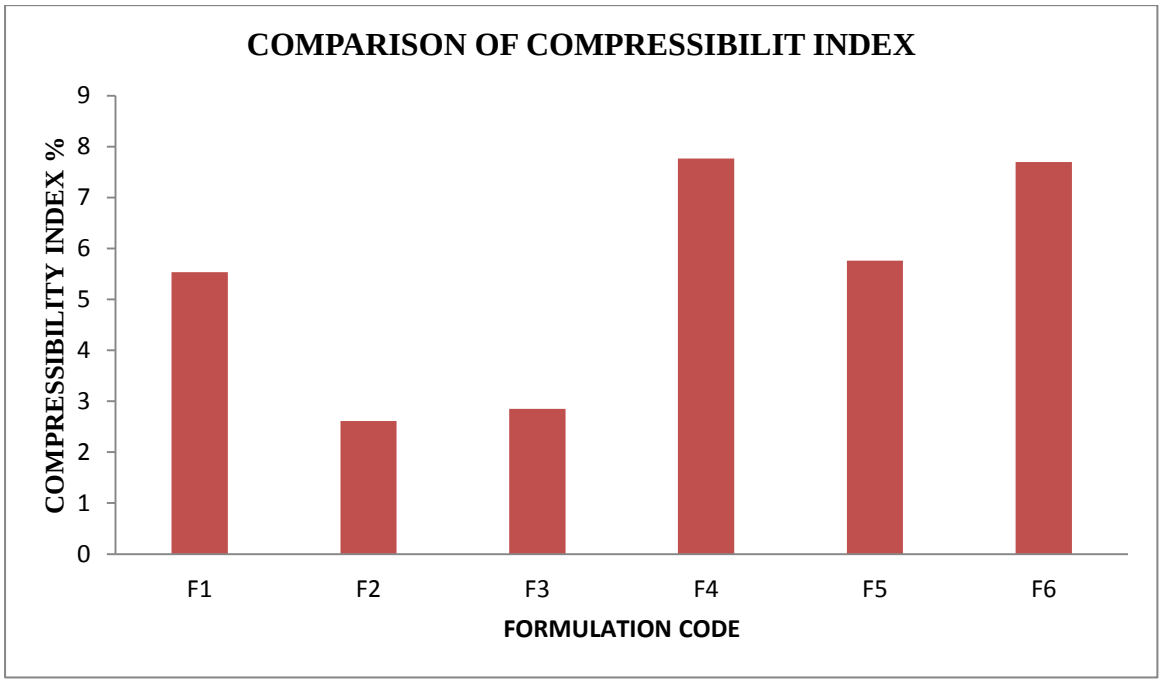


Fig 30: Comparison of Compressibility index of formulations F1-F6

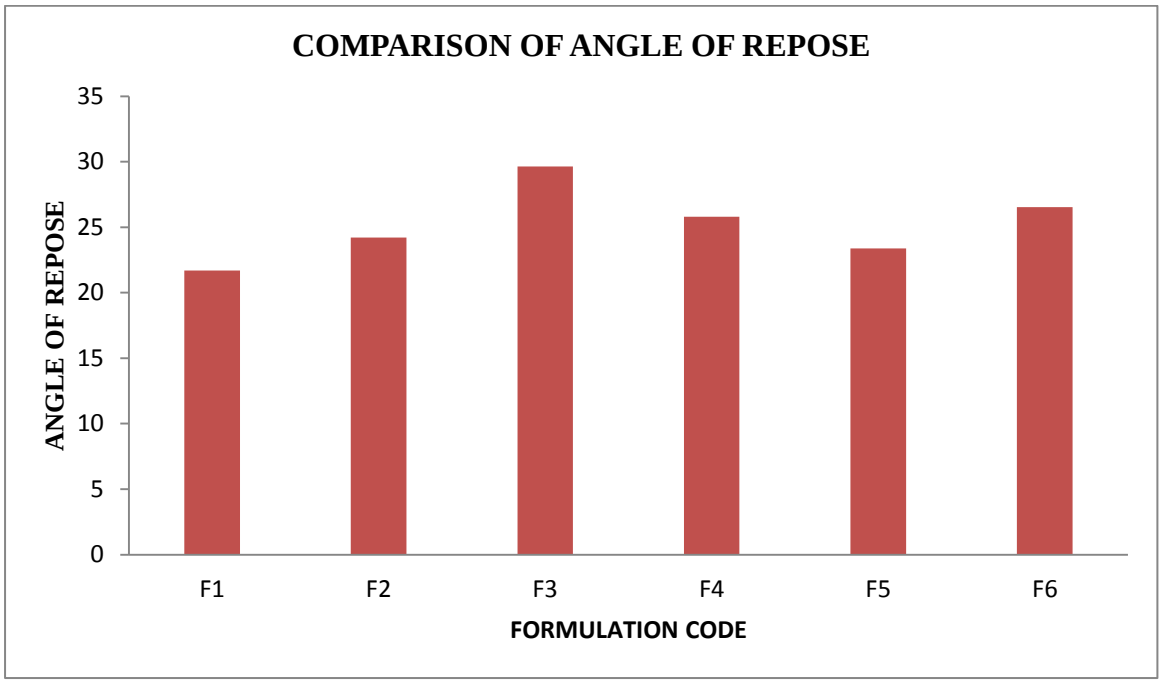


ANGLE OF REPOSE:

Table 25: Data for Angle of repose

SI.NO	FORMULATION	ANGLE OF REPOSE
1	F1	21^0.69' ± 0.325
2	F2	24^0.22' ± 0.826
3	F3	29^0.64' ± 0.418
4	F4	25^0.80' ± 0.488
5	F5	23^0.39' ± 0.075
6	F6	26^0.54' ± 0.870

Fig 31: Comparison of angle of repose



Therefore from the above results we can conclude that the tablets blend has good flow properties.

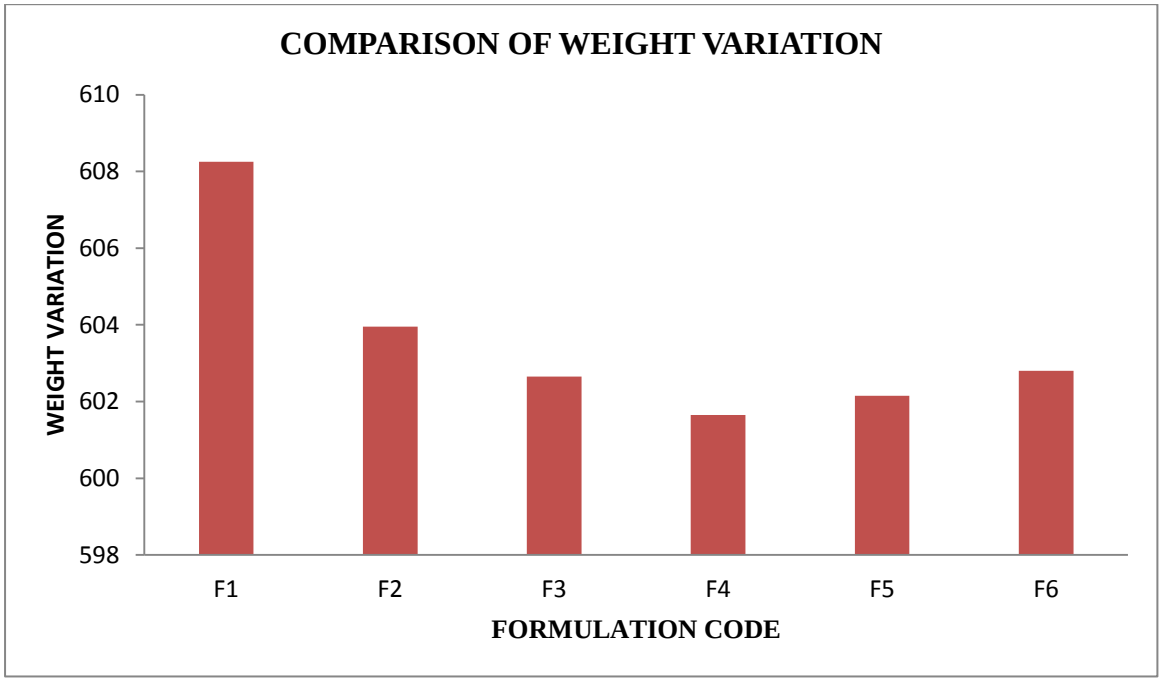
POST COMPRESSION EVALUATION:

Weight variation:

Table 26: Weight Variation data

SI.NO	FORMULATION CODE	WEIGHT VARIATION
1	F1	608.25±1.8477
2	F2	603.95±0.8322
3	F3	602.65±0.5925
4	F4	601.65±0.368
5	F5	602.15±0.4807
6	F6	602.8±0.626

