FORMULATION AND EVALUATION OF CAPECITABINE IMMEDIATE RELEASE TABLETS

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI-32

In partial fulfillment for the award of the degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

Register no: 26111008

UNDER THE GUIDANCE OF

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Approved by Pharmacy Council of India, New Delhi, and
All India Council for Technical Education. New Delhi.

THE CERTIFICATE

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DECLARATION

I hereby declare that the thesis entitled **"FORMULATION AND EVALUATION OF CAPECITABINE IMMEDIATE RELEASE TABLETS"** has been originally carried out by me under the supervision and guidance of **Mr. R.Amarnath.,** (Industrial guide) and **DR. R.Kumaravel Rajan, Mpharm., PhD,** (Institutional Guide) Asst. Professor, Department of Pharmaceutics, C.L. Baid Metha college of Pharmacy,Chennai-97, during the academic year 2012-2013

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List of Abbreviations

API	Active pharmaceutical Ingredient
CI	Compressibility Index
FTIR	Fourier transformer infrared spectroscopy
HPLC	High Performance Liquid Chromatography
HPMC	Hydroxy Propyl Methyl Cellulose
HR	Hausner Ratio
IP	Indian Pharmacopoeia
IR	Immediate release
MCC	Microcrystalline cellulose
PEG	Poly ethylene glycol
RH	Relative Humidity
RPM	Rotations per minute
SSG	Sodium starch glycolate
USP	United States Pharmacopoeia
UV	Ultra Violet

Nomenclature

%	Percentage
µg/ml	Microgram/millilitre
Conc	Concentration
gm/cc	Gram/cubic centimetre
Hr	Hour
Kg/cm2	Kilogram/square centimetre
Min	Minute
Mm	Millimetre
Mg	Milligrams
Ng	Nanogram
Sec	Seconds

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1. INTRODUCTION

1.1 *Immediate Release (IR) Preparations:*[1, 2]

The Oral route of administration still continues to be the most preferred route due to its manifold advantages including ease of administration, accurate dosage, self-medication, versatility and most importantly patient compliance. Therefore, oral solid dosage forms are more popular.

These preparations are primarily intended to achieve faster onset of action for drugs such as analgesics, antipyretics, and coronary vasodilators. It is designed to disintegrate and release their medicaments with no special rate controlling features. Other advantages include enhanced oral bioavailability through transmucosal delivery and pregastric absorption, convenience in drug administration to dysphasic patients, especially the elderly and bedridden, and new business opportunities.

Conventional IR formulations include fast disintegrating tablets and granules that use effervescent mixtures, such as sodium carbonate (or sodium bicarbonate) and citric acid (or tartaric acid), and superdisintegrants, such as sodium starch glycolate, croscarmellose sodium and crospovidone. Current technologies in fast-dispersing dosage forms include modified tableting systems, floss or Shear form technology, which employs application of centrifugal force and controlled temperature and freeze-drying.

Immediate release drug delivery system is a conventional type of drug delivery. These are the dosage forms in which ≥ 85% of labelled amount dissolves with in 30 min. However for immediate release tablets, tablet disintegrants play an important role in ensuring that the tablet matrix break up on contact with fluid in the stomach to allow the release the active drug which then become available in whole or in part, for absorption from gastrointestinal tract.

Advantages of immediate release drug delivery system:

- Release the drug immediately.
- More flexibility in adjusting the dose.
- It can be prepared with minimum dose of drug.
- There is no dose dumping problem
- Immediate release drug delivery systems can be used in both initial stage and final stage of disease.

1.*2 Current technologies in oral drug delivery*:[3]

Over the last 3 decades, many novel oral drug therapeutic systems have been invented along with the appreciable development of drug delivery technology. Although these advanced DDS are manufactured or fabricated in traditional pharmaceutical formulations such as Tablets, Capsules, Sachets, Suspensions, Emulsions, and Solutions, they are superior to the conventional oral dosage forms in terms of their therapeutic efficacies, toxicities, and stabilities.

Based on the desired therapeutic objectives, oral DDS may be assorted into three categories:

- Immediate-release preparations,
- Controlled-release preparations and
- Targeted- release preparations.

1.3 *Excipients used in tablets*[4]

Excipients are inert substances used as diluents or vehicles for a drug. In the pharmaceutical industry many exciepients are used. All of these must meet certain criteria as follows:-

- They must be physiological inert.
- They must be acceptable to regulatory agencies
- They must be physiologically and chemically stable.

- They must be free of any bacteria considered to be pathogenic or otherwise objectionable.
- They must be not interfere with the bioavailability of the drug.
- They must be commercially available in the form and purity commensurate to pharmaceutical standards.
- Cost must be relatively inexpensive.

To assure that no excipient interferences with the utilization of the drug, the formulator must carefully and critically evaluate combinations of the drug with each of the contemplated excipients and must ascertain compliance of each ingredient with existing standards and regulations.

The screening of drug-excipients and excipient-excipient interactions should be carried out routinely in preformulations studies.

1.3.1 Fillers (Diluents)

Tablet fillers of comprise a heterogeneous group of substances. Since they often comprise the bulk of the tablet, selection of a candidate from this group as a carrier for a drug is of prime importance.

1.3.2 Binders

Binders are the glue that holds powders together to form granules. They are the adhesives that are added to tablet formulations to provide the cohesiveness required for that bonding together of the granules under compaction to form a tablet. The quantity used and the method of application must be carefully regulated, since the tablet must remain intact when swallowed and then release its medicament.

1.3.3 Lubricants

Lubricants are used in tablet formulation to ease the ejection of the tablet from the die, to prevent sticking of tablets to the punches, and to prevent excessive wear on punches and dies. They function by interposing a film of low shear strength at the interface between the tablet and the die wall and the punch face.

In selecting a lubricant, the following should be considered:

- Lubricants markedly reduce the bonding properties of many excipients.
- Over blending is one of the main causes of lubrication problems. Lubricants should be added last to the granulation and tumble-blended for not more than 10 min.
- Lubricant efficiency is a function of particle size; therefore, the finest grade available should be used and screened through a 100-300 mesh screen before use.
- Examples of lubricants commonly used are magnesium stearate, talc, starch.

1.3.4 Disintegrants

Disintegrants are used in tablet preparation to break the tablet faster. But some of the disintegrants are also having property of enhancing solubility of insoluble drug.

Bioavailability of a drug depends in absorption of the drug, which is affected by solubility of the drug in gastrointestinal fluid and permeability of the drug across gastrointestinal membrane. The drugs solubility mainly depends on physical – chemical characteristics of the drug. However, the rate of drug dissolution is greatly influenced by disintegration of the tablet.

The drug will dissolve at a slower rate from a non disintegrating tablet due to exposure of limited surface area to the fluid. The disintegration test is an official test and hence a batch of tablet must meet the stated requirements of disintegration.

Disintegrants, an important excipient of the tablet formulation, is always added to tablet to induce breakup of tablet when it comes in cling 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.

1.4 *Tablet manufacturing methods:*[5,6]

There are three basic methods of manufacturing:

- Direct Compression
- Dry granulation
- Wet granulation
- Fluidized bed granulation

Granulation:

Introduction:-

Granulation process has been widely used in the pharmaceutical industry for the preparation of material for tableting. Other process which involves the granule formation includes microencapsulation, multi-particulate system for modified release mechanism and to prepare granules to be used by patient directly. Primarily granules are prepared to improve flow and compression characteristics of the blend but there are many other reasons and sometimes multiple reasons for granulation such as-

- Improving flow properties of the mix and hence the uniformity of the dose
- Increasing the bulk density of a product
- Facilitating metering or volumetric dispensing
- Controlling the rate of drug release
- Decrease dust generation and reduce employee exposure to drug product
- Improving product appearance

Reasons for Granulation

1) To prevent segregation of the constituents of the powder mix

Segregation (or demixing) is primarily due to differences in the size or density of the components of the mix.

- The smaller or denser particles concentrating at the base of a container.
- The larger or less dense ones above them.

- An ideal granulation will contain all the constituents of the mix in the correct proportion in each granule and segregation of the ingredients will not occur.

2) To improve the flow properties of the mix

Many powders because of their small size irregular shape and surface characteristics are cohesive and don't flow well. Poor flow will often result in a wide weight variation with in the final product owing to variable fill of tablet dies etc.

3) To improve the compaction characteristics of the mix

The granulation of toxic materials will reduce the hazard associated with the generation of toxic dust that may arise when handling powders.

1.4.1 Direct Compression

This method is used when a group of ingredients can be blended and placed in a tablet press to make a tablet without any of the ingredients having to be changed. This is not very common because many tablets have active pharmaceutical ingredients which will not allow for direct compression due to their concentration or the excipients used in formulation are not conducive to direct compression.

Granulation is the process of collecting particles together by creating bonds between them. There are several different methods of granulation. The most popular, which is used by over 70% of formulation in tablet manufacture is wet granulation. Dry granulation is another method used to form granules.

1.4.2 Wet granulation*:*

Wet granulation is the most widely used process of granulation in the pharmaceutical industry. It involves addition of a liquid solution (with or without binder) to powders, to form a wet mass or it forms granules by adding the powder together with an adhesive, instead of by compaction. The wet mass is dried and

then sized to obtained granules. The liquid added binds the moist powder particles by a combination of capillary and viscous forces in the wet state. More permanent bonds are formed during subsequent drying which leads to the formation of agglomerates.

Important steps involved in the wet granulation

- Mixing of the drug(s) and excipients
- Preparation of binder solution
- Mixing of binder solution with powder mixture to form wet mass.
- Coarse screening of wet mass using a suitable sieve (6-12 screens).
- Drying of moist granules.
- Screening of dry granules through a suitable sieve (14-20 screens).
- Mixing of screened granules with disintegrant, glidant and lubricant.
- Compression of lubricated granules to tablet.

1.5 *Tablet coating* [7, 8]

Coated tablets are defined as the tablets covered with one or more layers of mixture of various substances such as natural or synthetic resins, gums, inactive and insoluble filler, sugar, plasticizer, polyhydric alcohol, waxes, authorized coloring material coating may also contain active ingredient. Substances used for coating are usually applied as solution or suspension under conditions where vehicle evaporates.

The purpose of tablet coating:

1. Cover the unpleasant taste, odor and color

2. Physical and chemical protection in medicine from environment (light, moisture, and air)

3. Control of drug release as in enteric coating or sustained release

4. Improve the appearance of tablets

5. Assist and facilitate the identification of drug

6. Easing the process of blistering

Basic principles of tablet coating:

- Insulation which influences the release pattern as little as possible and does not markedly change the appearance.
- Modified release with specific requirements and release mechanism adapted to body function in the digestive tract.
- Color coating which provides insulation or is combined with modified release coating.

Types of tablet coating process:

1. Sugar coating
2. Film coating
3. Enteric coating
4. Controlled release coating
5. Specialized coating
6. Compressed coating
7. Electrostatic coating
8. Dip coating
9. Vacuum film coating

1.5.1 Film coating:

Film coating is deposition of a thin film of polymer surrounding the tablet core. Conventional Pan Equipment's may be used but now a day's more sophisticated equipment's are employed to have a high degree of automation and coating time.

Advantages of film coating:

- It is a less time consuming technique.
- Not much labor is required.
- It has no adverse effects on disintegration of tablets.
- The product cost is low because the material used for coating is quite cheap.

- It protects the drug from atmosphere changes such as light, air, and moisture
- Coating is resistant to cracking and chipping.
- Film coating of tablets does not increase the weight of the tablet.
- No water proof coating is required before the actual film coating.
- The tablets become elegant.

Ideal film coating materials:

- Solubility in solvents of choice for coating preparation.
- Solubility required for the intended. Use, e.g.; free water solubility, slow water solubility or pH-dependent solubility.
- Capacity to produce an elegant looking product.
- Stability in the presence of heat, light, moisture, air and the substrate being coated, the film properties should not change with aging.
- Essentially no color, no taste or odor.
- Compatibility with common coating solution additives.
- Non-toxicity with no pharmacological activity, and ease of application to the particles or tablets.
- Resistance to cracking and provision of adequate moisture, light, odor or drug sublimation barrier when desired.
- No bridging or filling of these de bossed tablets surface by the film former.
- Ease of printing procedure on high-speed equipment.

Process description*:*

Film coating is deposition of a thin film of polymer surrounding the tablet core. Conventional pan equipment's may be used but now a day's more sophisticated equipment's are employed to have a high degree of automation and coating time. The polymer is solubilized in to solvent. Other additives like plasticizer and pigments are added. Resulting solution is sprayed on to a rotated tablet bed. The drying conditions cause removal of the solvent, giving thin deposition material around each tablet core.

Process details:

Usually spray process is employed in preparation of film coated tablets. "Accelacota" is the prototype of perforated cylindrical drum providing high drying

air capacity. Fluidized bed equipment has made considerable impact where tablets are moving in a stream of air passing through the perforated bottom of a cylindrical column. With a smaller cylindrical insert, the stream of cores is rising in the center of the device together with a spray mist applied in the middle of the bottom. For fluidized bed coating, very hard tablets (hardness>20N) have to be used.

Basic process requirement for film coating:

The fundamental requirements are independent of the actual type of equipment's being used and include adequate means of atomizing the spray liquid for application to the tablet core, adequate mixing and agitation of tablet bed, sufficient heat input in the form of drying air to provide the latent heat of evaporation of the solvent. This is particularly important with aqueous-based spraying and good exhaust facilities to remove dust and solvent laden air.

Materials used in film coating

1. Film formers (which may be enteric or non-enteric)
2. Solvents
3. Plasticizers
4. Colorants
5. Opaquent extenders
6. Miscellaneous coating solution components

I. *Film formers*: This may be enteric or non-enteric

Enteric Materials:

- Cellulose acetate phthalate
- Acrylate polymer
- Hydroxy propyl methylcellulose phthalate
- Polyvinyl acetate phthalate

Non-enteric material:

- Hydroxy propyl methylcellulose
- Ethyl cellulose
- Hydroxy propylcellulose

- Povidone
- Sodium carboxyl methyl cellulose
- Polyethylene glycols
- Acrylate polymer

. **II. Solvents**

Mostly solvents are used either alone or in combination with water, methanol, iso-propanol, chloroform, acetone, methylene chloride etc. Water is more used because no environmental and economic considerations.

III. Plasticizers:

Commonly used plasticizers are castor oil, PG, glycerin, lower molecular weight (200-400 series) PEGS, surfactants etc. For aqueous coating PEGS are more used while castor oil and spans are primarily used for organic-solvent based coating solution.

IV. *Colorants*:

These make the dosage form aesthetic and help manufacturers to control product during manufacturing and is a means of identification for user. Most common colorants in use are certified FD & C or D & C colorants.

V. *Opaquant-Extenders*:

Most commonly used materials are titanium dioxide, Silicate (talc & aluminum silicates), carbonates (magnesium carbonates), Oxides (magnesium oxide) & Hydroxides (aluminum hydroxides).

VI. *Miscellaneous coating solution components*

Flavors, sweeteners, surfactants, antioxidants etc. may be incorporated into the coating solution.

Coating equipments:

Most of the coating processes use one of three general types of equipment's.

- The standard Coating pan
- The Perforated Coating pan
- The Fluidized bed coater

Important Parameters in Tablet Coating Process:-

Tablet coating is a complex process that is affected by many variables. Some of those variables can be evaluated or controlled, others can't. Here are some of the parameters you should check when evaluating coating process to determine the source of defective coated tablets.

1. Control: Many problems occur in coating when you can't control every important parameter, such as temperature, pan pressure, spray rates, and atomization pressure. But, the tablet's surface temperature can be measure with additional tools (out from the coating equipment) by using infra-red thermometer (laser thermometer).

2. Tablet quality: Tablets must have the proper porosity, surface, hardness, and moisture content. You can't have consistent coating without consistent tablet quality.

3. Waiting period: Most tablets cannot be coated immediately after they've been compressed. The energy within the tablets is still fairly high and they are still warm. In addition, tablet hardness changes over 24 to 48 hours. Let the tablets rest at least that long before you coat them meanwhile you can check the uncoated tablet for assay, dissolution or other specification by quality control. After the QC released the tablet, then you can start the coating process.

Parameters in Film Coating Tablet Process

4. Batch size: Variation in batch size changes the required pan speed, gun geometry, spray rates, and temperature. The more your batch sizes vary the more quality issues that will arise in the coating process. Usually, the greater batch size or the greater number of tablets in pan coating the pan speed to spin faster. Vice versa, if the number of tablets or the smaller the batch size, pan speeds spin also reduced.

5. Coating Solution preparation: Track the solution temperature, mixer speed, and storage time. Standard operation procedure for the coating solution manufacturing should be there.

6. Spray gun calibration: We should calibrate or check the calibration of the guns every time you change products. This means checking the gun's overall condition and its filter, nozzle alignment, and needle condition.

7. Spray Gun Position/Geometry: Geometry refers to the gun-to-gun alignment, gun-to-tablet bed alignment, and distance from the gun to the end of the pan. Furthermore, make sure all the guns are pointed in exactly the same direction and are maintaining the same spray pattern. Make certain that the tubing and connections are tight and do not interfere with alignment.

8. Gun nozzles: The spray gun nozzles must be kept clean and free of product buildup. Use a flashlight during coating to look into the cabinet and check the nozzles.

9. Pan loading: A visual inspection is critical when coating tablets that are friable or that chip or break easily. That's why, while loading the tablets, we can search for tablets that are broken, capped, chipped, or covered with black speck and check for any defects that occur. We can also check the tablets during initial pan rotation, or after preheating.

10. Cleaning: Each component of the spraying system should be cleaned and dried before re-installing it after a product changeover. In tablet coating, small changes in almost any parameter can lead to big differences in results. The more consistent you make operations, and the tablet, the less you must rely on the skill of the operator. Coating may be something of an art, but you'll get better results when you apply a little science to it.