Fig 32: Comparison of Weight Variation

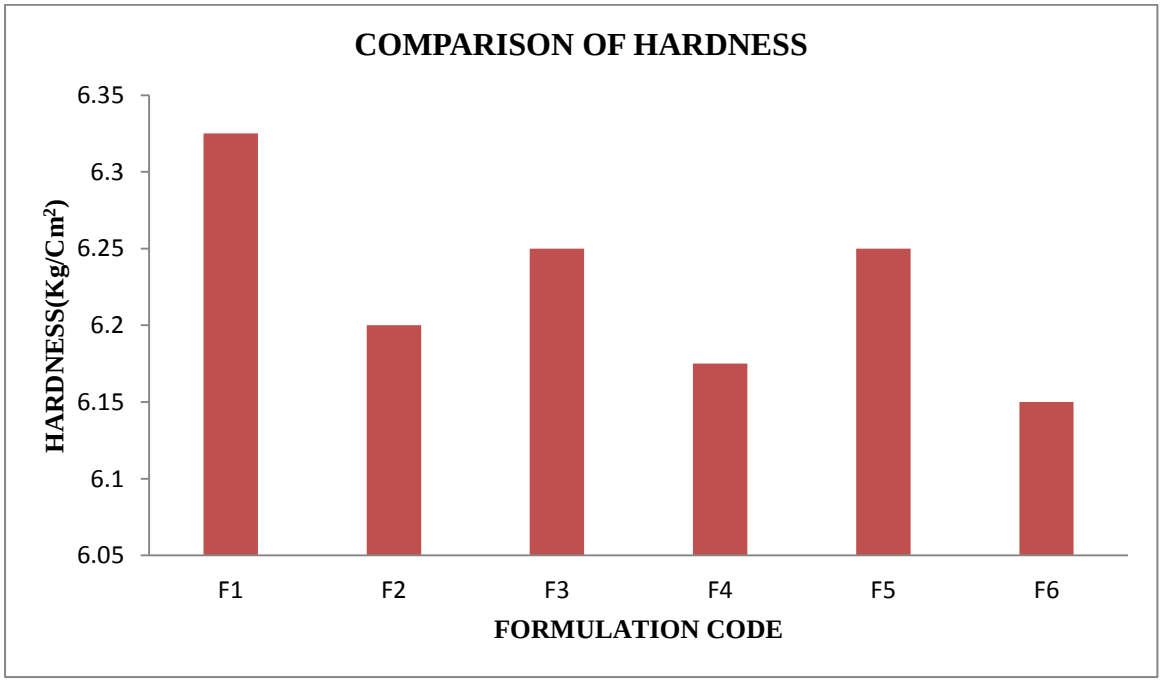


TABLET HARDNESS:

Table 27: Hardness data

SI.NO	FORMULATION CODE	HARDNESS(Kg/cm^2)
1	F1	6.325 ±0.1027
2	F2	6.2 ±0.0632
3	F3	6.25 ±0.079
4	F4	6.175 ±0.0553
5	F5	6.25 ±0.079
6	F6	6.15 ±0.0474

Fig 33: Comparison of hardness

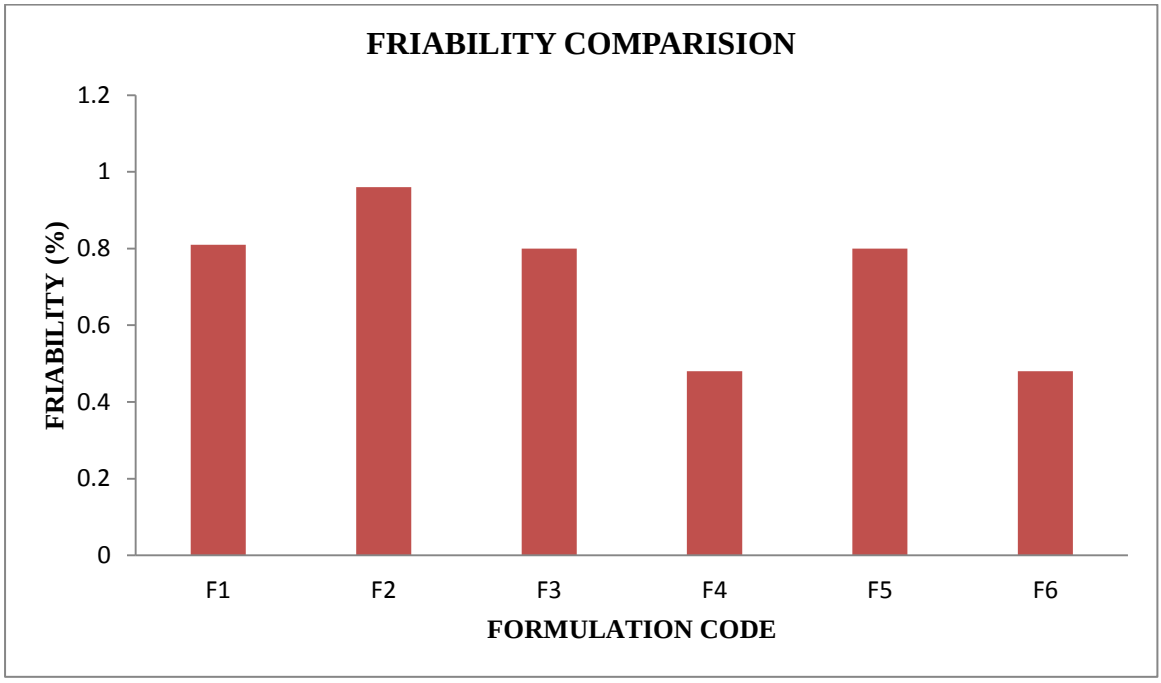


FRIABILITY

Table 28: Friability data

SI.NO	FORMULATION CODE	FRIABILITY (%)
1	F1	0.81
2	F2	0.96
3	F3	0.80
4	F4	0.48
5	F5	0.80
6	F6	0.48

Fig 34: Comparison of friability

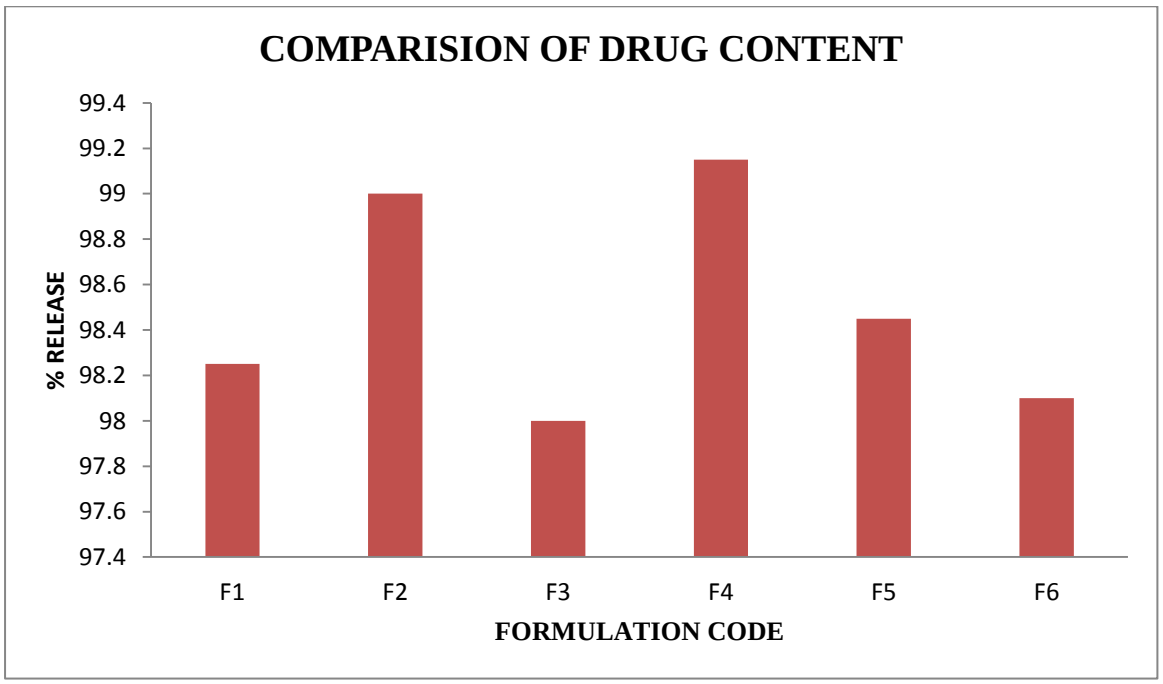


DRUG CONTENT UNIFORMITY:

Table 29: Drug content data

SI.NO	FORMULATION CODE	DRUG CONTENT (%)
1	F1	98.25
2	F2	99.0
3	F3	98.0
4	F4	99.15
5	F5	98.45
6	F6	98.1

Fig 35: Comparison of drug content



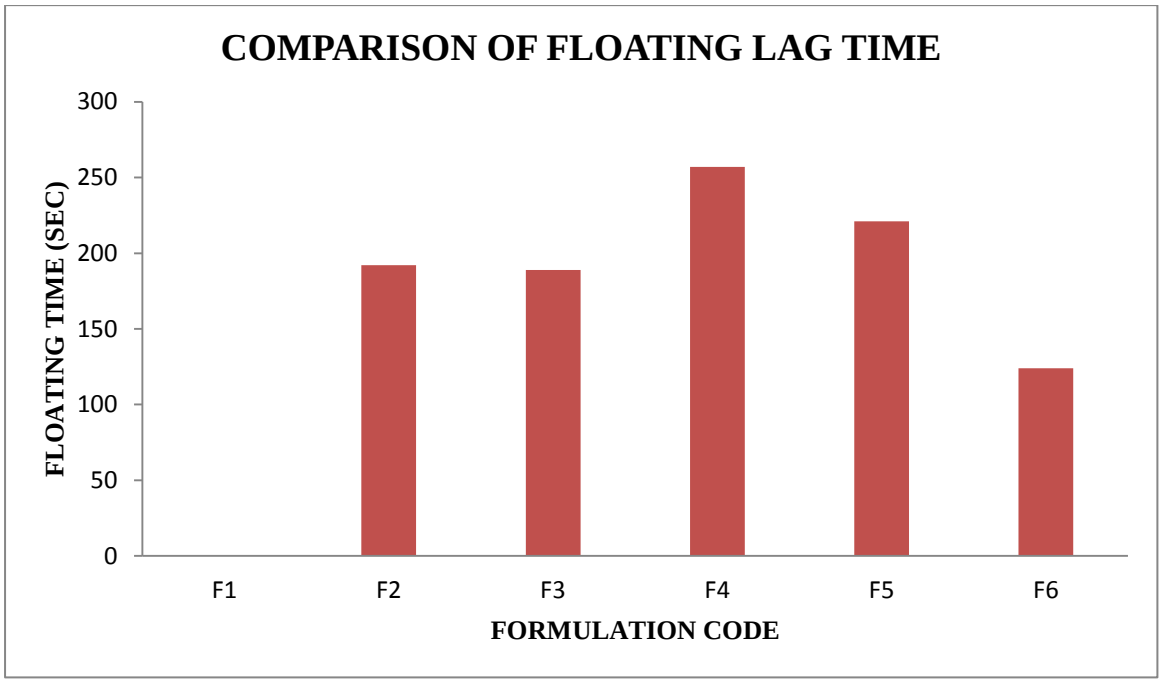
***In-Vitro* Buoyancy studies**

Floating Lag time

Table 30: Data of Floating lag time

SI.NO	FORMULATION CODE	FLOATING LAG TIME (SEC)	TOTAL FLOATING TIME
1	F1	-	Remains at the bottom
2	F2	192	14 hours
3	F3	189	16 hours
4	F4	257	18 hours
5	F5	221	18 hours
6	F6	124	18 hours

Fig 36: Comparison of Floating lag time

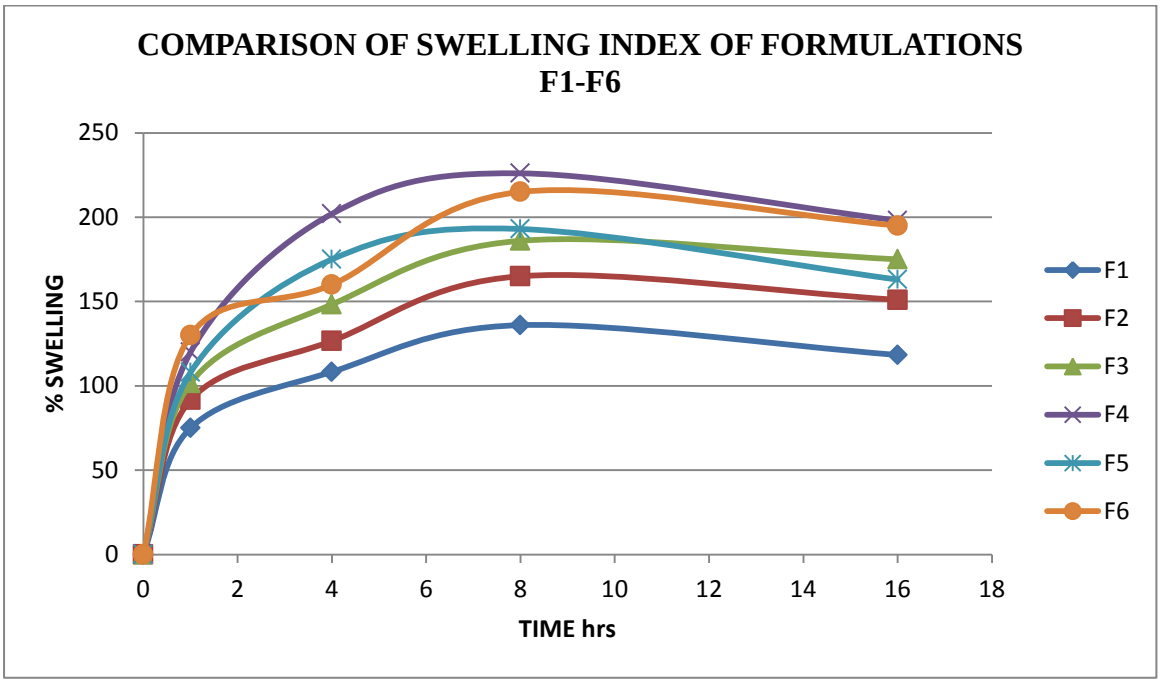


Swelling index:

Table 31: Data for swelling index

SI.NO.	TIME	Swelling Index(%) for different formulations					
		F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0
2	1	75	91.6	101.6	120	108	130
3	4	108.3	126.6	148.3	201	175	160
4	8	136	165	186	226	193	215
5	16	118.3	151	175	198	163	195

Fig 37: Comparison of swelling index



***In-Vitro* Dissolution studies:**

Table 32: *In-Vitro* Dissolution Study data for formulation F1

SI.NO	TIME(hrs)	% Cumulative drug release
1	1	43.6±0.285
2	4	61.5±0.122
3	8	84.9±0.285
4	16	94.2±0.326
5	20	93.4±0.163

Fig 38: Dissolution profile of F1

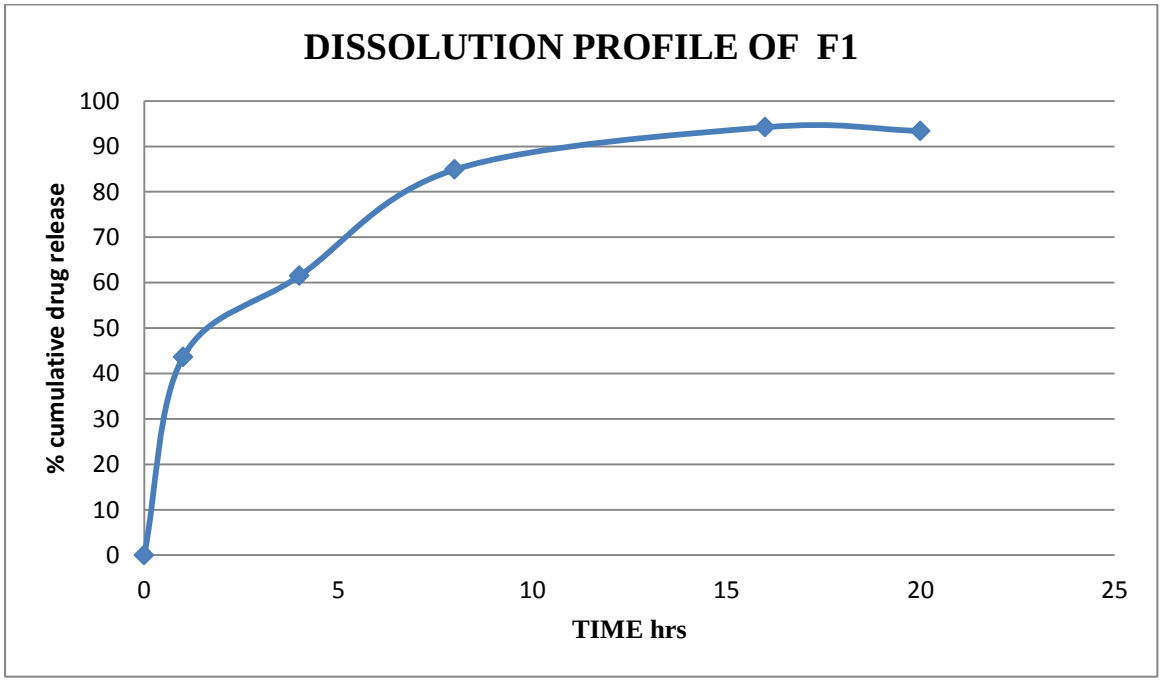


Table 33: *In-Vitro* Dissolution data for formulation F2

SI.NO	TIME (hrs)	% Cumulative drug release
1	1	44.1±0.122
2	4	66.6±1.428
3	8	80.2±0.285
4	16	88.1±0.367
5	20	95.8±0.040

Fig 39: Dissolution profile of F2

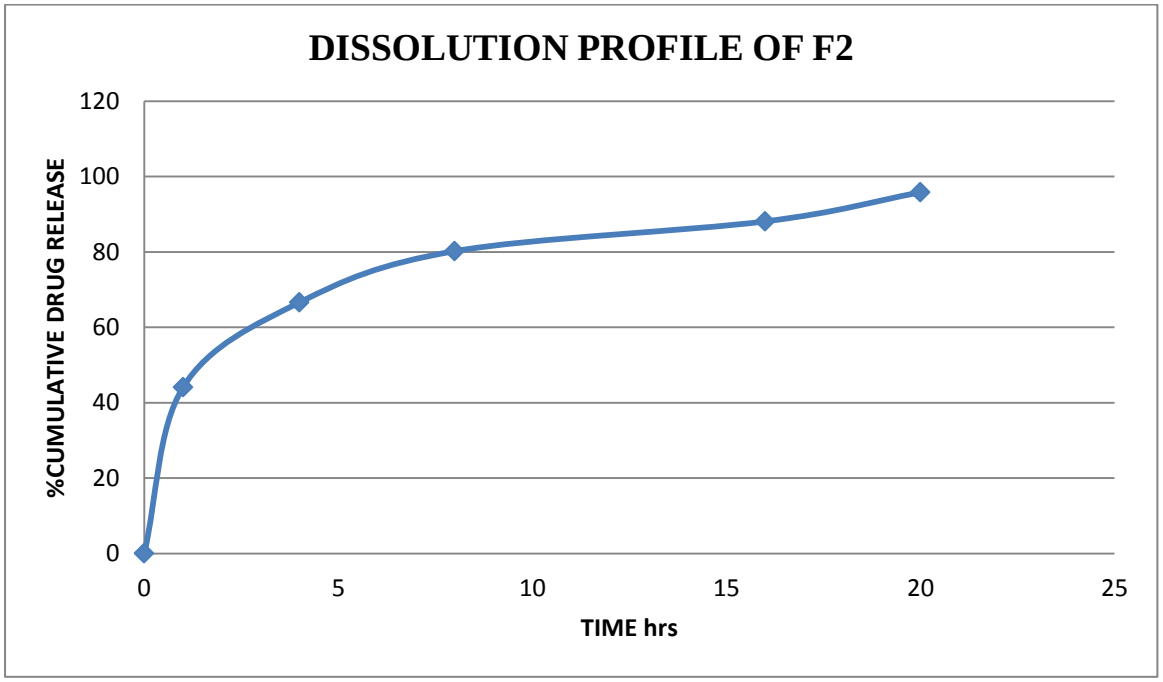


Table 34: *In-Vitro* Dissolution data for formulation of F3

SI.NO	TIME(hrs)	% Cumulative drug release
1	1	38.9±1.714
2	4	57.3±0.816
3	8	85.5±3.347
4	16	91.0±0.326
5	20	95.9±0.449