1.6 *Immediate release preparations:*

1.6.1 Mechanism of drug release:[9]

On exposure to aqueous fluids, hydrophilic matrices take up water and the polymer starts hydrating to form a gel layer. Drug release is controlled by diffusion barriers/ by surface erosions. An initial burst of soluble drug may occur due to surface leaching when a matrix containing a swellable glassy polymer

comes in to contact with an aqueous medium, there is an abrupt change from a glassy to rubbery state associate with swelling process with time, water infiltration deep in to a case increasing the thickness by the gel layer. The outer layer becomes fully hydrated and starts dissolving or eroding. When water reaches the center of the system and the concentration of drug falls below the solubility value, the release rate of the drug begins to reduce. At the same time an increase in thickness of the barrier layer with time increases the diffusion path length, reducing the rate of drug release.

1.6.2 Super disintegrants in immediate release:[10]

These are especially important for an immediate release product where rapid release of dug substance is required. A disintegrant can be added to powder blend for direct compression.

Super Disintegrants	Example of	Mechanism of Action	Special comment
Croscarmellose **Ac-Di-Sol** **Nymeee ZSX** **Primellose** **Solutab** **Vivasol**	Cross linked cellulose	Swells 4-8 folds in < 10 seconds. Swelling and wicking both	Swells in two dimensions Direct compression or granulation -Starch free
Crospovidone **Crospovidon M** **Kollidon** **Polyplasodone**	Crosslinked PVP	Swells very little and returns to original size after compression but act by capillary action	Water insoluble and spongy in nature so get porous tablet
Sodium starch glycolate **Explotab** **Primogel**	Crosslinked Starch	Swells 7-12 folds in < 30 seconds	Swells in three dimensions and high level serve as sustain release matrix
Alginic acid NF **Satialgine**	Cross linked Alginic acid	Rapid swelling in aqueous medium or wicking action	Promote disintegration in both dry or wet granulation.

Table 1: List of Super Disintegrants

1.6.3 Mechanism Of Tablet Disintegration:[11]

Disintegrants, an important excipient of the tablet formulation, are always added to tablet to induce breakup of tablet when it comes in contact with aqueous fluid and this process of desegregation of constituent particles before the drug dissolution occurs, is known as disintegration process and excipients which induce this process are known as disintegrants. [Shangraw RF, et, al., 1980].

The tablet breaks to primary particles by one or more of the mechanisms:

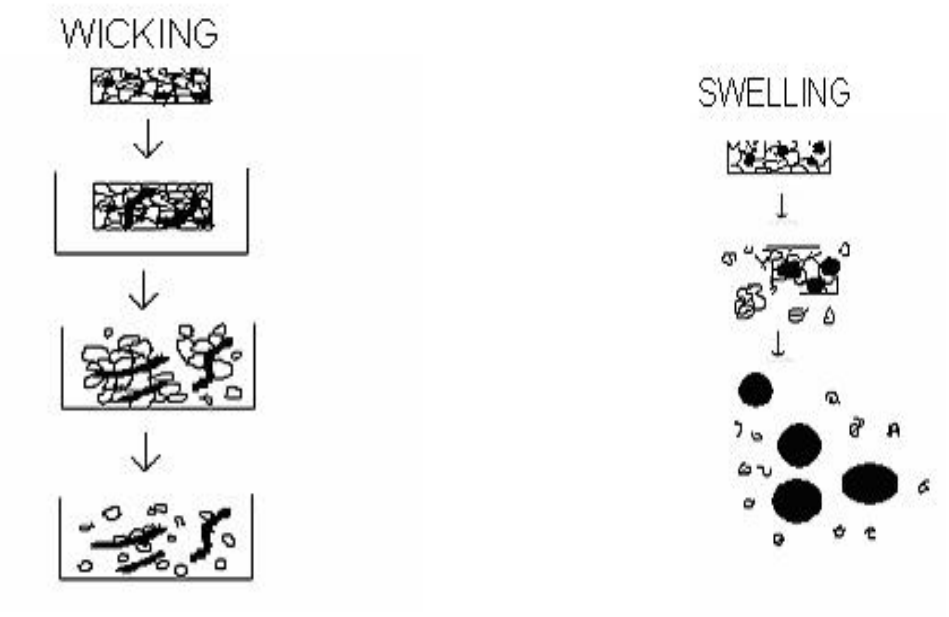
- capillary action (Wicking)
- swelling
- Due to deformation
- Due to release of gases

Capillary action (Wicking)

Effective disintegrants that do not swell are believed to impart their disintegrating action through porosity and capillary action. Tablet porosity provides way for the penetration of fluid into tablets. The disintegrant particles (with cohesiveness and compressibility) themselves act to enhance porosity and provide these capillaries into the tablet. Liquid is drawn up or leak into these ways by capillary action and rupture the inter-particulate bonds causing the tablet to break into small particles

Swelling

Not all disintegrants swell in contact with water swelling is believed to be a mechanism in which; certain disintegrating agents (like starch) impart their disintegrating effect. By swelling on contact with water the adhesiveness of other ingredients in a tablet is overcome causing the tablet to disintegrate.

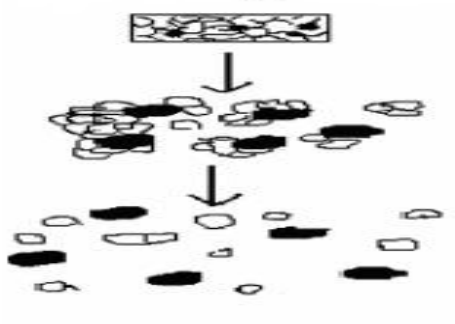


Water is pulled into pores by disintegrants and reduces the physical bonding between particles.	Particles swell and break up the matrix from within; swelling sets up; localized stress spreads throughout the matrix.

Figure-1: Mechanism of Disintegration by Wiciking and Swelling[12]

***Due to deformation*:**

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



Particles swell to precompression size and break up the matrix

Figure-2: Mechanism of tablet disintegration by deformation

***Due to release of gases*:**

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when we needs to formulate very rapidly dissolving tablets or fast disintegrating tablets.

1.7 *Biopharmaceutics Classification System*:

The Biopharmaceutics Classification System is a guide for predicting the intestinal drug absorption provided by the U.S Food and Drug Administration.

This system restricts the prediction using the parameters solubility and intestinal permeability. The solubility classification is based on a United States Pharmacopoeia (USP) aperture. The intestinal permeability classification is based on a comparison to the intravenous injection. All those factors are highly important because 85% of the most sold drugs in the United States and Europe are orally administered.

According to the Biopharmaceutics Classification System, drug substances are classified as follows:

- **Class I - high permeability, high solubility**

Those compounds are well absorbed and their absorption rate is usually higher than excretion.

- **Class II - high permeability, low solubility**

The bioavailability of those products is limited by their solvation rate. A correlation between the *in vivo* bioavailability and the *in vitro* solvation can be found.

- **Class III - low permeability, high solubility**

The absorption is limited by the permeation rate but the drug is solvated very fast. If the formulation does not change the permeability or gastro-intestinal duration time, then class I criteria can be applied.

- **Class IV - low permeability, low solubility**

Those compounds have a poor bioavailability. Usually they are not well absorbed over the intestinal mucosa and a high variability is expected.

The drugs are classified in BCS on the basis of following parameters:

1. Solubility
2. Permeability
3. Dissolution

The class boundaries for these parameters are:

1. Solubility class boundaries- It is based on the highest dose strength of an immediate release product. A drug is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1 to 7.5. The volume estimate of 250 ml is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass of water.

2. Permeability class boundaries- It is based indirectly on the extent of absorption of a drug substance in humans and directly on the measurement of rates of mass transfer across human intestinal membrane. Alternatively non-human systems capable of predicting drug absorption in humans can be used (such as in-vitro culture methods). A drug substance is considered highly permeable when the extent of absorption in humans is determined to be 90% or more of the administered dose based on a mass-balance determination or in comparison to an intravenous dose.

3. Dissolution class boundaries- An immediate release product is considered rapidly dissolving when no less than 85% of the labeled amount of the drug substance dissolves within 15 minutes using USP Dissolution Apparatus 1 at 100 RPM or Apparatus 2 at 50 RPM in a volume of 900 ml or less in the following media: 0.1 N HCl or simulated gastric fluid or pH 4.5 buffer and pH 6.8 buffer or simulated intestinal fluid.

1.8 *Cancer:*[13, 14]

Cancer known medically as a malignant neoplasm, is a broad group of various diseases, all involving unregulated cell growth. It is a disease characterized by a loss in the normal control mechanisms that govern cell survival, proliferation and differentiation. Cells that have undergone neoplastic transformation usually express cell surface antigens that may be of normal fetal type, may display other signs of apparent immaturity, and may exhibit qualitative or quantitative chromosomal abnormalities, including various translocations and the appearance of amplified gene sequences. It is now well –established that a small subpopulation of cells, referred to as tumour stem cells, reside within a tumour mass. They retain the ability to undergo repeated cycles of proliferation as well as to migrate to distant sites in the body to colonize various oragans in the process called metastasis. Cells divide and grow uncontrollably. It may also spread to more distant parts of the body through the lymphatic system or bloodstream. Malignanat neoplasm is cancerous while benign neoplasm is not cancerous. The invasive and metastatic process as well as a series of metabolic abnormalities associated with cancer result

in tumor-related symptoms and eventual death of the patient unless the neoplasm can be eradicated with treatment. There are over 200 different known cancers that afflict humans.

Cancer is a leading cause of death group worldwide and accounted for 7.4 million deaths (around 13% of all deaths) in 2004. Deaths from cancer worldwide are projected to continue rising, with an estimated 11.5 million deaths in 2030.

Classification:[15]

There are five broad groups that are used to classify cancer

1. Carcinomas:

These are characterized by cells that cover internal and external parts of the body, such as lung, breast and colon cancer.

2. Sarcomas:

These are characterized by cells that are located in bone, cartilage, fat, connective tissue, muscle and other supportive tissues.

3. Lymphomas:

These are cancers that begin in the lymph nodes and immune system tissues.

4. Leukemias:

These are cancers that begin in the bone marrow and often accumulate in the blood stream.

5. Adenomas:

These are cancers that arise in the thyroid, the pituitary gland, the adrenal gland and other glandular tissues.

Risk factors for cancer:[16]

• Tobacco use

• Alcohol use

• Dietary factors, including insufficient fruit and vegetable intake

• Overweight and obesity

• Physical inactivity

• Chronic infections from helicobacter pylori, hepatitis B virus (HBV), hepatitis C virus (HCV) and some types of human papilloma virus (HPV)

• Environmental and occupational risks including ionizing and non-ionizing radiation

Detection[17]

Cancer can be detected in a number of ways, including the presence of certain signs and symptoms, screening tests or medical imaging. Once a possible cancer is detected it is diagnosed by microscopic examination of a tissue sample. The chances of surviving the disease vary greatly by the type and location of the cancer and the extent of disease at the start of treatment. Physicians use information from symptoms and several other procedures to diagnose cancer. Imaging techniques such as X-rays, CT scans, MRI scans, PET scans, endoscopy and ultrasound scans are used regularly to detect where a tumor is located and what organs may be affected by it. Biopsies and various bio marker tests were also used to detect specific cancers

Treatment:

. Cancer treatment depends on the type of cancer, the stage of cancer, age, health status and additional personal characteristics. The treatment of most cancer patients requires a skillful interdigitation of multiple modalities of treatment. Each of these forms of treatment carries its own risks and benefits.

Cancer is usually treated with

- Chemotherapy
- Radiation therapy
- Surgery Biological therapy
- Hormone therapy
- Gene therapy

One of the greatest challenges of therapeutics is to adjust dose to achieve a therapeutic, but nontoxic, outcome. While it is customary to base dose on body surface area for individual patients, this practice is not based on solid data. Dose adjustment based on renal function or on pharmacokinetic monitoring does help meet specific targets such as desired drug concentration in plasma or area under the concentration-time curve (AUC), a measure of tissue exposure to the agent in question.

1.8.1 Cancer Chemotherapy:[18]

Cancer chemotherapy strives to cause a lethal cytotoxic event or apoptosis in the cancer cell that can arrest a tumor's progression. The attack is generally directed toward DNA or against metabolic sites essential to cell replication. For example, the availability of purines and pyrimidines, which are the building blocks for DNA or RNA synthesis. The ultimate goal of chemotherapy is a cure (that is, long-term, disease-free survival). A true cure requires the eradication of every neoplastic cell. If a cure is not attainable, then the goal becomes control of the disease (stop the cancer from enlarging and spreading) to extend survival and maintain the best quality of life. Earlier diagnosis of cancer lead to increased cure rates. In advanced stages of cancer, the likelihood of controlling the cancer is far from reality and the goal is palliation (that is, alleviation of symptoms and avoidance of life-threatening toxicity). This means that chemotherapeutic drugs may be used to relieve symptoms caused by the cancer and improve the quality of life, even though the drugs may not lengthen life.

Indications for treatment:

- Chemotherapy is indicated when neoplasms are disseminated and are not amenable to surgery.
- It is also used as a supplemental treatment, to attack micrometastases following surgery and radiation treatment in which case it is called adjuvant chemotherapy.

- Chemotherapy given prior to the surgical procedure in an attempt to shrink the cancer is referred as neoadjuvant chemotherapy.
- Chemotherapy given in lower doses to assist in prolonging a remission is known as maintenance chemotherapy.

Dosage factors:[19]

One of the main factors limiting the ability of chemotherapy to achieve cure is the problem of effective dosing. For chemotherapy, therapeutic selectivity is dependent on the difference between the dose- response curves of normal and tumor tissues. At present, there are three main approaches to dose-intense delivery of chemotherapy:

- By dose escalation where by the doses of the anticancer agents are increased.
- To administer anticancer agents in a dose-intense manner by reducing the interval between treatment cycles.
- Sequential scheduling of either agents or of combination regimens.

Each of these strategies is presently being applied to a wide range of cancers, and in general, such dose-intense regimens have significantly improves clinical outcomes.

1.8.2 *Antineoplastic agent*[20]

Antineoplastic agents are the drugs used in the treatment of cancer. The two key aspects of cellular life are

- DNA synthesis and mitosis to produce new cells.
- Cell differentiation which produces specialized cells.

Normally cells have control mechanisms to modulate these two processes by growth factor or growth inhibitors. A balance between cell growth and cell death is maintained, cell death is actively regulated by process known as “apoptosis”. Apoptosis is defined as a process of cell shrinkage, membrane blabbing and nuclear condensation.

In cancer cell, this regulatory process is aberrant; they produce over production of growth factor and avoid apoptosis which continue to multiply in an unregulated manner. The unregulated growth causes damage to DNA, resulting in mutations to genes, that encode from protein controlling cell division.

1.8.3 *Classification*

Antineoplastic agents are classified according to their mechanism of action into:

- Alkylating agents
- Antimetabolites
- Antibiotics
- Plant products
- Enzymes
- Hormones
- Immunotherapy
- Monoclonal Antibodies
- Radiotherapeutic Agents
- Cytoprotective Agent

The present drug capecitabine comes under the Antimetabolites class as pyrimidine analogue.

Antimetabolites:

They are structurally related to normal compounds that exist within the cell. They generally interfere with the availability of normal purine or pyrimidine nucleotide precursors, either by inhibiting their synthesis or by competing with them in DNA or RNA synthesis. Their maximal cytotoxic effects are in S-phase.

Pyrimidine analogues:

The structural modification of these metabolites may be on the pyrimidine ring. The possible mechanisms of action are

- Inhibition of kinases or enzyme involved in biosynthesis of pyrimidine.
- Incorporation into DNA or RNA leading to miscoding.
- Inhibition of DNA polymerase.

1.8.4 *Breast cancer*[21]

Breast cancer is a type of cancer originating from breast tissue, most commonly from the inner lining of milk ducts or the lobules that supply the ducts with milk. Cancers originating from ducts are known as ductal carcinomas, while those originating from lobules are known as lobular carcinomas. Breast cancer occurs in humans and other mammals. While the overwhelming majority of human cases occur in women, male breast cancer can also occur.

Breast cancer, like other cancers, occurs because of an interaction between the environment and a defective gene. Normal cells divide as many times as needed and stop. They attach to other cells and stay in place in tissues. Cells become cancerous when mutations destroy their ability to stop dividing, to attach to other cells and to stay where they belong.

The management of primary breast cancer has undergone a remarkable evolution as a result of major efforts at early diagnosis and the implementation of combined modality approaches incorporating systemic chemotherapy as an adjuvant to surgery and radiation therapy.

1.8.5 Colorectal cancer[22,23]

Colorectal cancer, commonly known as colon cancer or bowel cancer, is a cancer from uncontrolled cell growth in the colon or rectum (parts of the large intestine), or in the appendix. Genetic analysis shows that colon and rectal tumours are essentially genetically the same cancer. Symptoms of colorectal cancer typically include rectal bleeding and anemia which are sometimes associated with weight loss and changes in bowel habits.

Most colorectal cancer occurs due to lifestyle and increasing age with only a minority of cases associated with underlying genetic disorders. It typically starts in the lining of the bowel and if left untreated, can grow into the muscle layers underneath, and then through the bowel wall. Screening is effective at decreasing the chance of dying from colorectal cancer. Localized bowel cancer is usually diagnosed through sigmoidoscopy or colonoscopy.

Cancers that are confined within the wall of the colon are often curable with surgery while cancer that has spread widely around the body is usually not curable and management then focuses on extending the person's life via chemotherapy and improving quality of life.

Signs and Symptoms:

The symptoms and signs of colorectal cancer depend on the location of tumor in the bowel and whether it has spread elsewhere in the body. The classic warning signs

- Worsening constipation
- Blood in stool
- Weight loss
- Fever
- Loss of appetite
- Nausea or Vomiting

While rectal bleeding or anemia are high risk features in those over the age of 50.

Causes

Greater than 75-95% of colon cancer occurs in people with little or no genetic risk. Other risk factors include older age, male gender, high intake of fat, alcohol or red meat, obesity, smoking and a lack of physical exercise.

People with inflammatory bowel disease (ulcerative colitis and Crohn's disease) are at increased risk of colon cancer. The risk is greater the longer a person has had the disease and the worse the severity of inflammation

Those with a family history in two or more first degree relatives have a two to threefold greater risk of disease and this group accounts for about 20% of all cases. A number of genetic syndromes are also associated with higher rates of colorectal cancer.

2. Literature Review

M. R. Chorawala[24] *et al.,* (2012) explained that the management of cancer involves surgery, radiotherapy and chemotherapy. Development of chemoresistance is a persistent problem during the chemotherapy treatment. Cytotoxic drugs that selectively, but not exclusively, target actively proliferating cells include such diverse groups as DNA-alkylating agents, anti-metabolites, intercalating agents and mitotic inhibitors. Resistance constitutes a lack of response to drug-induced tumour growth inhibition Attempts to overcome resistance involves the use of combination drug therapy using different classes of drugs with minimally overlapping toxicities to allow maximal dosages, necessary for bone marrow recovery. Adjuvant therapy with p-glycoprotein inhibitors and in specific instances, the use of growth factor and protein kinase C inhibitors are newer experimental approaches that may also prove effective in delaying onset of resistance. Gene knockout using antisense molecules may be effective way of blocking drug resistance.

Jigar A Patel[25] *et al*., (2011) The task of developing Immediate release tablet is accomplished by using a suitable diluents and super disintegrants. Faster disintegration of the tablet administrated orally minimizes absorption time and improves its bioavailability in less time. Immediate Release tablet of Antibiotic drug is formulated using dry granulation using super disintegrant croscarmellose sodium. Azithromycin is Antibiotic drug is used to treat STDs due to Chlamydia and gonorrhea, community-acquired pneumonia, pelvic inflammatory disease, pediatric otitis media and pharyngitis, and Mycobacterium avium complex (MAC) in patients with advanced HIV disease. One of the important studies included in the present investigation is of study on process parameter effect on performance of the Immediate Release tablets. The effect of selected process parameters on critical properties of Immediate release (IR) tablets were studied, like effect of disintegration time, friability, dissolution profile.

Biljana Govedarica[26] *et al*., (2011) Paracetamol (PAR) crystals exhibit poor compressibility, flow ability. To improve the mechanical strength of tablets several kinds of "Paracetamol for direct compression" are present on the market. Current research demonstrated the best tablet properties with coated Paracetamol Furthermore, coated Paracetamol in combination with both investigated super disintegrants such as Vivasol® and Polyplasdone® XL-10 shows faster disintegration time and dissolution rate in comparison to Paracetamol for direct compression. Eventually, the major advantages of the formulation with coated Paracetamol for industrial production are decrease of friability and superiority in terms of flowability, compressibility, quick disintegration and dissolution.

Nansri Saha Ghosh[27] *et al*., (2011) The "objective" of this project work was to formulate a stable safe and effective film coated Immediate release solid dosage form of "Ranitidine HCl" that spontaneously release the drug when expose into GIT for producing anti-ulcer effect. One of the major steps in formulation development activity is the development of "Film coating formulation and process" using hydroxyl propyl methyl cellulose (HPMC-2208) and starch acetate film former.

Rajesh Agrawal [28]*et al*., (2010) studied the Granulation of a powder or mixture of powder is done in order to improve flow, uniformity of contents better compressibility, improve density and to aid pharmaceutical dosing of the actives. The review article updates about the latest developments in technologies behind most commonly used wet granulation process. Article deals with in depth basic information about granule growth mechanisms during granulation. The article also provides an insight to the in-process variables and factors influencing the granulation end point and its determination when a high shear mixer granulator of laboratory commercial scale is utilized for industrial production.

Shirsand SB[29] *et al.*, (2010) studied the fast disintegrating tablets of Prochlorperazine Maleate was designed with a view to enhance patient compliance by direct compression method. In this method crospovidone (3%w/w) and croscarmellose sodium up to 5%w/w in combination were used as super disintegrants.

Narasimhan[30] (2009) reported a serious hand-and-foot syndrome in black patients treated with Capecitabine. It is one of the well-known adverse events associated with Capecitabine,a prodrug of 5-Fluorouracil (5-FU).HFS,also known as erythrodysesthesia, manifests as acral erythema with swelling and dysesthesia of the palms and plantar aspects of the feet and in the absence of dosage reduction or stoppage of the drug, progresses to moist desquamation and ulceration with serious infections and loss of function. In black patients, we observed that Capecitabine given in the recommended dosage leads to hyper pigmentation of the palms and soles, followed by a distinct keratoderma like thickening not seen in white patients.

Abhay Gupta[31] *et al.*, (2009) the correlation between disintegration and dissolution for Immediate release tablets containing a high solubility drug and to identify formulations where disintegration test, instead of the dissolution test, may be used as the acceptance criteria based on International Conference on Harmonization guidelines.

Sagar Bhise[32] *et al.*, (2009) The super disintegrants acts as hydrophilic carrier for poorly water insoluble drug. So this present article investigates the solubilizing properties of super disintegrants and hence enhancement of the dissolution profile of a model drug furosemide (poorly water insoluble) using solid dispersion (SD) with crosspovidone, crosscarmellose sodium and sodium starch glycolate (SSG) by using kneading technique. The 1:1 (w/w) and 1:2 (w/w) solid dispersions were prepared by kneading method using solvent water and ethanol in 1:1 ratio. Dissolution studies using the USP paddle method were performed for solid dispersions of Furosemide at 37 ± 0.5oC and 50 rpm in simulated gastric fluid (SGF) of pH 1.2. Fourier transformer Infrared (FTIR) spectroscopy, Differential

scanning calorimetry (DSC), and X-ray diffractometry (XRD) were performed to identify the physicochemical interaction between drug and carrier, hence its effect on dissolution. IR spectroscopy, XRD, and DSC showed change in the crystal structure towards amorphous one of Furosemide (FRMD). Dissolution of Furosemide improved significantly 1:2 solid dispersion indicated increase in dissolution 5.40 fold. From this study it was concluded that the solubility and dissolution of model drug Furosemide was increased due to solid deposition of drug upon surface of hydrophilic and strongly swelling super disintegrants which enhanced the wettability and dispersibility of poorly water soluble drug Furosemide which is prerequisite step for poorly water soluble drug.

Sekar[33] *et al.*, (2009) developed immediate release tablets of Telmisartan which is anti –Hypertensive drug of BCS class-2 by using Crospovidone as a intragranular and extragranular level of addition to increase the rate of drug release from the dosage form to increase dissolution rate and hence its bioavailability. It was found that Immediate release tablets with proper hardness disintegration time and with increase rate of dissolution can be made using polyplasdone XL-10.

Rai K[34] *et al.*, (2009) developed immediate release tablets of Raloxifen hydrochloride by wet granulation method. Raloxifen was formulated as Immediate release tablets by using different binders like ethyl cellulose, HPMC and various disintegrants like crospovidone and croscarmellose sodium .The optimized formula shows good *in vitro* drug release of 87% within 45 minutes.

Jain C P[35] *et al.*, (2009) investigated on formulation and evaluation of fast dissolving tablets of Valsartan, in this investigation fast dissolving tablets of Valsartan were prepared using different super disintegrants by direct compression method. The drug release from FDT's increased with increasing concentration of super disintegrants and was found to be highest with formulations containing Crospovidone .In the present study it can be concluded from the characterization of fast dissolving tablets of Valsartan that formulation containing Crospovidone is most acceptable.

Pani[36] ***et al.*****, (2008)** developed immediate release tablets of Nateglinide and were formulated by using various proportions of different super disintegrants such as croscarmellose sodium, sodium starch glycolate, kyron by non-aqueous wet granulation technique. It was indicated that the Immediate release tablets of Netaglinide can be formulated by using optimum concentration of kyron, sodium starch glycolate and croscarmellose sodium. Good correlation was established between *in vitro* dissolution time and rate for each of three super disintegrants at that concentrations were studied.

Mallikarjuna Settee C[37]**, *et al.,* (2008)** Aceclofenac fast dispersible tablet have been prepared by wet granulation method. Effect of super disintegrants such as croscarmellose sodium, sodium starch glycolate and Crospovidone on wetting time, disintegration time, drug content, *in vitro* release. The disintegration time and dissolution parameters increased with the increase in level of sodium starch glycolate.

Babu[38] ***et al.*****, (2007*)*** have prepared solid dispersions of Piroxicam in five super disintegrants namely primogel, microcrystalline cellulose, crospovidone, pregelatinized starch, croscarmellose sodium and with water soluble carriers polyvinyl pyrolidone and polyethylene glycol. Solid dispersions of Piroxicam in super disintegrants gave a marked enhancement in its dissolution rate and dissolution efficiency. Solid dispersion in super disintegrants could be used as an effective and efficient technique for enhancing the dissolution rate of Piroxicam a poorly soluble drug.

Honary[39] ***et al., (*2007)** has studied the effect of film coating solution containing different grades of HPMC (E5,E15 and E50) with and without polyethylene glycol (with various molecular weights), for the characterization of pharmaceutical products.

Sunil A. Agnihotri[40] ***et al., (*2006)** This paper describes the synthesis of Capecitabine-loaded semi-interpenetrating network hydrogel microspheres of chitosan-poly (ethylene oxide-*g*-acrylamide) by emulsion crosslinking using

glutaraldehyde. Poly (ethylene oxide) was grafted with polyacrylamide by free radical polymerization using ceric ammonium nitrate as a redox initiator. Capecitabine, an anticancer drug, was successfully loaded into microspheres by changing experimental variables such as grafting ratio of the graft copolymer, ratio of the graft copolymer to chitosan, amount of cross linking agent and percentage of drug loading in order to optimize process variables on drug encapsulation efficiency, release rates, size and morphology of the microspheres. A 2^4 full factorial design was employed to evaluate the combined effect of selected independent variables on percentage of drug release at 5 h (response). Grafting, interpenetrating network formation and chemical stability of the Capecitabine after encapsulation into microspheres was confirmed by Fourier infrared spectra (FTIR). Differential scanning calorimetry (DSC) and X-ray diffractometry (XRD) studies were made on drug-loaded microspheres to investigate the crystalline nature of drug after encapsulation. Results indicated amorphous dispersion of Capecitabine in the polymer matrix. *In vitro* release studies were performed in simulated gastric fluid (pH 1.2) for the initial 2 h, followed by simulated intestinal fluid (pH 7.4) until complete dissolution. The release of Capecitabine was continued up to 10 h.

Eric Beyssac[41] *et al.*, (2006*)* The drug studied was Acetaminophen in the form of Immediate release (IR) tablets. The second purpose was to establish a level A *in vitro/in vivo* correlation that could predict the bioavailability of a drug instead of using difficult, time-consuming and expensive *in vivo* bioequivalence studies. The artificial digestive system was used to estimate the availability of Acetaminophen IR tablets for absorption in fasted and fed states. The same study was performed *in vivo* under similar conditions. Compared to USP II method, the novel *in vitro* model demonstrated a high level of efficacy in mimicking the behavior of Acetaminophen IR tablets in vivo in fasted and fed states.

Bhagawati[42]*et al.*, (2005) formulated Cefixime with various disintegrants like croscarmellose sodium, sodium starch glycolate and crospovidone and using starch and PVP K30 as binders. They used direct compression as the method of preparation of tablets. Even though the mean disintegration time decrease with sodium starch glycolate and Crospovidone.

Prakash K[43]***et al.*****, (2005)** studied on formulation and evaluation of Metronidazole fast dispersible tablets using some disintegrants such as potato starch, pregelatinised starch, sodium starch glycolate and microcrystalline cellulose. Starchpaste (10%) was used as binding agent and concluded that dispersible tablets of Metronidazole prepared using primojel as disintegrant showed rapid disintegration, dissolution rates compared to other formulations.

Stan forth[44]***et al., (*****2004)** studied the microcrystalline cellulose excipient having improved compressibility whether utilized in direct compression dry granulation or wet granulation and possess excellent disintegrating and dissolution properties when exposed to gastrointestinal fluid.

Mira Jivraj[45] ***et al.*****, (2000)** studied that many formulation scientists ranked microcrystalline cellulose as the most useful filler for direct compression. It reveals that the popularity ascribed to its excellent compactibility at low pressures, high dilution potential and superior disintegration properties. This study concluded that as a result of its low bulk density, microcrystalline cellulose has a high dilution potential.

Tang[46] **(2000)** has studied the effect of film coating on the release of Chloramphenicol maleate tablets and was observed that film coating of aqueous solution of hydroxylpropyl methyl cellulose improves the dissolution profile. It was found that the increased dissolution rate is due to the easy penetration of solvent into the HPMC, which helps in wetting of core tablet.

Preetha[47] **(2000)** has studied the effect of mode of incorporation of super disintegrants such as croscarmellose sodium, sodium starch glycolate and Crospovidone on dissolution. The results indicated that the formulation containing croscarmellose sodium has shown best release profile than the other super disintegrants due to rapid swelling action of the polymer.

3. Aim and Objective

The object of the present research is to produce a generic tablet which was robust, stable and of an acceptable formulation when compared to the reference original product, thereby fulfilling the requirements of essential similarity to the innovator or reference product.

The investigation is concerned with development of Capecitabine Immediate release dosage (IR) form, which can be used for the treatment of colorectal carcinoma and breast cancer.

The Immediate Release tablet dosage form of Capecitabine prepared by Direct compression and Wet Granulation technique to compare and evaluate the *in vitro* drug release profile of the formulation. Another object of the investigation is to include the super disintegrant with different concentration as the intra-granular and extra-granular agent to facilitate the drug release.

The prepared dosage form to be tested for physical characteristics of tablet, and *In vitro* drug release study, Dissolution efficiency (DE), Determination of similarity factor (*f1, f2*), Stability study with respect to the innovator drug product.

4. Plan of Work:

The present research work relates to development of immediate release tablets of Capecitabine by direct compression and wet granulation methods using HPMC, SSG, MCC and Lactose anhydrous and comparision of the *in vitro* dissolution profile of Capecitabine with that of the innovator Xeloda.

4.1. The schematic representation for Plan of Work:

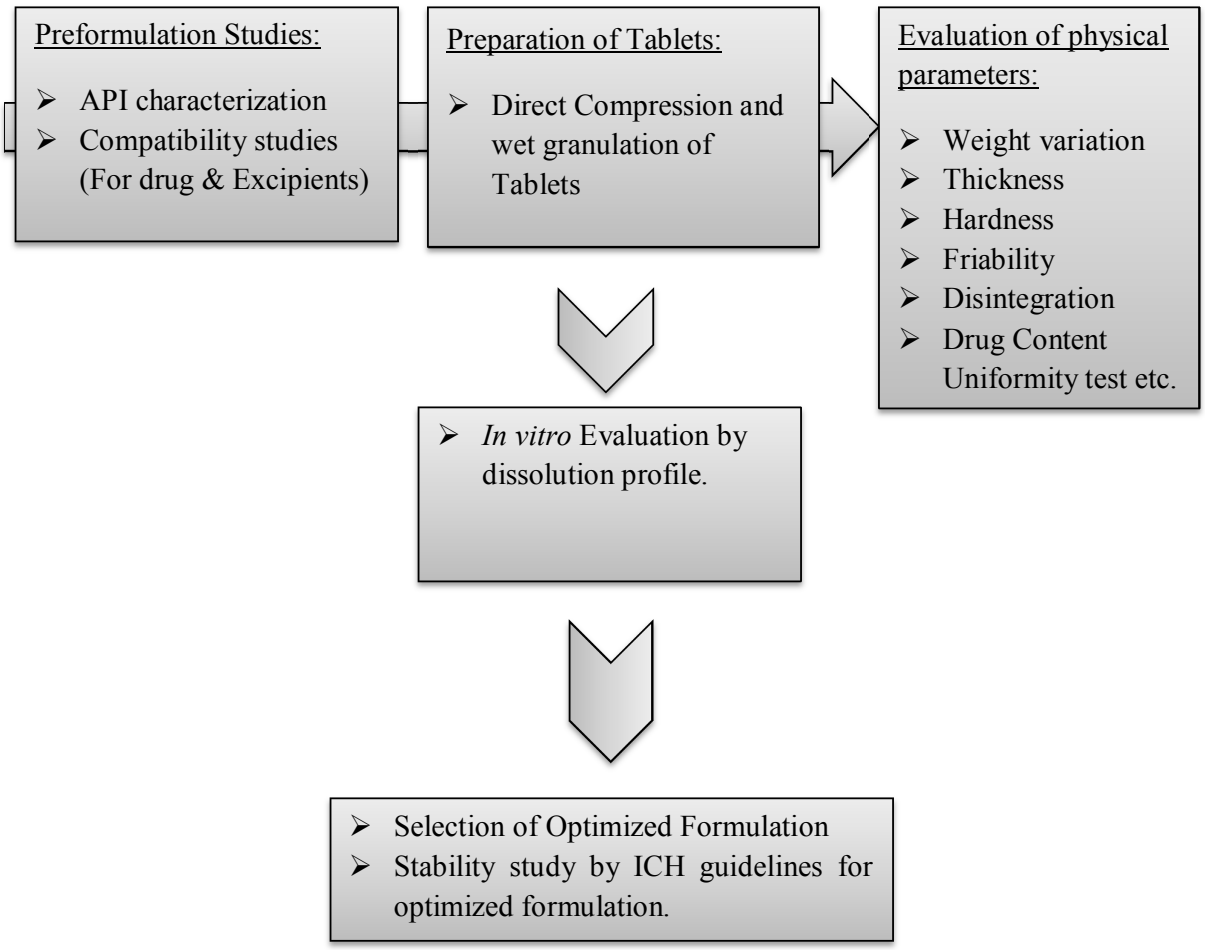


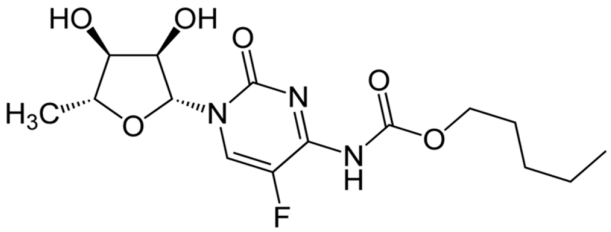
Figure No 3: Plan of work-schematic representation

5. Drug and Excipient profile

5.1 *Drug profile:* [48, 49]

Name : Capecitabine

Structure :



IUPAC Name	:	Pentyl[1-(3,4-dihydroxy-5-methyltetrahydrofuran-2-yl)-5-fluoro-2-oxo-1H pyrimidin-4-yl]carbamate
Molecular Formula	:	$C_{15}H_{22}FN_3O_6$
Molecular Weight	:	359.35
Melting point	:	110-121° C
LogP	:	0.4
Solubility	:	It is soluble in water (26mg/ml)
Category	:	Antineoplastic.
T½	:	Approximately 38-45 minutes.