Fig 40: Dissolution profile of F3

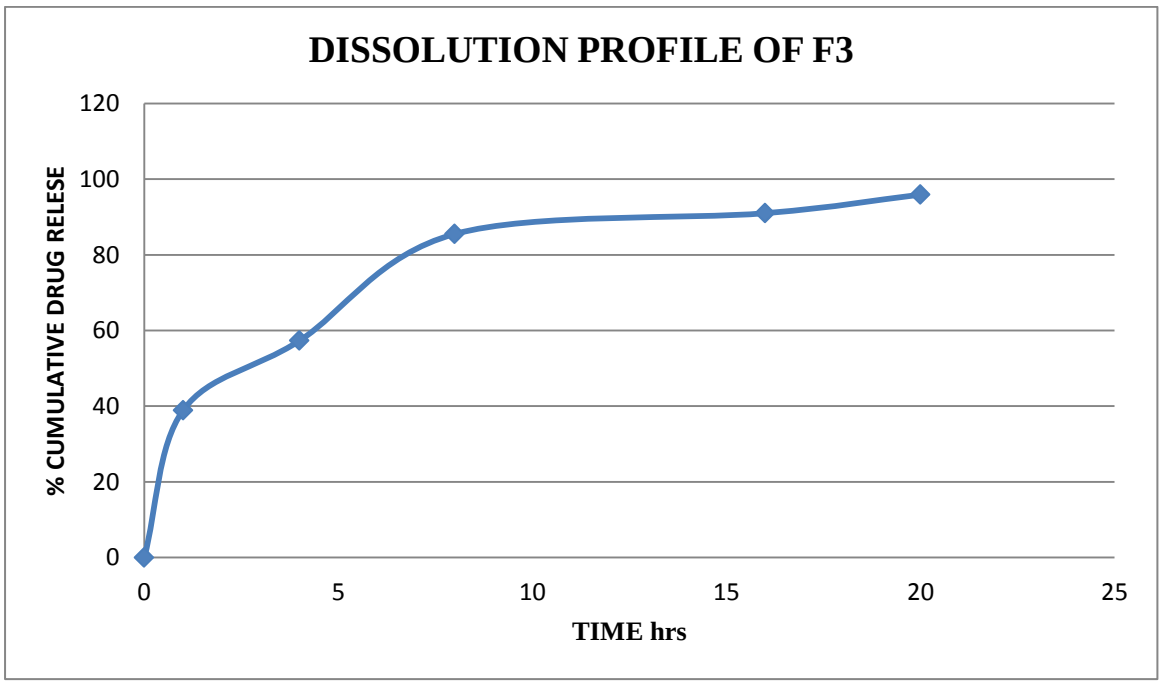


Table 35: *In-Vitro* Dissolution data for formulation of F4

SI.NO	TIME (hrs)	% Cumulative drug release
1	1	36.3±0.898
2	4	57.2±0.367
3	8	77.4±0.653
4	16	84.4±0.408
5	20	94.3±1.020

Fig 41: Dissolution profile of F4

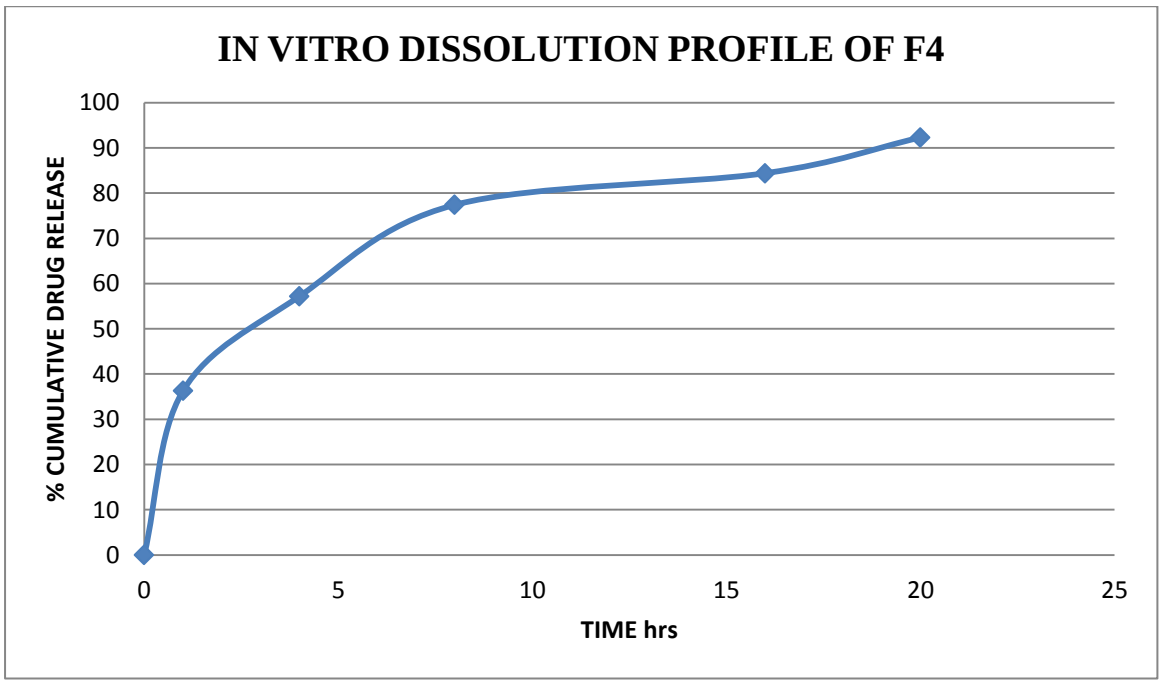


Table 36: *In-Vitro* Dissolution data for formulation of F5

SI.NO	TIME (hrs)	% Cumulative drug release
1	1	39.9±0.571
2	4	62.6±0.612
3	8	88.2±2.204
4	16	94.4±0.081
5	20	94.3±0.816

Fig 42: Dissolution profile of F5

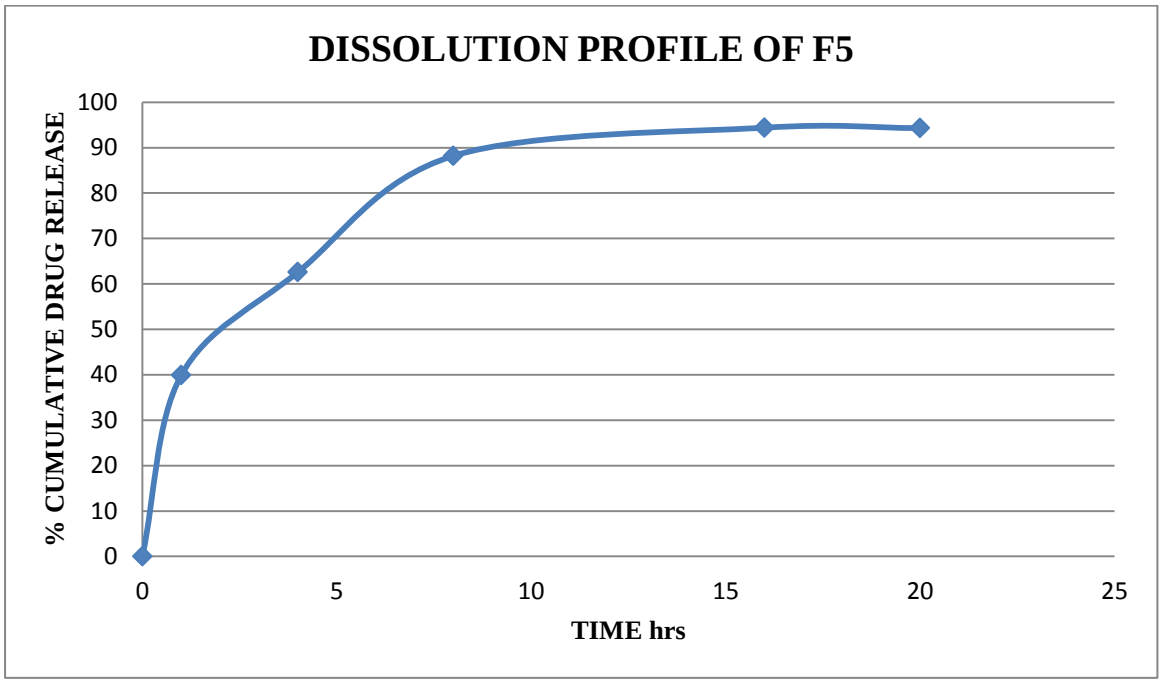


Table 37: *In-Vitro* Dissolution data for formulation of F6

SI.NO	TIME(hrs)	% Cumulative drug release
1	1	40±0.530
2	4	61.9±0.163
3	8	93.3±0.244
4	16	93.9±0.081
5	20	99.1±0.040