Dose	:	The usual starting dose is 2,500 mg/m^2/day in two divided doses, 12 hours apart. One cycle includes two weeks of treatment followed by one week without treatment. Cycles can be repeated every three weeks.
BCS	:	Class Type III (High solubility, Low permeability)

Pharmacokinetics:

***Absorption*:**

Readily absorbed through GI tract (approximately 70%). Time to reach peak plasma concentration for Capecitabine is approximately 1.5 hours and for 5-fluorouracil is 2 hours. Food decreased peak plasma concentration is 60% and area under curve is 35% for Capecitabine and decreased peak plasma concentration (c_{max}) 4.3% and area under curve 21% for 5-fluorouracil.Food delayed T_{max} is 1.5hours.

***Protein binding*:**

Less than 60% protein binding (mainly albumin).

***Metabolism*:**

Metabolized by thymidine phosphorylase to fluorouracil.

***Elimination*:**

Capecitabine and its metabolites are predominantly excreted in urine. About 95.5% of administered Capecitabine dose is recovered in urine. Fecal excretion is minimal (2.6%). The major metabolite excreted in urine is FBAL which represents 57% of the administered dose. About 3% of the administered dose is excreted in urine as unchanged drug.

Mechanism of Action:

Capecitabine is a prodrug that is selectively tumour-activated to its cytotoxic moiety, fluorouracil, by thymidine phosphorylase, an enzyme found in higher concentrations in many tumors compared to normal tissues or plasma. Fluorouracil is further metabolized to two active metabolites, 5-fluoro-2'-deoxyuridine 5'-monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP), within normal and tumour cells. These metabolites cause cell injury by two different mechanisms. First, FdUMP and the folate cofactor, N5-10-methylenetetrahydrofolate, bind to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding inhibits the formation of thymidylate from 2'-deaxyuridylate. Thymidylate is the necessary precursor of thymidine triphosphate, which is essential for the synthesis of DNA, therefore a deficiency of this compound can inhibit cell division. Secondly, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate (UTP) during the synthesis of RNA. This metabolic error can interfere with RNA processing and protein synthesis through the production of fraudulent RNA.

Indications and usage:

Capecitabine is a nucleoside metabolic inhibitor with anti-neoplastic activity. It is used in the treatment of

- Adjuvant colon cancer Stage III Dukes' C - used as first-line monotherapy.
- Metastatic colon rectal cancer

  - First line as monotherapy when treatment with fluoro pyrimidine monotherapy alone is preferred.
- Metastatic breast cancer

  -as monotherapy, if the patient has failed paclitaxel based treatment, and if anthracycline based treatment has either failed or cannot be continued for other reasons.

  -used in combination with docetaxel, after failure of anthracycline based treatment.

Adverse reactions: Most common adverse reactions are

- Cardiovascular : EKG changes, myocardial infarction, angina.
- Dermatological : Hand and foot syndrome.
- Gastrointestinal : Diarrhea, Nausea, stomatitis.
- Hematological : Neutropenia, anemia and thrombocytopenia
- Hepatic : Hyperbilirubinemia.

Drug interactions:

- **Anticoagulants :** May interact with warfarin and increase bleeding risk.
- **Phenytoin :**. May inhibit cytochrome CYP2C9 enzyme, and therefore increase levels of substrates such as Phenytoin and other substrates of CYP2C9
- **Leucovorin :** The concomitant use of Leucovorin is not recommended. Leucovorin increased the toxicity of Capecitabine without any apparent advantage in response rate.

Pharmacodynamics:

Capecitabine is a fluoropyrimidine carbamate with antineoplastic activity indicated for the treatment of metastatic breast cancer and colon cancer. It is an orally administered systemic prodrug that has little pharmacologic activity until it is converted to fluorouracil by enzymes that are expressed in higher concentrations in many tumors. Fluorouracil it then metabolized both normal and tumor cells to 5-fluoro-2′-deoxyuridine 5′-monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP).

5.2*Excipient profile*:

5.2.1 Hydroxypropyl Methyl Cellulose (HPMC): [50]

Non-proprietary names:

IP : Hydroxypropylmethlcellulose

BP : Hypromellose

Ph Eur : Methylhydroxypropylcellulosm

USP : Hypromellose

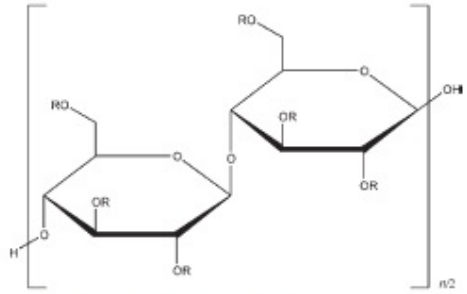
Synonyms

Benecel MHPC; E464; Hydroxypropyl Methylcellulose; HPMC; Methocel; methylcellulose Propylene glycol ether; methyl hydroxypropylcellulose; Metolose; Tylopur.

Chemical Name and CAS Registry Number

Cellulose hydroxypropyl methyl ether [9004-65-3]

Molecular structure:



where R is H, CH_3, or $CH_3CH(OH)CH_2$

Functional Category:

Coating agent**,** film former, rate controlling polymer for sustain release, stabilizing agent, suspending agent, tablet binder, viscosity increasing agent.

Description:

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.

Applications in Pharmaceutical Formulation or Technology:

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, HPMC is primarily used as a tablet binder (1), in film-coating,(2–7) and as a matrix for use in extended-release tablet formulations.(8–12) Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. 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. Hypromellose is also 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. In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

Incompatibilities:

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

Stability and Storage Conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively. The gel point is 50–90°C, depending upon the grade and concentration of material.

Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

Safety:

Hypromellose is generally regarded as a nontoxic and nonirritating material, although excessive oral consumption may have alaxative effect.

5.2.2 *Sodium starch glycolate:* [51]

Non proprietary name:

BP: Sodium starch glycolate;

USPNF: Sodium starch glycolate.

Synonyms:

Explotab, Primogel

Functional category:

Tablet and capsule disintegrant.

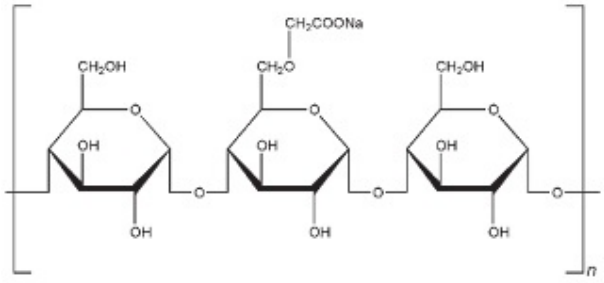
Chemical names:

Sodium carboxymethyl starch

CAS Registry Number:

9063-38-1

Structure:



Description:

Sodium starch glycolate is a white to off-white, odourless, tasteless, free flowing powder. It consists of oval or spherical granules, 30-100 μm in diameter with some less spherical granules ranging from 10-35 μm in diameter.

Solubility:

Practically insoluble in water. Sparingly soluble in ethanol (95%). In water it swells up to 300 times its volume.

Stability and storage conditions:

It is a stable material. It should be stored in a well closed container to protect from wide variations in humidity and temperature that may cause cracking.

Incompatibilities:

Incompatible with ascorbic acid.

Safety:

It is generally regarded as a non-toxic and non-irritant material. However, oral ingestion of large quantities may be harmful.

Applications:

As a disintegrant in tablet (wet granulation and direct compression and capsule formulation in 2-8% concentration.

5.2.3 *Lactose anhydrous:* [52]

Nonproprietary Names*:*

BP	:	Anhydrous Lactose
JP	:	Anhydrous Lactose
PhEur	:	Lactose, Anhydrous
USP-NF	:	Anhydrous Lactose

Synonyms:

Anhydrous 60M; Anhydrous Direct Tableting (DT); Anhydro DT High Velocity; Anhydrous Impalpable; Lactopress Anhydrous;Lactopress Anhydrous 250; lactosum anhydricum; lattosio; milksugar; SuperTab 21AN; SuperTab 22AN; saccharum lactis.

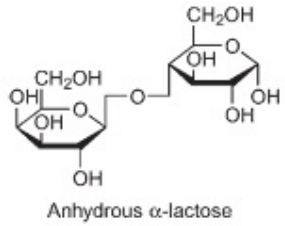
Chemical Name:

O-b-D-Galactopyranosyl-(1→4)-b-D-glucopyranose

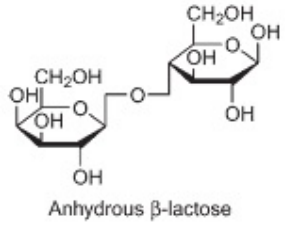
Empirical Formula:

$C_{12}H_{22}O_{11}$

Structure:



Anhydrous α-lactose



Anhydrous β-lactose

Molecular weight:

342.3

Functional Category:

Directly compressible tablet excipient; dry powder inhaler carrier; lyophilization aid; tablet and capsule diluent; tablet and capsule filler.

Applications in Pharmaceutical Formulation:

Anhydrous lactose is widely used in direct compression tableting applications, and as a tablet and capsule filler and binder. It can be used with moisture-sensitive drugs due to its low moisture content. It may also be used in intravenous injections.

Description:

Anhydrous lactose occurs as white to off-white crystalline particles or powder. Typically contains 70–80% anhydrous b-lactose and 20–30% anhydrous a-lactose.

Solubility:

Soluble in water; sparingly soluble in ethanol (95%) and ether; 40 g/100mL at 258C for typical Sheffield Pharma Ingredients Products.

Stability and Storage Conditions*:*

Mold growth may occur under humid conditions (80% RH and above). It can be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Lactose anhydrous is incompatible with strong oxidizers. This accelerates the hydrolysis of the ester and amidine groups. Lactose anhydrous is a reducing sugar with the potential to interact with primary (5) and secondary amines (6) (Maillard reaction) when stored under conditions of high humidity for extended periods.

5.2.4 *Microcrystalline cellulose (Avicel pH 112):* [53]

Non Proprietary Names

BP : Microcrystalline Cellulose

JP : Microcrystalline Cellulose

PhEur : Cellulose, Microcrystalline

USP-NF : Microcrystalline Cellulose

Synonyms:

Avicel pH; Celex; Cellulose gel; hellulosum microcristallinum; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; ethispheres .

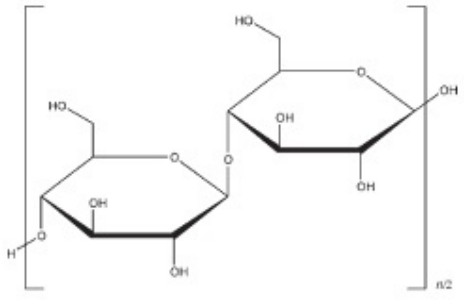
Chemical Name:

Cellulose

Empirical Formula and molecular weight:

$(C_6H_{10}O_5)_n \approx 36000$ where $n \approx 220$

Molecular structure:



Functional Category:

Adsorbent; suspending agent; as a diluents in tablets and capsules; tablet disintegrant.

Description:

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

Stability and Storage Conditions

Microcrystalline cellulose is a stable through 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.

Applications

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

Safety:

Generally regarded as safe.

5.2.5 *Magnesium stearate:* [54]

Non-proprietary names:

BP	:	Magnesium stearate
JP	:	Magnesium stearate
PhEur	:	Magnesiistearas
USPNF	:	Magnesium stearate

Synonyms:

Magnesium octadecanoate, octadecanoic acid magnesium salt and stearic acid magnesium salt.

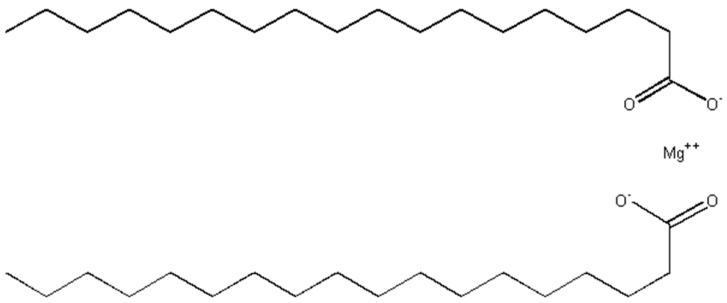
Chemical name:

Octadecanoic acid magnesium salt

Structural formula:

[CH3 (CH2)16COO] 2Mg

Molecular Structure:



Molecular weight:

591.34

Functional category:

Tablet and capsule lubricant.

Melting point:

117-150^{0}C

Description:

Magnesium stearate is a fine, 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 touch and readily adheres to the skin.

Solubility:

It is practically insoluble in ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Applications:

It is widely used in cosmetics, foods and pharmaceutical formulations. It is primarily used as a lubricant in the manufacturing of tablets and capsules, in the concentration of 0.25-5.0%. It is also used in barrier creams.

Stability and storage conditions:

It should be stored in a well closed container in a cool, dry place.

Incompatibilities:

It is incompatible with strong oxidizing agents, strong acids, alkalis and iron salts. It cannot be used in products containing aspirin, some vitamins and most alkaloidal salts.

6. Materials and Methods

6.1 Materials and Instruments

6.1.1 Materials

Table No 2: List of Materials and Suppliers

S. No	Materials	Manufacturer/Supplier
1	**Capecitabine**	Aarthi drugs private limited Mumbai, India.
2	**Anhydrous lactose**	Signet pharma agencies, Mumbai, India.
3	**Microcrystalline cellulose (Avicel pH 112)**	Signet pharma agencies, Mumbai, India.
4	**HPMC E-5 (Hypromellose E-5)**	Signet pharma agencies, Mumbai, India.
5	**Magnesium stearate**	Signet chemical corporation, Mumbai, India.
6	**Opadry pink**	Ideal cures Pvt. Ltd Mumbai, India.

6.1.2 Instruments

Table No 3: List of Instruments and Suppliers

S. No	Instruments	Manufacturer/Supplier
1	**Digital balance**	Mettler Toledo dr-203, Switzerland
2	**Sieves**	Jayanth test sieves. Mumbai
3	**Kalweka blender**	Cadmach machinery co.pvt.lt, Ahmadabad
4	**Mini rotary tablet punching machine**	REMEC, mini press, Ahmadabad
5	**Friabillator**	Electro lab EF-2, Friabillator (USP), Mumbai
6	**Hardness tester**	Electro lab, Mumbai
7	**Digimatic vernier calipers**	Electro lab, Mumbai
8	**Tray drier**	Platinum pharma tech. Hyderabad
9	**Disintegration tester**	Electrolab, Mumbai
10	**Digital tablet dissolution apparatus USP**	Electrolab, Mumbai
11	**Tap density apparatus**	Electrolab, Mumbai
12	**Electromagnetic sieve shaker**	Electro pharma, Mode EMS-8, Mumbai
13	**Ultra Sonicator**	Electro lab, Mumbai
14	**Mechanical stirrer**	Remi motors, Mumbai
15	**UV/Visible spectro-photometer**	Electro lab, Mumbai
16	**Halogen Moisture Analyzer (LOD)**	Mettler Toledo
17	**FBD (Fluid bed drier)**	U Mong Pharma tech pvt.ltd Mumbai
18	**pH meter**	Electro lab, Mumbai
19	**Hot air oven**	Elket motors, Mumbai

6.2. Methods:

6.2.1 Preformulation Studies[55,56,57]

Preformulation may be described as a stage of development during which the physicochemical and biopharmaceutical properties of a drug substance are characterized. It is an 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.

6.2.1.1 Angle of repose:

Angle of Repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane. The angle of repose is determined by funnel method. The funnel is fixed at a particular height (2.5 cm) on a burette stand. The powder sample was passed through the funnel allowing it to form a pile. No more granules are added as the pile touches the tip of the funnel. This region is encircled to measure radius. The same procedure is done for triplicate, the average value is taken. The values are given in table28The angle of repose is calculated by using equation.

$$\text{Angle of Repose } (\theta) = \text{Tan}^{-1} (h/r)$$

Where,

h = height of pile

r = radius of the base of the pile

θ = angle of repose

Table No 4: Angle of repose and corresponding flow properties

Angle of Repose	Flow property
<25	Excellent
25-30	Good
30-40	Passable
>40	Very Poor

6.2.1.2 Bulk density determination:

Weighed quantity of the powder (W) is taken in a graduated measuring cylinder and volume (V_0) is measured, the readings were shown in Table 28. Bulk density is calculated using the formula

Bulk density (BD) = Weight of the powder/ Volume of powder

6.2.1.3 Tapped density determination:

Weighed quantity of powder (W) is taken in a graduated cylinder and the volume is measured. The graduated cylinder was fixed in the 'Tapped Densitometer' and tapped for 500, 750 and 1250 times until the difference in the volume after consecutive tappings was less than 2%. The final reading was denoted by (V_f). The volume of blend was used to calculate the tapped density, Hausner's ratio and Carr's Index.

$$\text{Tapped density (TD)} = W/V_f \text{ g/ml}$$

6.2.1.4 Carr's Index:

Carr's index is also known as compressibility. It is indirectly related to the relative flow rate, cohesiveness and particle size. It is simple, fast and popular method of predicting powder flow characteristics.

Table No 5: Carr's Index and corresponding flow properties

Carr's Index (%)	Flow
5-15	Excellent
16-18	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Very very poor

Carr's index was calculated by using the formula:

$$\text{Carr's Index} = \frac{(\text{Tapped Density} - \text{Bulk Density})}{\text{Tapped Density}} \times 100$$

6.2.1.5 Hausner ratio:

Hausner ratio indicates the flow properties of the powder and measured by the ratio of tapped density to bulk density. The relationship between Hauser's ratio and flow property was shown in Table No 6.

Table No 6: Hausner ratio and corresponding flow properties

Hausner Ratio	**Property**
0-1.2	Free flowing
1.2-1.6	Cohesive Powder

Hausner ratio was calculated by using the formula.

Hausner Ratio = Tapped density / Bulk density

Hausner Ratio = V_0/V_f

where, V_0= Initial volume

V_f = Final volume

6.2.1.6 Compressibility Index (% Compressibility):

Carr's compressibility index i.e., % compressibility indicates the flow property and packing ability of the tablet. It is determined by measuring both the bulk and tapped density of a powder. When the % compressibility ranges from 5 to 16, the materials have acceptable flow property and packing ability. Compressibility Index was calculated using following equation:

$$CI\ (\%) = [(Dt - Db)/Dt] \times 100$$

Where,

Dt = tapped density,

Db = bulk density

Table No 7: Acceptance criteria of flow properties

Compressibility Index	Flow Character	Hausner Ratio
1 – 10	Excellent	1.00 – 1.11
11 – 15	Good	1.12 – 1.18
16 – 20	Fair	1.19 – 1.25
21 – 25	Passable	1.26 – 1.34
26 – 31	Poor	1.35 – 1.45
32 – 37	Very Poor	1.46 – 1.59
> 38	Very Very Poor	> 1.60

6.2.1.7 Drug excipient interaction studies (FT-IR):

Infrared spectroscopy is one of the most powerful analytical technique when it comes to the determination of presence of various functional groups involved in making up the molecule. It provides very well accountable spectral data regarding any change in the functional group characteristics of a drug molecule occurring in the process of formulation.IR spectra of capecitabine and its formulation were obtained by KBr pellet method using Perkin Elmer spectrum RX1 FT-IR spectrophotometer model.

6.2.2 Preparation of tablets

6.2.2.1 *Preparation of Tablets by direct compression*:

Step 1: **Sifting of the drug and the excipients**

Capecitabine, Microcrystalline cellulose, Lactose anhydrous, Sodium starch glycolate and HPMC were weighed and sifted individually through 40 # mesh.

Step 2: Mixing

All the ingredients were transferred to poly bag and mixed for 10 min and blend was passed through 40 # mesh and mixed thoroughly.

Step 3: Blending and Lubrication

Magnesium stearate used as a lubricant was weighed, added and blended with the ingredients for 5 min.

Step 4: Compression and Coating

The mixture was compressed and film coated with Opadry pink.

6.2.2.2 *Preparation of Tablets by wet granulation*:

Step 1: Sifting of the drug and the excipients

Ingredients such as API, Microcrystalline cellulose, Lactose anhydrous and Sodium starch glycolate are sifted individually through 40 # mesh.

Step 2: Mixing

All the ingredients were transferred to poly bag and mixed for 10 min and blend was passed through 40 # mesh and mixed thoroughly. The binder solution was prepared by dissolving HPMC in sufficient quantity of purified water and added to the blend.

Step 3: Drying

The wet mass was passed through 12 # mesh and the granules obtained were dried at 60^0C for 30 min.

Step 4: Compression and coating

The prepared granules were lubricated with magnesium stearate and sodium starch glycolate is added as extragranular agent and passed through 40 # mesh and was compressed by using punches. Tablets obtained were coated using Opadry pink.

Table No 8: Composition of Capecetabine Immediate Release tablets

Batch No		F1	F2	F3	F4	F5	F6	F7	F8	F9
S.No	**Ingredients (mg/Tab)**	DC	WG	WG	WG	WG	WG	WG	WG	WG
1	**Capecitabine**	500	500	500	500	500	500	500	500	500
2	**Lactose Anhydrous**	105.5	101	92	92	88	86	85	83	83
3	**SSG**	10	12	15	10	9	7	6	6	6
4	**HPMC E5**	15	15	18	18	20	20	20	20	20
5	**Purified Water**	0	QS	QS	QS	QS	QS	QS	QS	QS
6	**MCC pH 112**	12	12	15	15	15	15	15	15	115
7	**SSG**	0	0	0	5	8	12	14	16	16
8	**Mg stearate**	7.5	10	10	10	10	10	10	10	10
9	**Opadry pink**	15	15	15	15	15	15	15	15	15
	Total	665	665	665	665	665	665	665	665	665

- DC- Direct Compression
- WG-Wet Granulation

6.2.3 Evaluation Parameters[58,59]:

6.2.3.1 General Appearance and Organoleptic Properties

The control of a general appearance of a tablet involves the measurement of a number of attributes such as a tablet's shape, size, colour, presence or absence of an odor, taste, surface texture, physical flaws and consistency, and legibility of any identifying markings.

6.2.3.2 Shape, Thickness and Dimension

Six tablets from each batch were selected and measured for thickness and diameter using digital Vernier calipers. The extent to which the thickness of each tablet deviated from ± 5% of the standard value was determined.

6.2.3.3 Weight variation test:

Twenty (20) tablets from each batch were individually weighed. The average weight and standard deviation were calculated, individual weight of each tablet was also calculated using the same and compared with average weight
Weight Variation limits as per USP and the values were showed in the table.

Table No 9: Weight Variation for solid dosage forms (USP)

Average weight in mg	% ± deviation allowed
130 or less	10
130-324	7.5
More than 324	5

6.2.3.4 Hardness test:

The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in Kg/cm^2.

6.2.3.5 Friability test:

20 tablets from each batch were selected randomly and weighed. These tablets were subjected to friability testing using Roche friabilator for 100 revolutions. Tablets were removed, de-dusted and weighed again. Following formula was used to calculate the % friability.

$$\%Friability = \text{Initial wt- Final wt / Initial wt x100}$$

6.2.3.6 Disintegration time:

The test was carried out on 6 tablets using Tablet disintegration tester. Distilled water at 37ºC ± 2ºC was used as a disintegration media and the time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

Disintegration time:

Uncoated tablet	:	Not more than 15 min
Coated tablet	:	Not more than 30 min

6.2.3.7 Dissolution Studies:

Dissolution is process by which a solid state enters a solution. In pharmaceutical industry it may be defined as the amount of drug substance that goes into solution per unit time under standardised conditions of liquid/solid interface, temperature and solvent composition. Dissolution is considered as one of the most important QC test performed on pharmaceutical dosage form and is now developing into a tool for predicting bioavailability.

Drug release studies of the prepared Capecitabine tablets was performed in a USP Dissolution Tester Apparatus, type- II (Paddle method) at 37 ± 0.5^0C. The paddles rotated at a speed of 50 rpm. The tablets were placed into 900 mL of deaerated water. Aliquots of 10 ml were withdrawn from the dissolution apparatus at different time intervals. The drug content was determined. At each time of withdrawal, 10 ml of fresh medium was replaced into the dissolution flask.

Table No 10: Dissolution conditions

Dissolution conditions	
Medium	Deaerated water
Volume	900ml
Temperature	37°C ± 0.5°C
Apparatus	USP type –II (paddle)
RPM	50
Time interval	5,10, 15, 20,upto 45 minutes

6.2.3.8 Content Uniformity:

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch. Due to increased awareness of physiological availability, the content uniformity test has been included in the monographs of all coated and uncoated tablets and all capsules intended for oral administration where the range of size of the dosage form available include 500mg or smaller sizes.

Method: Randomly select 30 tablets. 10 of these assayed individually. The Tablet pass the test if 9 of the 10 tablets must contain not less than 85% and not more than 115% of the labeled drug content and the 10th tablet may not contain less than 75% and more than 125% of the labeled content. If these conditions are not met, remaining 20 tablets assayed individually and none may fall outside of the 85 to 115% range.

Assay of Capcetabine:-

The estimation is done by HPLC. The chromatograph is equipped with;

Column: 4.6mm*25cm with 5micron packing L1 (C18 with octadecyl bonded to porous silica or ceramic micro particles)

Refrigerated Auto sampler

Detector : 250nm detector

Flow rate : 1ml/min

Column temperature : 40^0c

***Mobile phase*:-**

Solution-A:- Prepare a mixture of dilute acetic acid, and acetonitrile (60:35:5)

Solution-B:- Prepare a mixture of methanol, diluted acetic acid, and acetonitrile (80:15:5)

Diluent :- Prepare a mixture of water, methanol, Acetonitrile (60:35:5)

Standard preparation:- Dissolve an accurately weighed quantity of USP Capecitabine RS in diluents, and sonicate if necessary, to obtain a solution having a concentration of about 0.6mg per ml.

***Assay preparation**:*

Grind 20 tablets to a fine powder. Dissolve an accurately weighed quantity of powdered tablets in diluents, dilute quantitatively with diluents, and sonicate if necessary, to obtain a solution having a known concentration of about 0.6mg/ml of Capecitabine, based on the label claim. Pass through a PVDF 0.45µm membrane filter, and use the filtrate.

The chromatograph is programmed as follows:-

Table No 11: Flow program

Time (minutes)	Solution A (%)	Solution B (%)	Elution
0-5	100	0	Isocratic
5-20	100→49	0→51	Linear gradient
20-30	49	51	Isocratic
30-31	49→100	51→0	Linear gradient
31-40	100	0	Equilibration

Procedure:

Separately inject equal volumes (about 10µl) of the standard preparation and the assay preparation into the chromatograph, record the chromatograms, and measure the response for the Capecitabine peaks.

6.2.4 Release kinetics[60]

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

1. Log cumulative percent drug remaining versus time (first order kinetic model)
2. Cumulative percent drug release versus square root of time (Higuchi's model)
3. Cumulative percent drug release versus time (zero order kinetic model)
4. Log cumulative Percent Drug released versus log time (Korsmeyers model)

Drug release kinetics-model fitting of the dissolution Data:

Whenever a new solid dosage form is developed or produces, it is necessary to ensure that drug dissolution occurs in an appropriate manner. Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time, t or Q = f (t). Some analytical definitions of the Q (t) function are commonly used such as zero order, first order, Higuchi, Korsmeyers-Peppas models. Other release parameters, such as dissolution time ($t_{x\%}$), dissolution efficacy (ED), difference factor (f_1), similarity factor (f_2) can be used to characterize drug dissolution / release profile.

6.2.4.1 Zero-order kinetics:

A zero-order release would be predicted by the following equation.

$$\mathbf{At = A_o - K_o t} \qquad \text{eq (1)}$$

Where, At = Drug release at time t

A_o = Initial drug concentration

K_o = Zero-order rate constant (hr)

When the data is plotted as cumulative percent drug release versus time if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to k_o.

Use: This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in case of some transdermal systems etc. the pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a prolonged pharmacological action.

6.2.4.2 First-order kinetics:

A first order release would be predicted by the following equation.

$$\text{Log } C = \text{Log } Co - K_t / 2.303 \qquad \text{eq(2)}$$

Where C = Amount of drug remained at time t

C_o = Initial amount of drug

K = First-order rate constant

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line indicating the release follows first-order kinetics, the constant k can be obtained by multiplying 2.303 with slope values

Use: The pharmaceutical dosage forms containing water-soluble drugs in porous matrices, follows this type of dissolution profile. The release of the drug is proportional to the amount of drug remaining in its interior so that the amount of drug release by unit of time diminishes

6.2.4.3 Higuchi model:

Drug release from the matrix devices by diffusion has been described by following Higuchis classical diffusion equation.

$$\mathbf{Q = [DE/ \tau(2A- ECs) C_{st}]} \qquad \text{eq(3)}$$

Where, Q = Amount of drug release at time t

D = Diffusion coefficient of the drug in the matrix

A = Total amount of drug in unit volume of matrix

C_s = Solubility of the drug in the matrix

E = Porosity of the matrix

T = Time in hrs at which q is the amount of drug is release

Equation-3 may be simplified if one assumes that D, Cs and A are constant. Then equation-3 becomes

$$\mathbf{Q = K_t ½} \qquad \text{eq (4)}$$

When the data is plotted according to equation-4 i.e. cumulative drug release versus Square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to k.

Use: The relation can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in case of some water soluble drugs.

6.2.4.4 Korsmeyer Peppas model:

In order to understand the mode of release of drug from swellable matrices, the data were fitted to the following equation

$$\mathbf{M_t / M_{ά} = Kt^n} \qquad \text{eq (5)}$$

Where, $M_t / M_{ά}$ = Fraction of drug released at time't'

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

n = Diffusion exponent related to the mechanism of release.

The above equation can be simplified by applying log on both sides we get

$$\mathbf{Log\ M_t / M_{ά} = Log\ K + n\ Log\ t} \qquad \text{eq (6)}$$

When the data is plotted as a log of drug released versus log time, yields a straight line with a slope equal to n and the k can be obtained from y- intercept.

The value of n for a cylinder is <0.45 for Fickian release, > 0.45 and < 0.89 for Non-Fickian release, 0.89 for the case 2 release and > 0.89 for super case2 type release.

6.2.5 Similarity Factor and Dissimilarity Factor Calculation

The similarity factor (f_2) was defined by CDER, FDA, and EMEA as the "logarithmic reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and Ditropan release profiles".

Dissimilarity or difference factor (f_1) describes the relative error between two dissolution profiles. It approximates the percent error between the curves. The percent error is zero when the test and Ditropan release profiles are identical and increases proportionally with the dissimilarity between the two profiles.

There are several methods for dissolution profile comparison. f_2 is the simplest among those methods. Moore & Flanner proposed a model independent mathematical approach to compare the dissolution profile using two factors f_1 & f_2.

$$f_1 = \{ [\sum_{t=1}^{n} | R_t - T_t |] / [\sum_{t=1}^{n} R_t] \} . 100 \qquad \text{eq (1)}$$

$$f_2 = 50. \text{Log} \{ [1 + (1/n) \sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} . 100\} \qquad \text{eq (2)}$$

Where 'R_t' and 'T_t' are the cumulative percentage dissolved at each of the selected n time point of the Ditropan & test product respectively. The factor f_1 is proportional to the average difference between the two profiles, where as factor f_2 is inversely proportional to the averaged squared difference between the two profiles, with emphasis on the larger difference among all the time points. The similarity factor f_2 and its significance is shown in the following

6.2.6 Dissolution Efficiency:

The dissolution efficiency (DE) of a pharmaceutical dosage form (Khan and Rhodes, 1972; Khan, 1975) is defined as the area under the dissolution curve up to certain time *t*, expressed as a percentage of the area of rectangle described by 100% dissolution in the same time.It can be calculated by the following equation

$$D.E. = \frac{\int_0^t y \times dt}{y_{100} \times t} \times 100\%$$

where y is the drug percent dissolved at time t.

6.2.7 Stability Study:

For all the pharmaceutical dosage forms it is important to determine the stability of the dosage form. This will include storage at exaggerated temperature conditions, with the necessary extrapolations to ensure the product will, over its designed shelf life, provide medication for absorption at the same rate as when originally formulated. Specification which is list of tests, reference to the analytical procedures and proposed acceptance criteria, including the concept of different acceptable criteria for release and shelf life specifications are addressed in ICH guidelines.

The tablets of the optimized formulation are tested for stability for 3 months in accelerated and long term test conditions. The tablets are exposed to $40^0 \pm 2^0$C and 75±5% RH conditions for 3 months. The tablets are observed for change in physical appearance, moisture content, assay values, impurities and dissolution values at the end of first, second and third month. Stability was determined.