Fig 43: Dissolution profile of F6

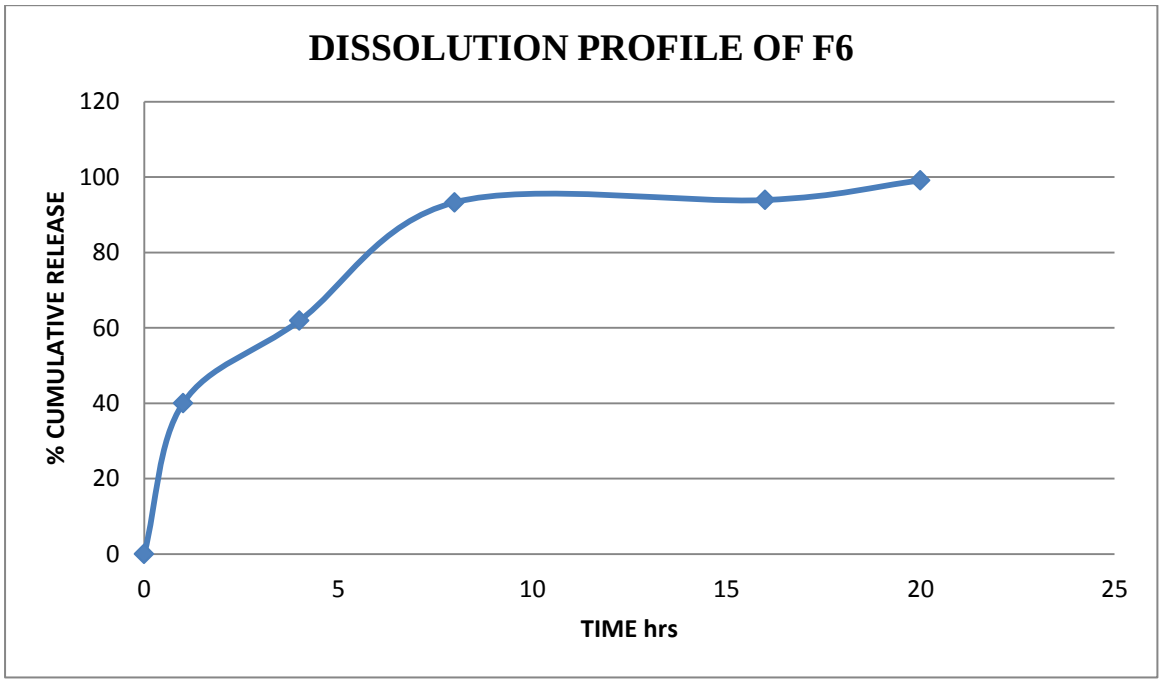
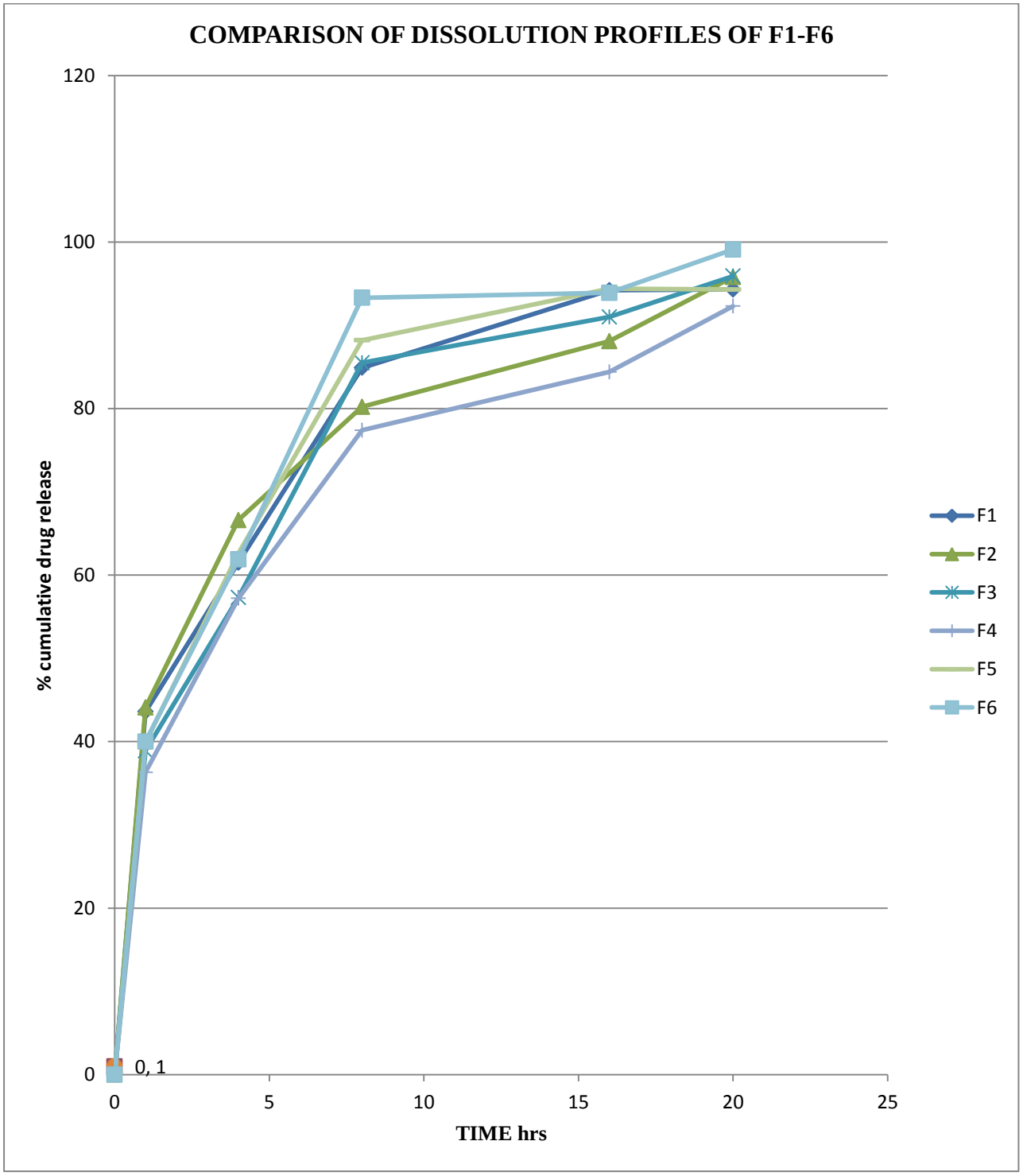


Fig 44: Comparision of In-Vitro Dissolution profiles of formulations F1-F6



PHARMACOKINETIC MODELING

Table 38: Pharmacokinetic modeling of F1

S.NO	TIME(hrs)	CPR	Log CPR	Log T	SQRT	% Drug retained	Log % Drug retained
1	1	43.6	1.6394	0	1	56.4	1.7512
2	4	61.5	1.7888	0.6020	2	38.5	1.5854
3	8	84.9	1.9289	0.9030	2.82	15.1	1.1789
4	16	94.2	1.9740	1.2041	4	5.8	0.7634
5	20	93.4	1.9703	1.3010	4.4721	6.6	0.8195

Fig 45: Pharmacokinetic modeling of F1

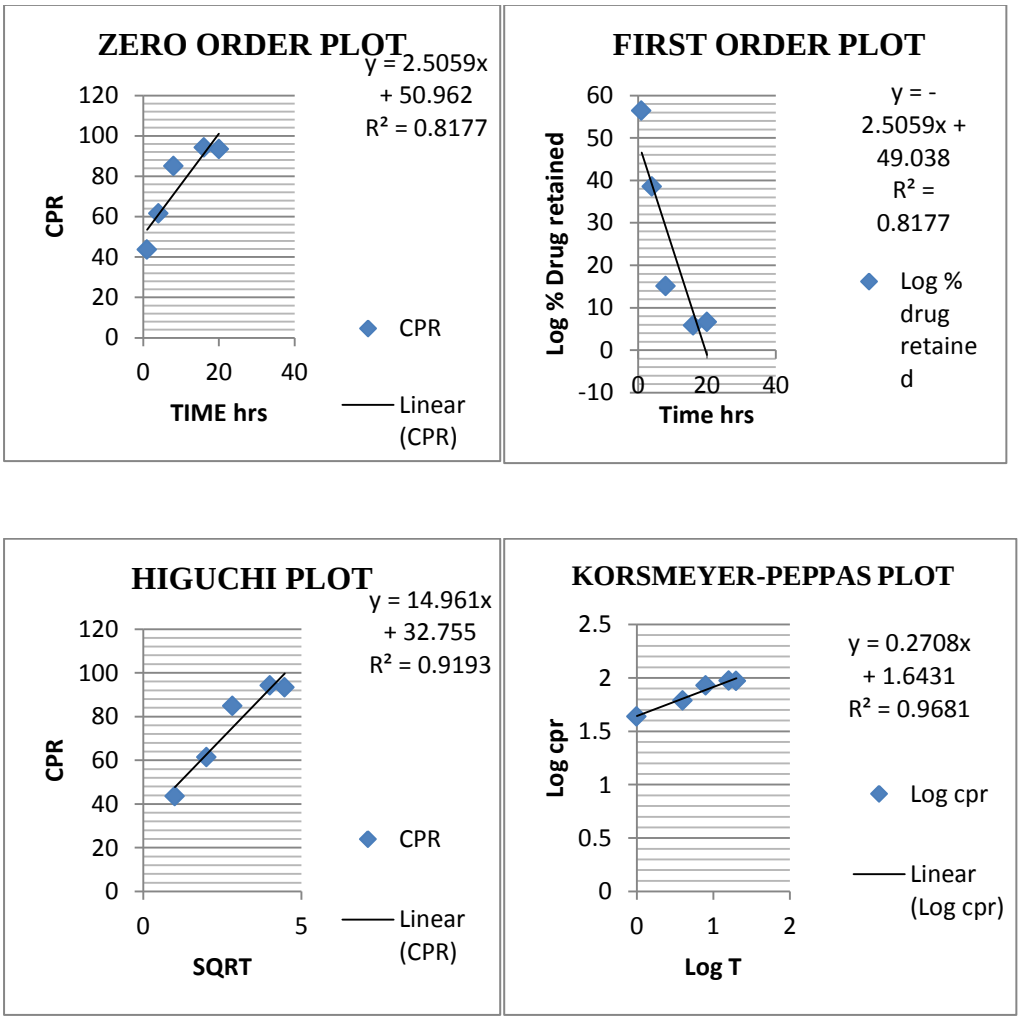


Table 39: Pharmacokinetic modeling of F2

S.NO	TIME(hrs)	CPR	Log CPR	Log T	SQRT	% DRUG RETAINED	Log % DRUG RETAINED
1	1	44.1	1.6444	0	1	55.9	1.7474
2	4	66.6	1.8234	0.6020	2	33.4	1.5237
3	8	80.2	1.9041	0.9030	2.8284	19.8	1.2966
4	16	88.1	1.9449	1.2041	4	11.9	1.0755
5	20	95.8	1.9813	1.3010	4.4721	4.2	0.6232