6.3 Innovator product details:

Table No:12 Innovator Details

Product Name	XELODA
Label Claim	500mg and 150mg
Composition	Each film coated tablet contains 150mg or 500mg of Capecitabine.
Manufactured by	Hoffmann la roche Pharmaceuticals
Description	Light peach film coated tablet of biconvex,oblong shape with the marking '500'on one side and 'Xeloda'on the other side.
Thickness	3.54mm
Storage	Stored at 25^0C
Dissolution Apparatus	USP Type II(Paddle type)
Dissolution Medium	Deaerated Water
Dissolution Medium Volume	900ml
Time Points	10,20,30,45 min
Speed	50 RPM

7. Results and Discussion:

7.1 *Preformulation:*

Table No 13: Results of physical characterization of the drug

S. No	Description	Result
1.	**Appearance**	White to yellowish powder
2.	**Odour**	Characteristic odour.
3.	**Solubility**	Soluble in water (26mg/ml)

7.2 *API characterization:*

Table No 14: Flow Properties of API

S. No	Flow Properties	Result
1.	**Bulk density (g/ml)**	0.298gm/ml
2.	**Tapped density (g/ml)**	0.506gm/ml
3.	**Compressibility index (%)**	13.14
4.	**Hausner's ratio**	1.13
5.	**Angle of repose**	31˚45'

7.3. Drug and excipients compatibility studies:

Table No 15: Drug-Excipient compatibility studies

S. No	Ingredients		Description	After 2 weeks	After 4 weeks
		Ratio	Initial	55^0C	$40+2^0$C/70+5% RH
1	**Capecitabine**	1	White	No change	No change
2	**Micro crystalline cellulose**	1	White	No change	No change
3	**Lactose anhydrous**	1	White	No change	No change
4	**Sodium starch glycolate**	1	White	No change	No change
5	**HPMC E5**	1	White	No change	No change
6	**Magnesium stearate**	1	White	No change	No change
7	**Capecitabine+Avicel (Ph 112)**	1:1	White	No change	No change
8	**Capecitabine+Lactose anhydrous**	1:1	White	No change	No change
9	**Capecitabine+Sodium starch glycolate**	1:0.5	White	No change	No change
10	**Capecitabine+HPMC E5**	1:0.5	White	No change	No change
11	**Capecitabine+ magnesium stearate**	1:0.25	White	No change	No change

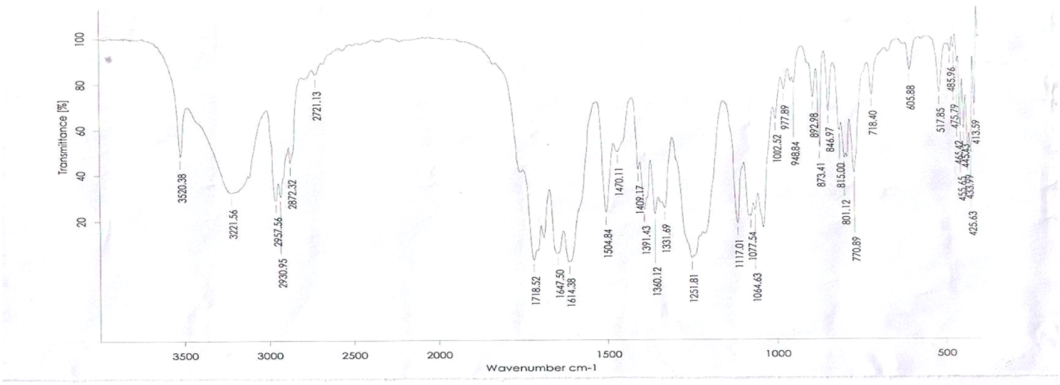


Figure No 4: FTIR spectrum of Capecitabine

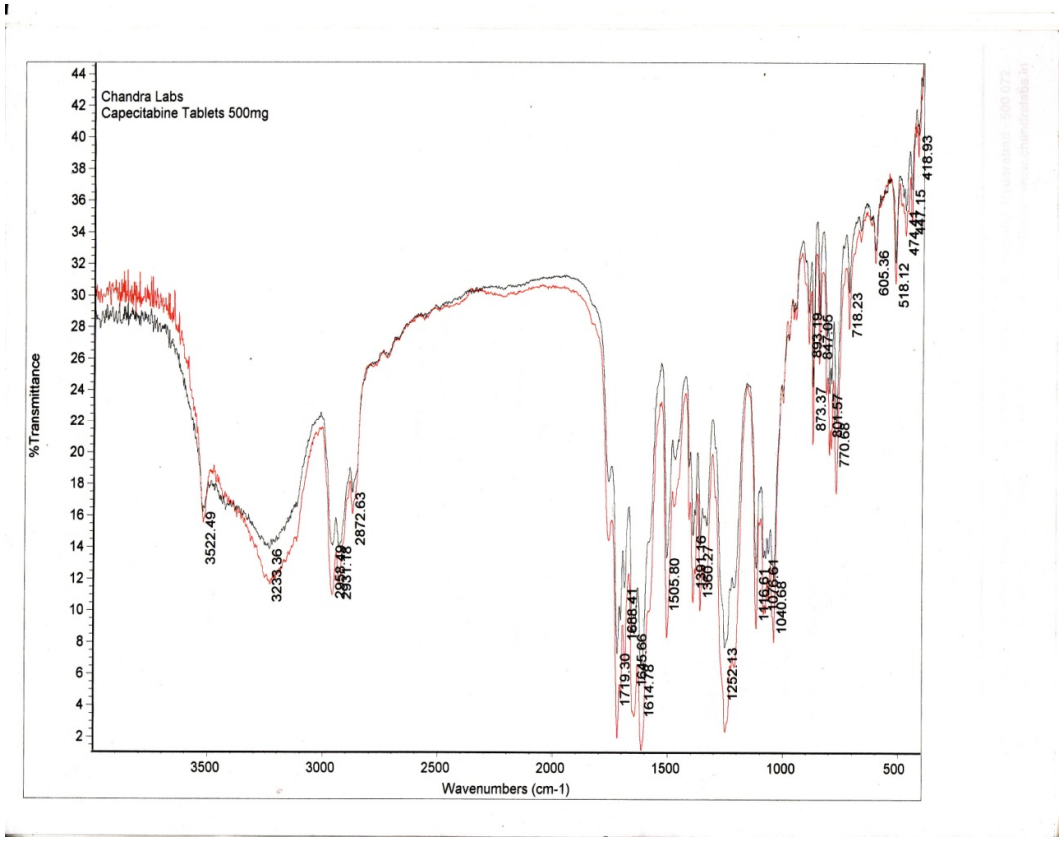


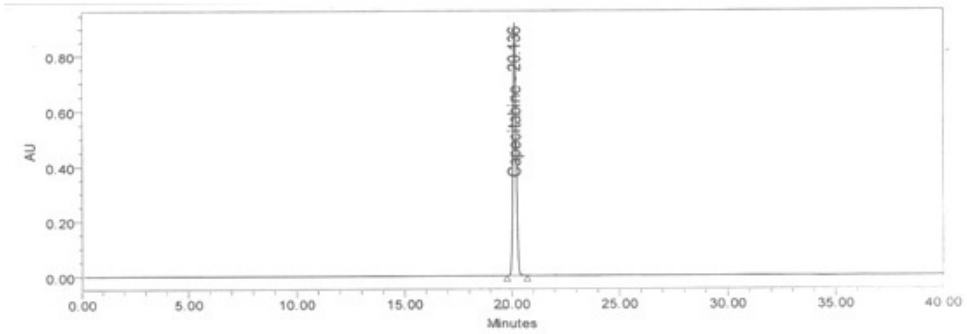
Figure No 5: FTIR spectrum of Capecitabine prepared formulation

7.4 ***Flow properties:***

Table No 16: Results of flow properties of lubricated blend

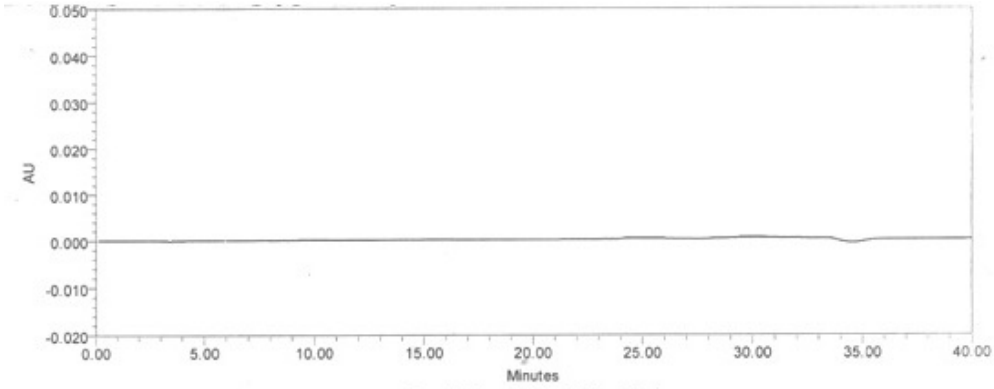
Batch code	Angle of Repose (θ)	Bulk density (gm/m)	Tapped density (gm/m)	Compressibility index (%)	Hausner's ratio
F1	43°21'	0.624	0.798	21.80	1.27
F2	37°23'	0.610	0.763	20.05	1.25
F3	36°31'	0.605	0.754	19.76	1.24
F4	38°22'	0.614	0.738	16.80	1.20
F5	34°28	0.616	0.726	15.15	1.17
F6	32°25'	0.612	0.714	14.28	1.16
F7	31°21'	0.625	0.724	13.67	1.15
F8	32°28'	0.625	0.714	12.46	1.14
F9	32^{0}28'	0.625	0.714	12.46	1.14

7.5 Assay (by HPLC):



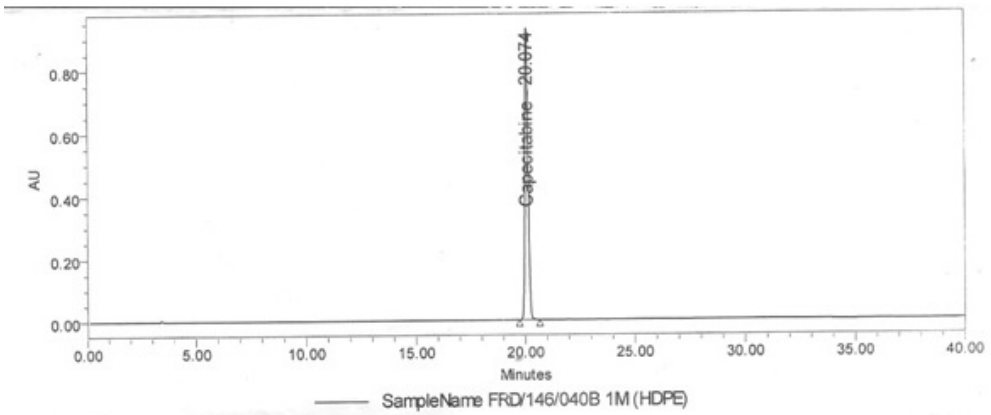
	Peak Name	Vial	RT	Area	% Area	Height (µV)	USP Tailing	USP Plate Count	RT Ratio	USP Resolution
1	Capecitabine	5	20.136	9486687	100.00	919787	1.05	86509		

Figure No 6: HPLC chromatogram for Capecitabine standard



	Peak Name	Vial	RT	Area	% Area	Height (µV)	USP Tailing	USP Plate Count	RT Ratio	USP Resolution
1	Capecitabine	1	20.121							

Figure No 7: HPLC chromatogram for Capecitabine blank



	Peak Name	Vial	RT	Area	% Area	Height (µV)	USP Tailing	USP Plate Count	RT Ratio	USP Resolution
1	Capecitabine	6	20.074	9538820	100.00	934843	1.05	89088		

Figure No 8: HPLC chromatogram for Capecitabine sample

7.6 *Results of evaluation of tablets:*

Table No 17: Evaluation of Tablets

S.No	Batch code	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Assay %w/v	Disintegration (min)
1.	**F1**	608±0.25	-	-	-	-	-
2.	**F2**	662±0.37	3.64±0.05	7.8±0.23	0.106±0.15	100.1	17min3sec
3.	**F3**	663±0.24	3.68±0.024	8.0±0.17	0.172±0.03	98.9	16min37sec
4.	**F4**	662±0.18	3.45±0.019	8.3±0.34	0.122±0.36	98.5	15min16sec
5.	**F5**	664±0.16	3.48±0.11	8.1±0.14	0.17±0.42	99.2	14min 45sec
6.	**F6**	663±0.41	3.41±0.035	8.4±0.17	0.13±0.015	98.7	13min12sec
7.	**F7**	663±0.12	3.47±0.053	8.8±0.38	0.182±0.012	101.8	12 min54sec
8.	**F8**	664±0.01	3.47±0.016	9.0±0.44	0.18±0.01	99.4	11min 52sec
9.	**F9**	664±0.05	3.47±0.11	9.0±0.41	0.18±0.05	99.4	11min 52 sec
10.	**Innovator**	665	3.54	9.0	0.0	98.8	12 min