Fig 46: Pharmacokinetic modeling of F2

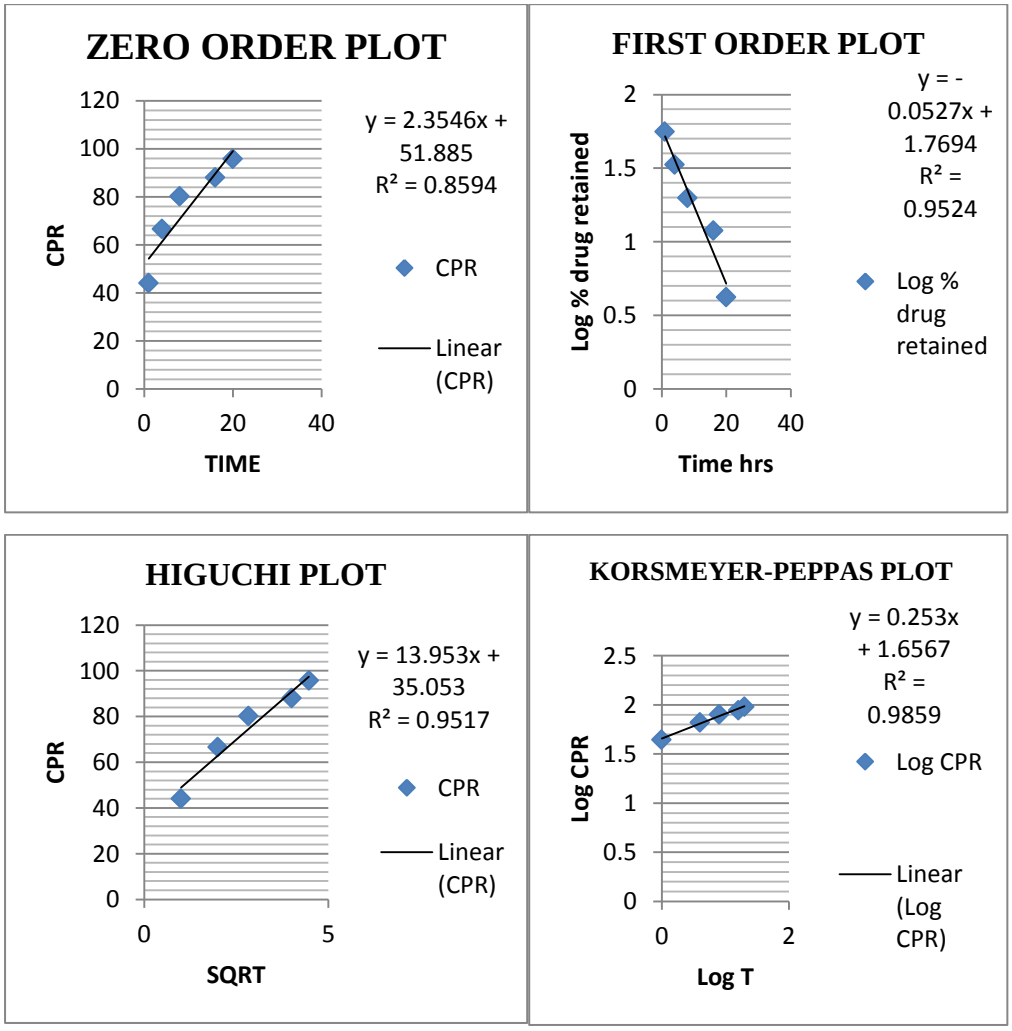


Table 40: Pharmacokinetic modeling of F3

S.NO	TIME(hrs)	CPR	Log CPR	Log T	SQRT	% Drug retained	Log % Drug retained
1	1	38.9	1.5899	0	1	61.1	1.786
2	4	57.3	1.7581	0.6020	2	42.7	1.630
3	8	85.5	1.9319	0.9030	2.82	14.5	1.1613
4	16	91	1.959	1.2041	4	9	0.9542
5	20	95.9	1.9818	1.3010	4.4721	4.1	0.6127

Fig 47: Pharmacokinetic modeling of F3

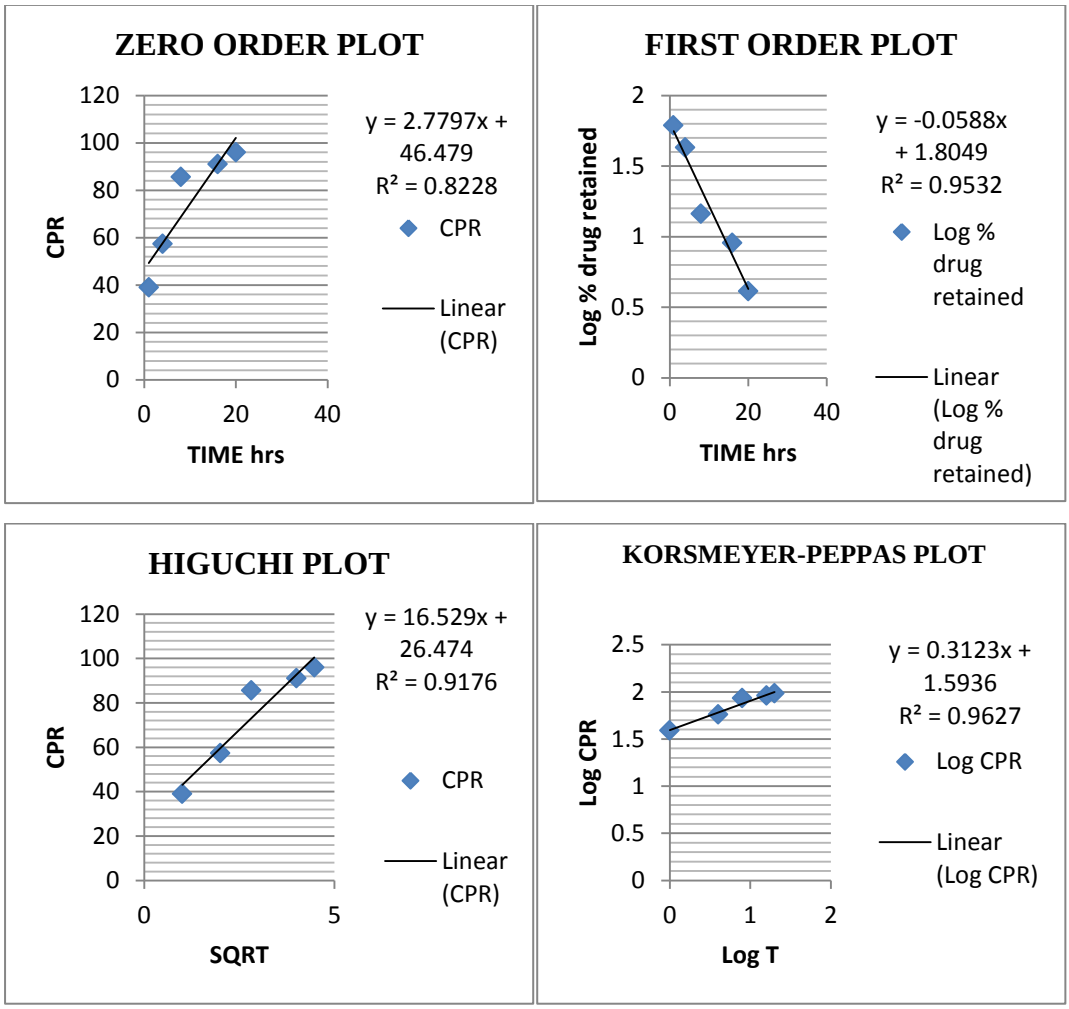


Table 41: Pharmacokinetic modeling of F4

S.NO	TIME(hrs)	CPR	Log CPR	Log T	SQRT	% Drug retained	Log % Drug retained
1	1	36.3	1.5599	0	1	63.7	1.8041
2	4	57.2	1.7573	0.6020	2	42.8	1.6314
3	8	77.4	1.8887	0.9030	2.82	22.6	1.3541
4	16	84.4	1.9263	1.2041	4	15.6	1.1931
5	20	92.3	1.9652	1.3010	4.4721	7.7	0.8864

Fig 48: Pharmacokinetic modeling of F4

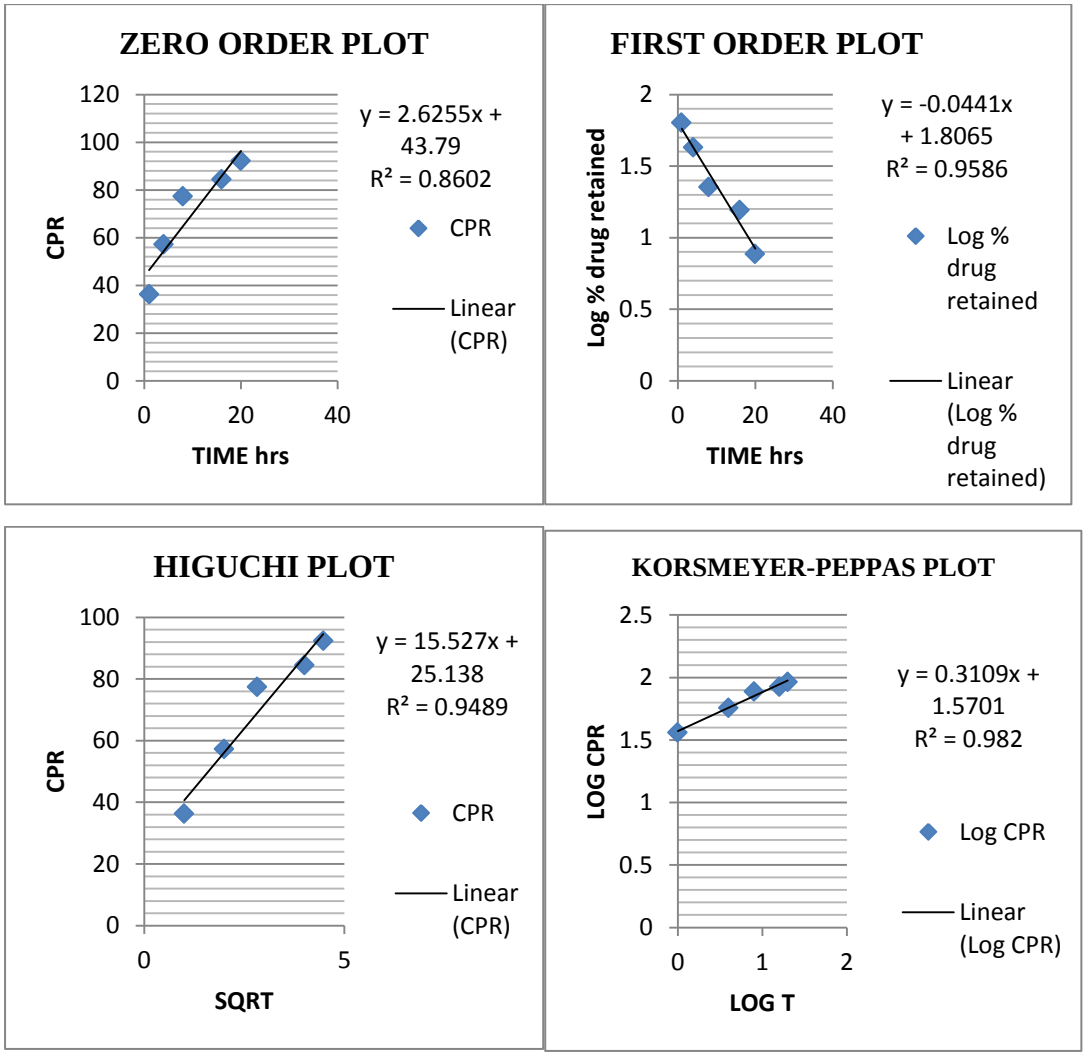


Table 42: Pharmacokinetic modeling of F5

S.NO	TIME(hrs)	CPR	Log CPR	Log T	SQRT	% Drug retained	Log % Drug retained
1	1	39.9	1.6009	0	1	60.1	1.7788
2	4	62.6	1.7965	0.6020	2	37.4	1.5728
3	8	88.2	1.9454	0.9030	2.82	11.8	1.0718
4	16	94.4	1.9749	1.2041	4	5.6	0.7481
5	20	94.3	1.9745	1.3010	4.4721	5.7	0.7558

Fig 49: Pharmacokinetic modeling of F5

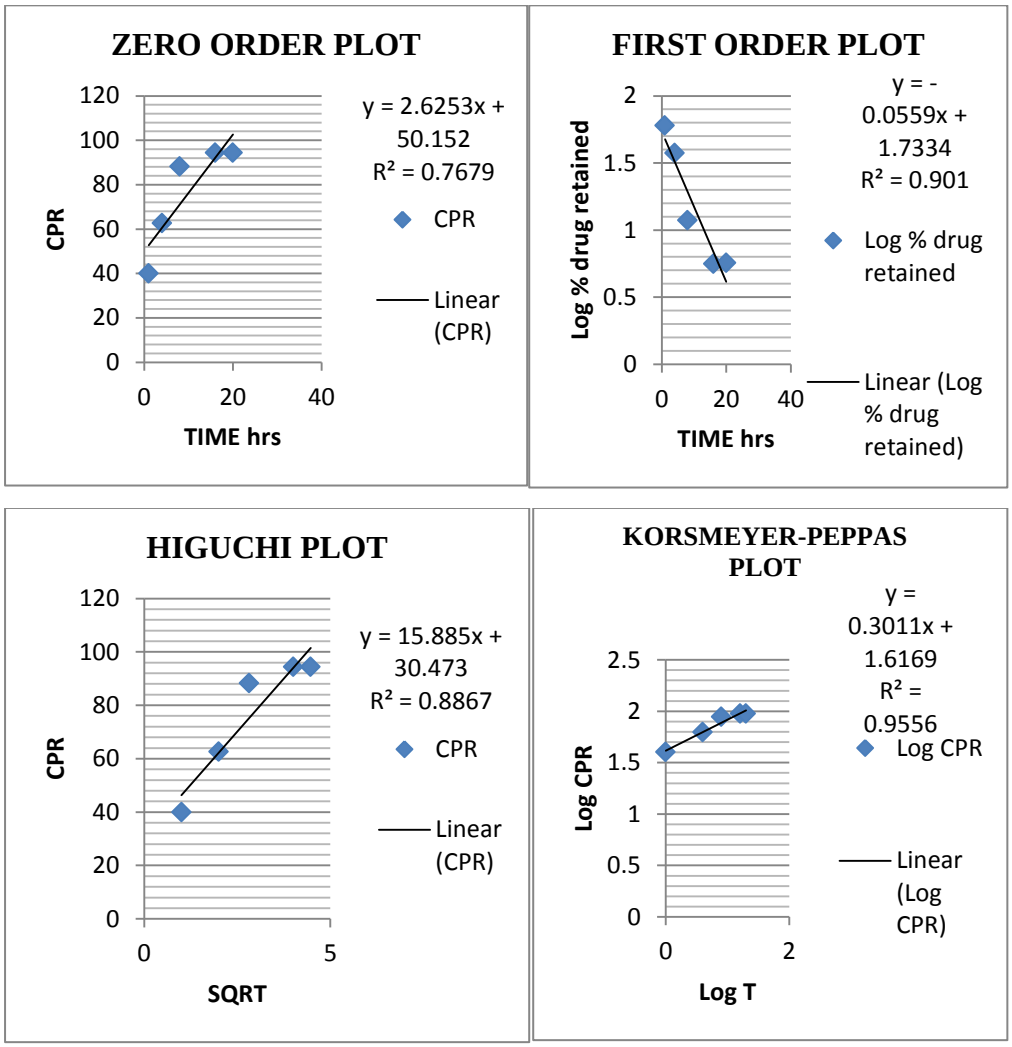


Table 43: Pharmacokinetic modeling of F6

S.NO	TIME(hrs)	CPR	Log CPR	Log T	SQRT	% Drug retained	Log % Drug retained
1	1	40.0	1.6020	0	1	60	1.7781
2	4	61.9	1.7916	0.6020	2	38.1	1.5809
3	8	93.3	1.9698	0.9030	2.82	6.7	0.8260
4	16	93.9	1.9726	1.2041	4	6.1	0.7853
5	20	99.1	1.9960	1.3010	4.4721	0.9	-0.0457