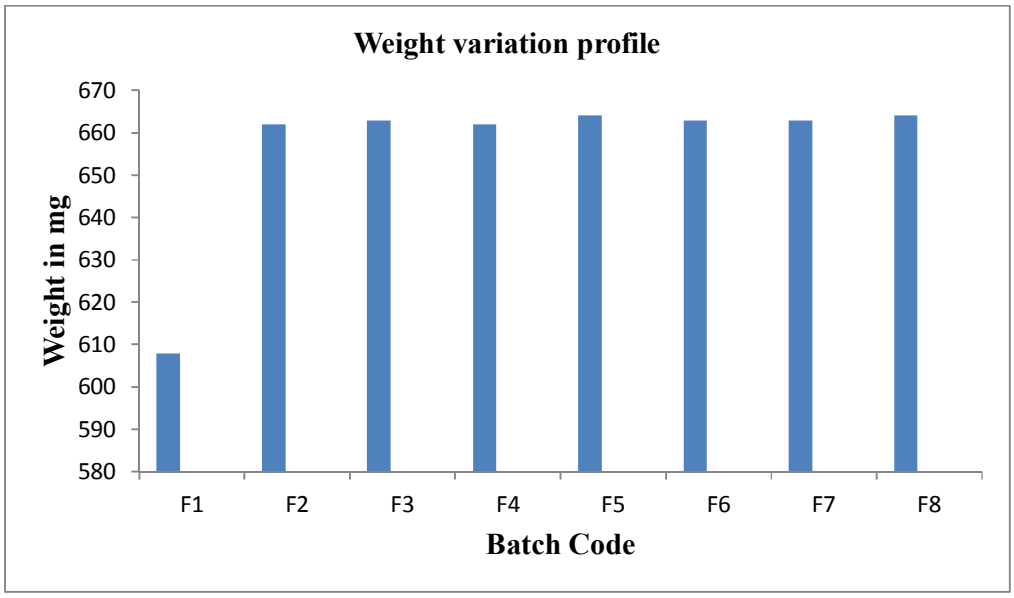


Figure No 9: Weight variation profile

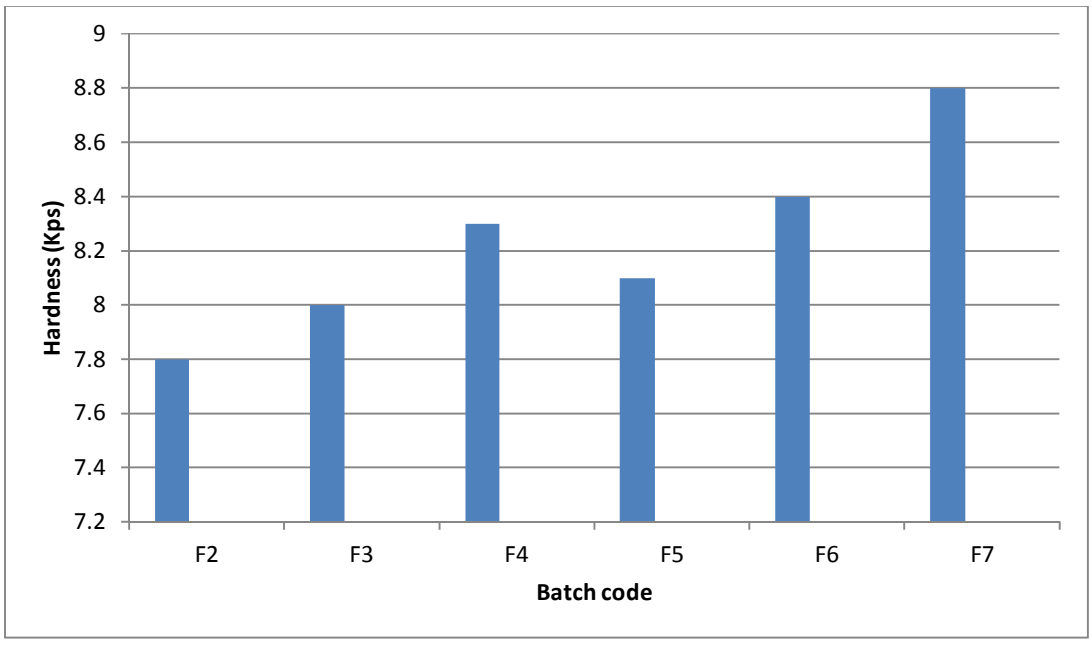


Figure No 10: Hardness profile

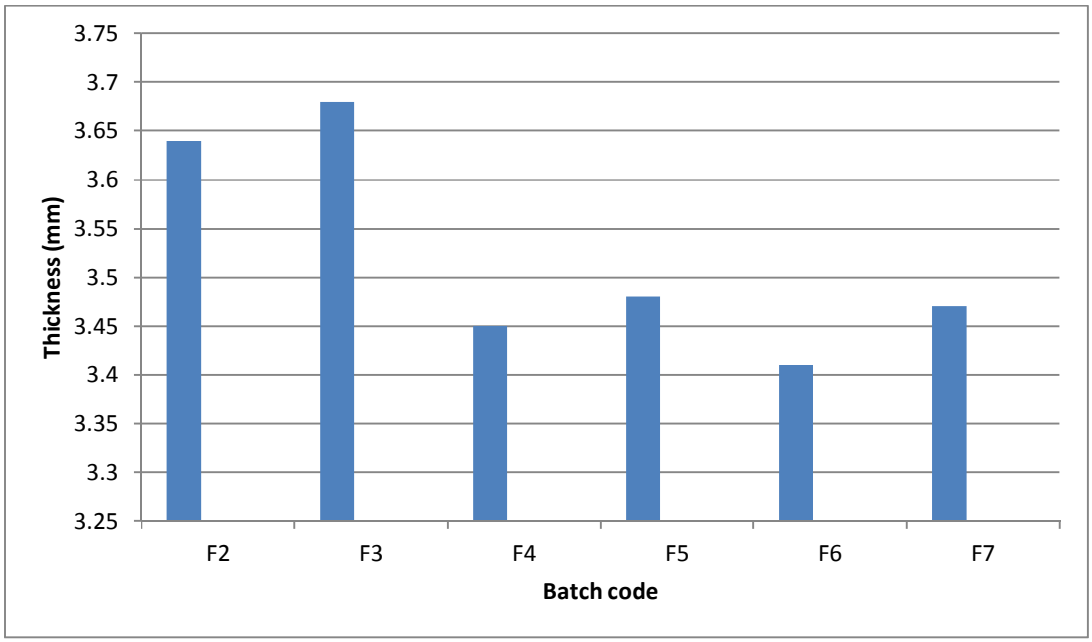


Figure No 11: Thickness profle

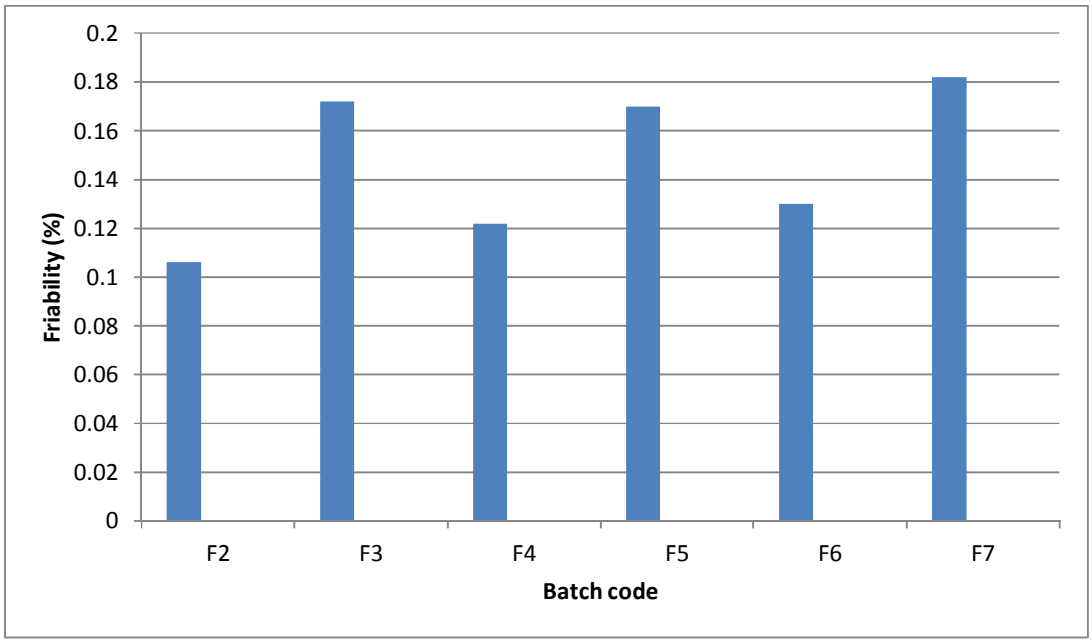


Figure No 12: Friability profile

7.7 In vitro dissolution studies:

Table 18: % Drug Release of Capecitabine from F2 to F9 and Innovator Product

S. No	Time (min)	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	Xeloda
1.	**0**	0	0	0	0	0	0	0	0	0
2.	**10**	38.6	40.3	46.5	47.2	49.8	52.5	54.2	54.2	52.3
3.	**20**	70.5	71.6	75.4	78.5	79.4	81.6	80.4	80.4	78.8
4.	**30**	78.9	80.1	84.5	86.3	88.7	90.3	91.2	91.2	89.5
5.	**45**	81.2	82.5	88.6	91.4	93.9	96	98.7	98.7	97.2

Table no 19: *Invitro* dissolution profile of Capecitabine IR tablets (F2)

S. No	Time (min)	Cumulative % drug release	Cumulative amount of drug released (mg)
1	10	38.6	193
2	20	70.5	352.5
3	30	78.9	394
4	45	81.2	406

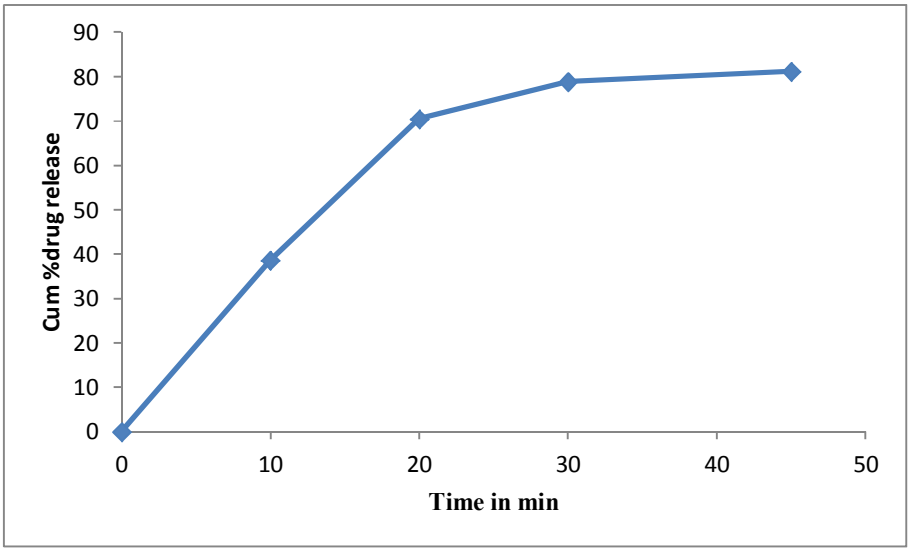


Figure No: 13 *Invitro* dissolution profile of Capecitabine IR tablets (F2)

Table no 20: *Invitro* dissolution profile of Capecitabine IR tablets (F3)

S No	Time (min)	Cumulative % drug release	Cumulative amount of drug released (mg)
1	10	40.3	201.5
2	20	71.6	358
3	30	80.1	400.5
4	45	82.5	406

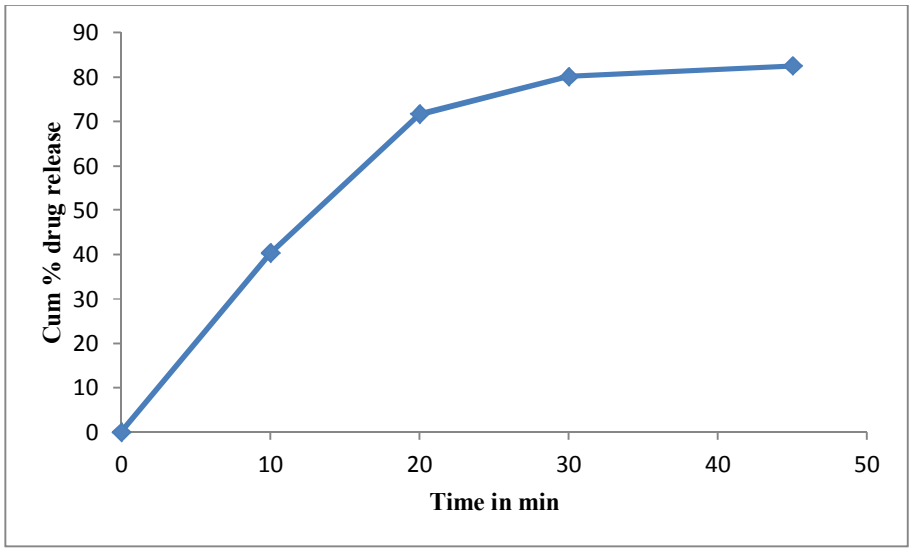


Figure No 14: *Invitro* dissolution profile of Capecitabine IR tablets (F3)

Table no 21 : *Invitro* dissolution of Capecitabine IR tablets (F4)

S No	Time (min)	Cumulative % drug release	Cumulative amount of drug released (mg)
1	10	40.3	232.5
2	20	71.6	377
3	30	80.1	422.5
4	45	82.5	443

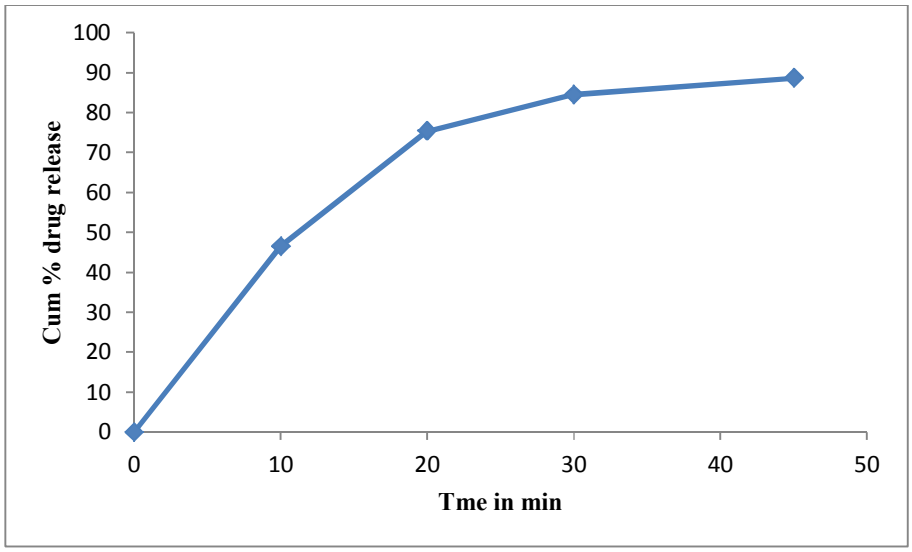


Figure No 15: *Invitro* dissolution profile of Capecitabine IR tablets (F4)

Table No: 22 *Invitro* dissolution of Capecitabine IR tablets (F5)

S No	Time (min)	Cumulative % drug release	Cumulative amount of drug released (mg)
1	10	47.2	236.0
2	20	78.5	392.5
3	30	86.3	431.5
4	45	91.4	457

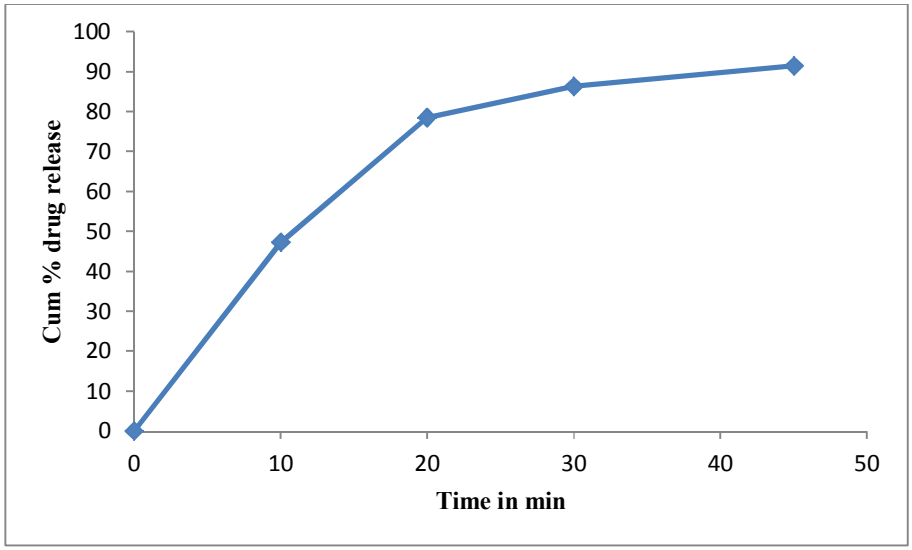


Figure No 16: *Invitro* dissolution profile of Capecitabine IR tablets (F5)

Table No:23 *Invitro* dissolution of Capecitabine IR tablets (F6)

S No	Time (min)	Cumulative % drug release	Cumulative amount of drug released (mg)
1	10	49.8	249
2	20	79.4	397
3	30	88.7	443
4	45	91.4	469.5

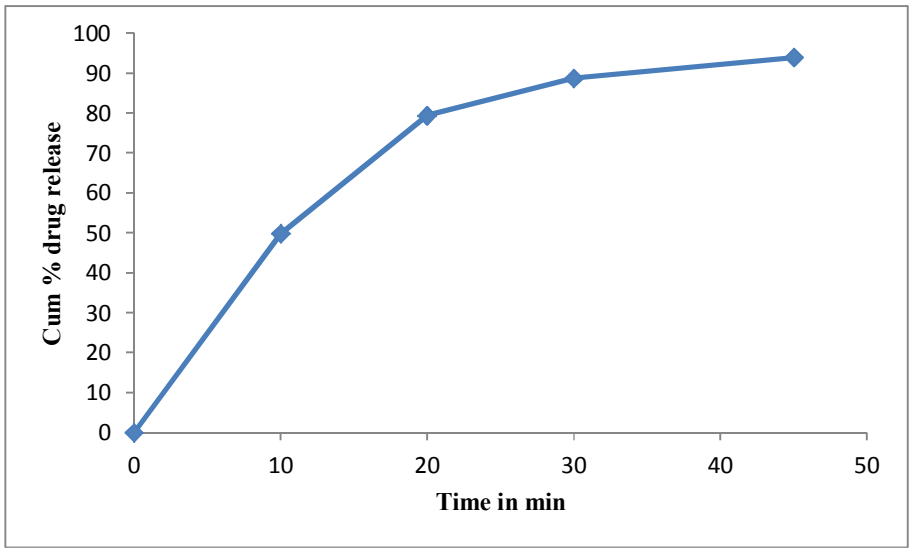


Figure No 17: *Invitro* dissolution profile of Capecitabine IR tablets (F6)

Table No 24: *Invitro* dissolution of Capecitabine IR tablets (F7)

S No	Time (min)	Cumulative % drug release	Cumulative amount of drug released (mg)
1	10	52.5	262
2	20	81.6	408
3	30	90.3	451
4	45	96	480

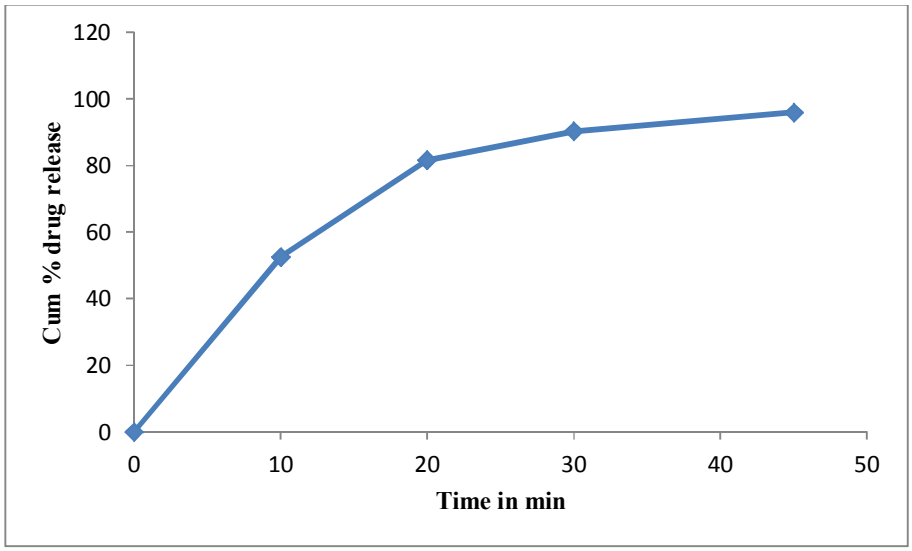


Figure No 18: *Invitro* dissolution profile of Capecitabine IR tablets (F7)

Table No 25: *Invitro* dissolution of Capecitabine IR tablets (F8)

S No	Time (min)	Cumulative % drug release	Cumulative amount of drug released (mg)
1	10	54.2	271
2	20	80.4	402
3	30	91.2	436
4	45	98.7	493.5

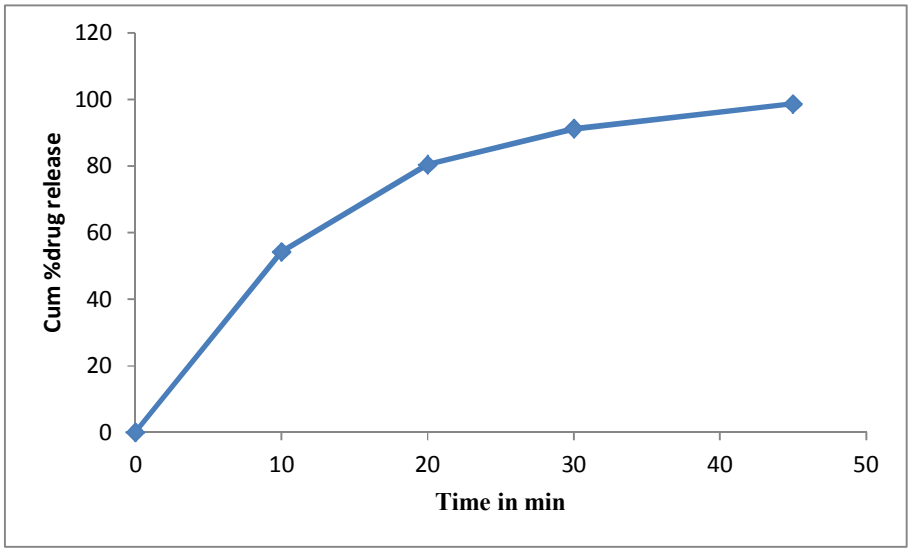


Figure No 19: *Invitro* dissolution profile of Capecitabine IR tablets (F8)