Fig 50: Pharmacokinetic modeling of F6

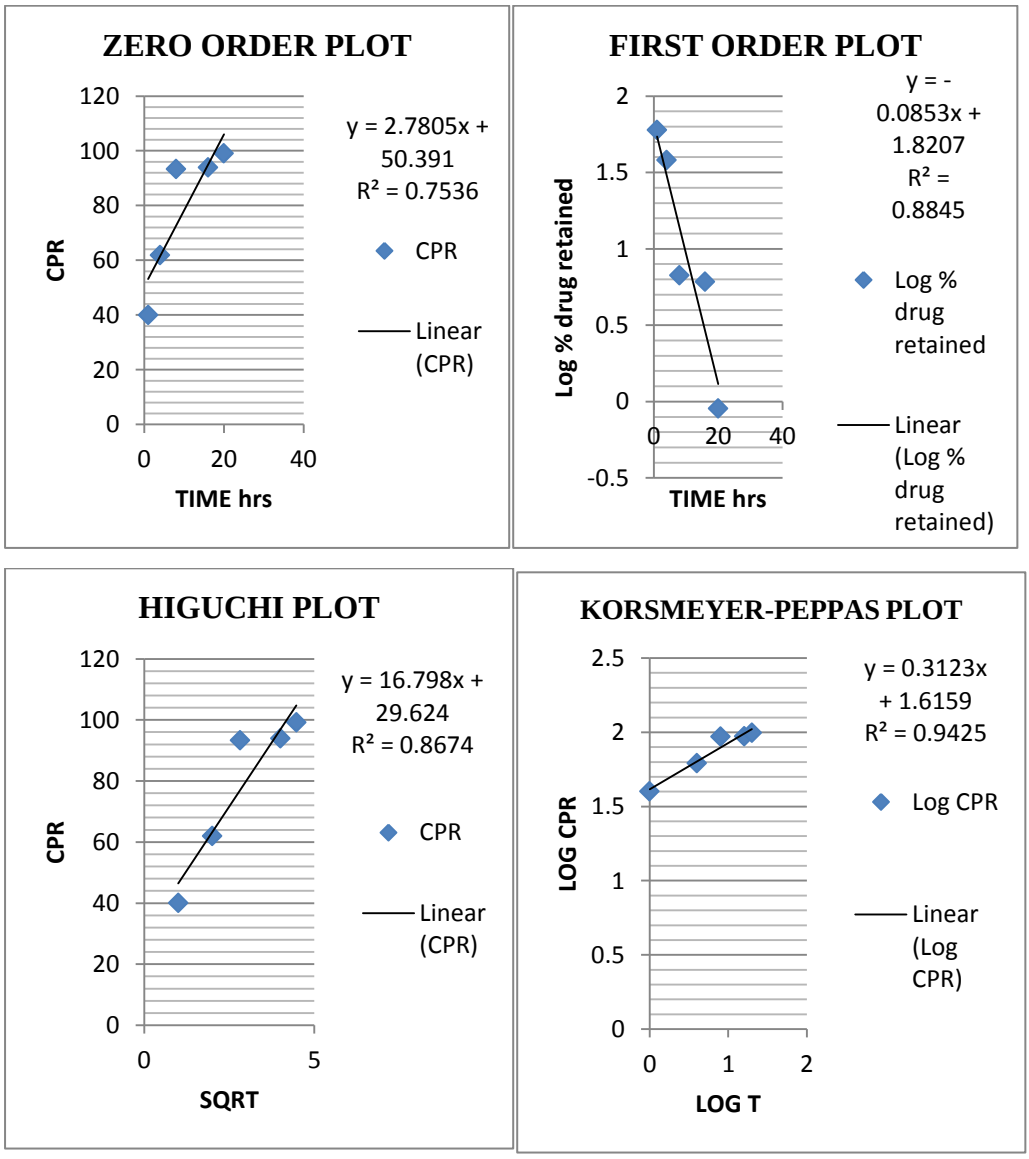


TABLE 44: SUMMARY OF PHRMACO KINETIC MODELING OF ALL THE FORMULATIONS.

S.NO	FORMULATION CODE	ZERO ORDER		FIRST ORDER		HIGUCHI		KORSMEYER-PEPPAS MODEL	
		R^2	SLOPE	R^2	SLOPE	R^2	SLOPE	R^2	N
1	F1	0.8177	2.5059	0.8177	2.5059	0.9193	14.961	0.9681	0.2708
2	F2	0.8594	2.3546	0.9524	0.0527	0.9517	13.953	0.9854	0.253
3	F3	0.8228	2.7797	0.9532	-0.0588	0.9176	16.529	0.9627	0.3123
4	F4	0.8602	2.6255	0.9586	-0.0441	0.9489	15.527	0.982	0.3109
5	F5	0.7679	2.6253	0.901	0.0559	0.8867	15.885	0.9556	0.3011
6	F6	0.7536	2.7085	0.8845	0.0853	0.8674	16.798	0.9425	0.3123

Table 45: **In-Vitro Dissolution of Formulation F4 after Stability studies**

Invitro dissolution after 30 days at 40°c / 75%RH			**Invitro dissolution after 90 days at 40°c / 75%RH**		
Dissolution medium	**Time in hours**	**Cumulative percentage drug release**	**Dissolution medium**	**Time in hours**	**Cumulative percentage drug release (%)**
0.1N HCl Solution	1	38.4±0.024	**0.1N HCl Solution**	1	34.1±0.002
	4	56.3±0.153		4	57.8±0.18
	8	78.2±0.085		8	77±0.125
	16	84.9±0.219		16	83.6±0.225
	20	92.3±0.135		20	92.1±0.216

Fig 51: Comparison of dissolution data of the optimized formulation F4 after 30 days and 90 days of stability studies with that of the Initial release.

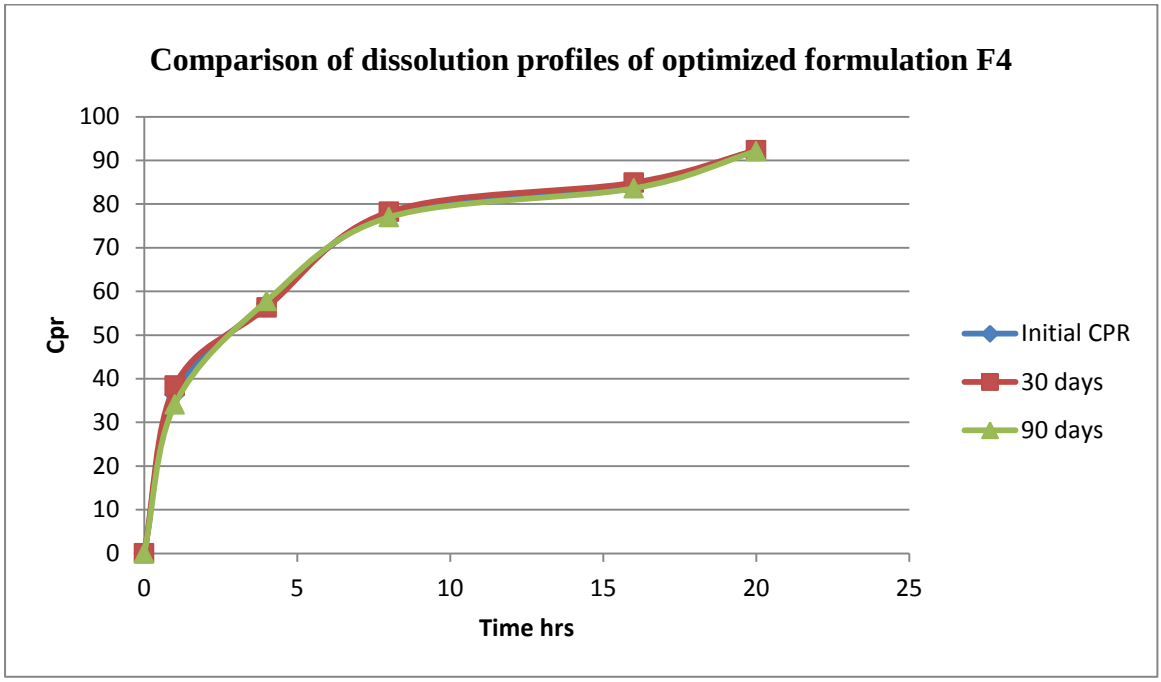


Table 46: Drug Content of ideal formulation after stability studies

SI.NO	Days	Drug content
1	30	99.11
2	90	98.49

Table 47: Data for Swelling index after 90 days of stability studies

SI.NO	TIME	SWELLING INDEX (%)	
		30days	90 days
1	1	109	115
2	4	194	189
3	8	220	218
4	16	185	175

DISCUSSION

In the present study the gastro-retentive dosage form of Imatinib was formulated and evaluated successfully.

In the preformulation studies the API was tested for its Solubility and Compatibility with excipients.

Solubility studies showed that the drug was highly soluble in DMSO, 0.1N HCl and in Water.

Compatibility studies are done for both physical and chemical compatibilities. Physical Compatibility studies showed that there is no characteristic change in the drug and excipient mixture after a period of 4 weeks.

Chemical compatibility studies were done by using FTIR spectroscopy and found that the drug and excipients do not have any chemical interactions.

Pre compression evaluation of the blend was done by means of Angle of repose, Bulk density, Tapped density, Hausner's ratio and Compressibility index.

The Hausner's ratios of all the formulations are in the range of 1.026 ± 0.003 to1.0829 ± 0.004 meanwhile the Compressibility index values are in the range of 2.8478 ± 0.271 to 7.764 ± 0.179 proving the fact that the tablet blend has good flow properties.

Angle of repose values were also conforming the same by showing the results in the range of 21^0.69' to 29^0.64'. Hence we can conclude that the tablet blend has got good flow properties.

Immediately after compression, the tablets were evaluated by several tests such as Weight variation, Hardness, Friability, Drug content uniformity, *In-Vitro* buoyancy and *In-Vitro* dissolution studies.

The weights of all the formulations are in the range of 601 to 608 showing that all the formulations are within the pharmacopeial limits of weight variation.

Friability results of all the formulations were found to be less than 1% and all the formulations passed the test.

During the *in-vitro* buoyancy studies the tablets were evaluated for their floating lag time and total floating time and the formulation F1 failed to float during the study, therefore the polymer ratio was increased from the next formulations. All the other formulations showed good floating lag time. When comparing all the formulations, the formulations F4, F5, F6 has total floating time of 18 hours with acceptable floating lag time.

The Swelling index studies showed that the swelling of a tablet increases with increase in the polymer ratio and the formulation F3, F4 showed higher swelling index than the others.

Drug content uniformity studies were done to find out the amount of API present in the prepared formulations. All the formulations had uniform drug content as per pharmacopeial limits.

The *in-vitro* dissolution studies were carried out for the time periods of 1,4,8,16,20 hours. It was found that all the formulations showed good release in the range of 93.4 to 99.1%, whereas formulation F4 showed 94.3% drug release in a controlled manner over a period of 20 hours, so that was chosen as the best formulation.

Pharmacokinetic modeling was done for all the formulations and found that the best formulation is obeying First order kinetics and fickian diffusion for drug release.

Finally the ideal formulation was subjected to stability studies for a period of 90 days and the drug release, drug content and swelling index were compared with that of the initial data and found that there was no significant change in the values indicating a stable formulation.

SUMMARY AND CONCLUSION

SUMMARY AND CONCLUSION

A total of 6 trials were formulated by direct compression method by using different polymers to find out the ideal formulation which can release the drug in a controlled manner over a period of 20 hours. Based on pre compression, post compression parameters and the drug release profile F4 was selected as the ideal formulation.

When the drug release was fitted in pharmacokinetic modeling the ideal formulation F4 was releasing in first order process with fickian diffusion.

The ideal formulation F4 was subjected to stability studies and found that there is no deviation of drug release to that of initial release. Therefore we conclude that a stable & effective dosage form giving the required drug release in a controlled manner was successfully formulated.

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