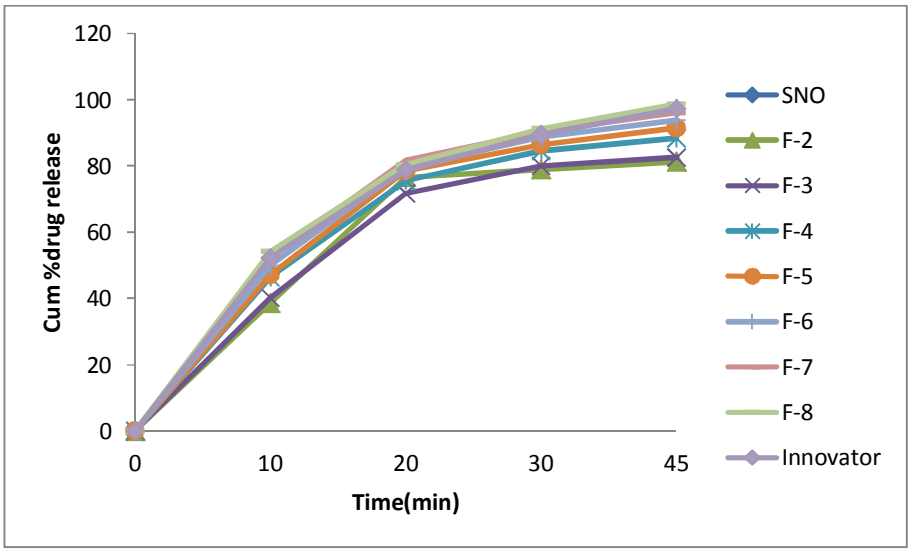


Figure No 20: Comparison of dissolution profiles of formulated batches

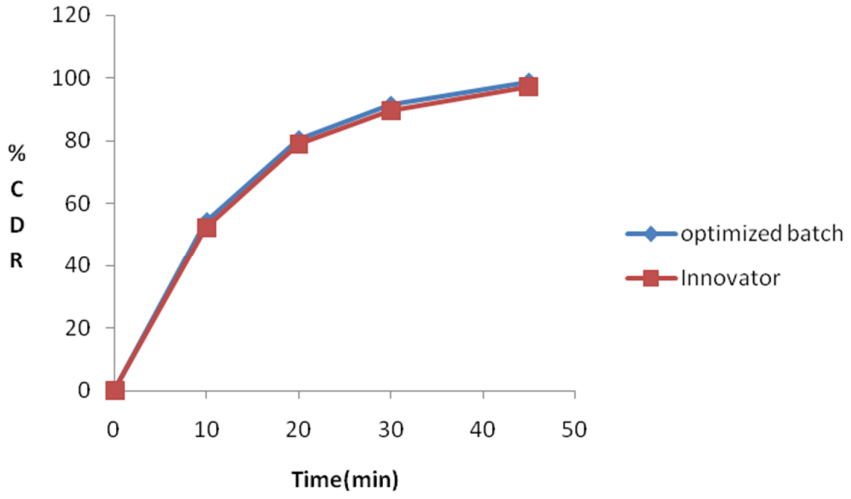


Figure No 21: Comparison of Optimized batch with the innovator sample

7.8 *Determination of release kinetics:*

Table No 26: Release kinetics

S No	Time (min)	Square root of time	Log time	Cum %drug release	Log Cum %drug release	Cum % drug remaining	Log Cum %drug remaining
1	0	0	0	0	0	100	2
2	10	3.16	1	54.2	1.73	45.8	1.66
3	20	4.47	1.30	83.5	1.92	16.5	1.21
4	30	5.48	1.47	91.2	1.95	8.8	0.94
5	45	6.71	1.65	98.7	1.99	1.3	0.11

Dissolution-Zero order kinetics

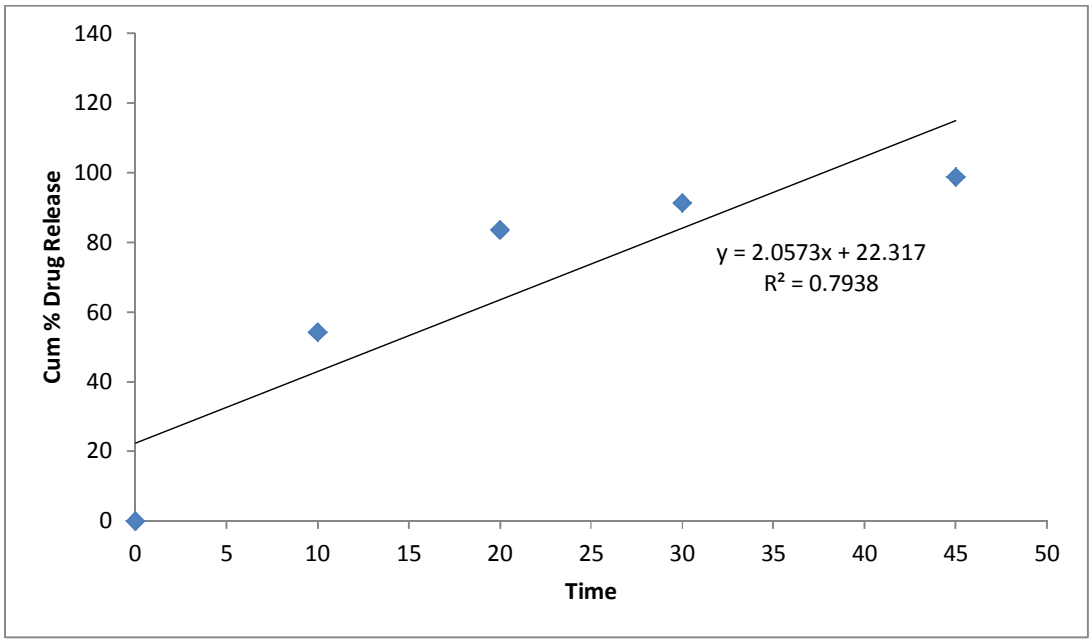


Figure No 22:formulation F8- Zero order kinetics

Dissolution- First order kinetics

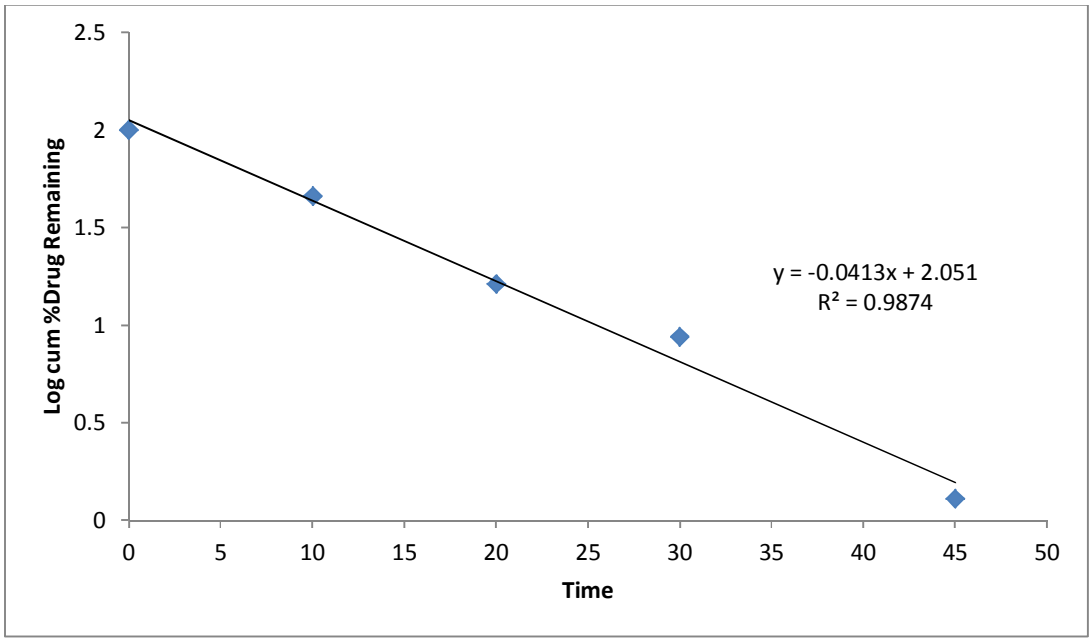


Figure No 23: Formulation F8-First order kinetics

Higuchi

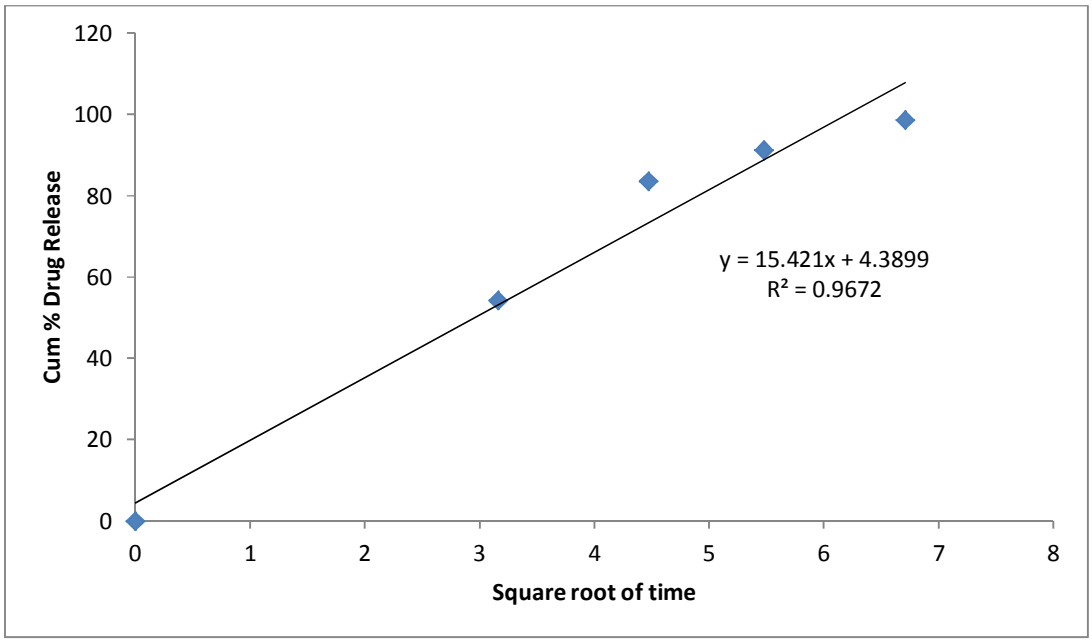


Figure No: 24 Formulation F8-Higuchi model

Korsmeyer and Peppas

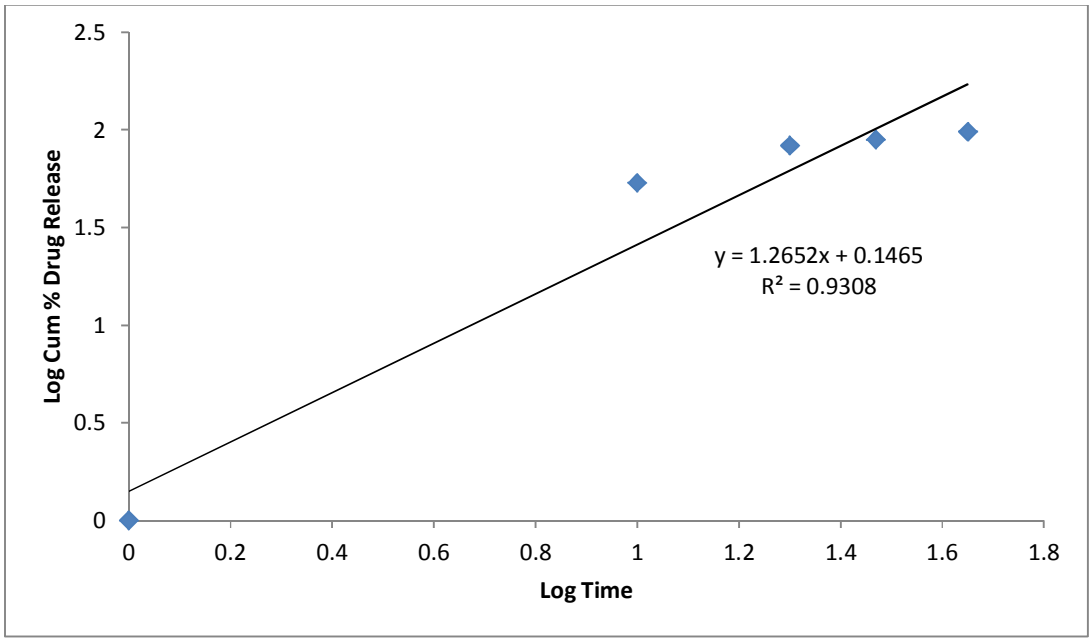


Figure No 25: Formulation F8-KorseMeyer Peppas model

7.9 *Difference Factor (f1) & Similarity Factor (f2) Calculation*

Table No 27: Similarity and Differential factor calculation

Time	Innovator Rt	F-8 Tt	{Rt-Tt}	$(Rt-Tt)^2$
10	52	54	1.9	3.61
20	79	80	1.6	2.56
30	90	91	1.7	2.89
45	97	99	1.5	2.25
sum (Rt-Tt)				6.7
sum $(Rt-Tt)^2$				11.31
sum Rt				317.8
Similarity factor f2 [Acceptance Criteria :50- 100]				85
Difference factor f1 [Acceptance Criteria : 0 - 15]				2

7.10 Dissolution Efficiency of IR tablets of Capecitabine

Table No:28 Dissolution Efficiency

Formulations	DissolutionEfficiency (%)
F2	73.5
F3	73.32
F4	73.78
F5	73.73
F6	72.1
F7	72.5
F8	72.6
Xeloda	72.22

7.11 Stability studies:

Dissolution of trial F – 8 tablets were comparable with reference product. So tablets of this batch were kept for stability studies. After 3 months the physical parameters of the tablets were same. Water content and related substance are within limits. The tablets were tested for Physical appearance, Assay, Relative substances, Dissolution, Moisture content at initial, 1st month, 2nd month and 3rd month in Accelerated conditions and at initial and 3rd month for long term test conditions

Table No 29: Stability Study data (Accelerated) of Trial F – 08

S. No	Parameters	Specifications	Test Condition			
			40 ± 2^{0}C & 75 ± 5% RH (Accelerated)			
			Day-0	Month-1	Month-2	Month-3
1.	**Description**	Light pink colored, oblong shaped tablets debossed with NC on one side and 500 on other side.	Complies	Complies	Complies	Complies
2.	**Moisture content**	-	1.314	1.324	1.33	1.34
3.	**Assay**	**90-110**	100.8	100.2	99.6	98.7
4.	**Related substances by HPLC**					
	I.Unknown impurity	**NMT 0.5**	0.175	0.014	0.035	0.025
	II.Total impurity	NMT 2.0	0.189	0.504	0.578	0.782
5.	**Dissolution**	**NLT than 75% at 45 min**	98.4	97.6	97.2	96.9

7.Discussion:

7.1 Preformulation:

API Analysis:

The experimental work started with the preformulation of raw material analysis of Capecitabine. The results of physical characterization of the drug like appearance,odour and solubility are given in **Table:13.** The results shows that physical characterization of the drug candidate (API) complies with the USP specifications

The flow properties of API such as bulk density the tapped density, Carr's index, Hausner's ratio and angle of repose values were depicted in the **Table: 14** and the results were found to be satisfactory.

Drug excipient compatibility studies:

The physical compatibility studies between drug and excipient were carried out at 55^0C for 2 weeks and at $40+2^0$C/70+5% RH for 4 weeks. The drug and excipients are taken in different ratios. The results show that there is no change from the initial white colour after 2 and 4 weeks indicating that there is no physical incompatibility. Results can be observed from **Table: 15**

. The FTIR spectrum from **figure 4**, of pure Capecitabine showed bands at 3522 for O-H stretch,2872 for C-H stretch,C=O at 1718 and N-H at 1614. The FTIR spectrum of prepared formulation from **figure 5,** indicate the absence of any interactions between Capecitabine and excipients in the formulation.

7.2 Preparation of tablets:

The tablets were prepared by direct compression and wet granulation methods. The F1 formulation is prepared by direct compression method and for the formulations from F2 to F9 wet granulation method is used. Two methods were used for the formulation to check which is the better method for the drug to get the optimized formulation with similar values to the innovator. The tablets are

prepared by using different excipients like diluents,binders and super disintegrants. Sodium starch glycolate is used as super disintegrant in the formulation.

7.3 Flow properties of lubricated blend*:*

The prepared granules of all the 9 formulations are taken for the study of flow properties. The flow properties of each formulation such as angle of repose,bulk density,tapped density,compressibility index and hausners ratio are determined and the flow properties are found to be poor for F1 formulation and for formulations from F2 to F9 the flow properties are satisfactory. The results are shown in **Table 16**

7.4 Evaluation of tablets:

The film coated tablets are evaluated for weight variation, thickness, hardness, frability, disintegration time and assay values. The results were shown in **Table: 17.**The values are in the range of 662 to 664 mg for weight variation for formulations F2 to F9 and 608 mg for formulation F1.Thickness and hardness values range from 3.41 to 3.68 mm and7.8 to 9kg/cm^2 respectively. Results are in the range of 0.10 to 0.18 for friability and 11 to 17 minutes for disintegration of tablets. Assay values are in the range of 98% to 101%.

7.5 Effect of direct compression on Capecitabine Immediate Release tablets:

For F1 formulation direct compression method is used.Dissolution test failed because of low fill weight of tablet. The dry state of the materials during mixing may induce static charges and lead to segregation due to which variation in weight is observed and dissolution values are not achieved.

7.6 Effect of wet granulation on Capecitabine Immediate Release tablets:

Formulations F2 to F9 were prepared by the method of wet granulation by taking sodium starch glycolate both as extra and intra granular agent in different

concentrations. The flow properties are satisfactory. The evaluation parameters are almost similar to that of innovator. Wet granulation showed good effect on dissolution release of Capecitabine.

7.7 Effect of super disintegrant (SSG) on Capecitabine Immediate Release tablets:

Sodium starch glycolate is taken as intragranular agent from formulation F1 to F3.It is taken both as intragranular and extragranular agent from formulation F4 to F9.SSG when taken as extragranular agent increases the wicking property of tablet which leads to the increase in dissolution rate.SSG shows more effect on drug release from tablets when taken as extragranular agent which can be inferred from the values of dissolution profile.

7.8 Drug release studies:

The *in vitro* drug release studies for F2 to F9 formulations were observed from **Table 18.**The percentage of drug release at the end of 10,20,30 and 45 min for formulations fF2 to F9 was determined. The percentage of drug release increased from F2 to F9.F8 (optimized formulation) shows 98.7% of drug release which is similar to that of innovator.

7.9 Release kinetic study for optimized F8 formulation:

The plot of cumulative percentage drug release as a function of time indicates that the formulation does not follow zero order or Korsmeyers Peppas model **Table: 26** the line of best fit obtained was first order release kinetics (R^2 =0.987) and Higuchi kinetics.

7.10 Reproducibility batch:

To check the reproducibility of batch,F9 batch was prepared with the same formula of F8.The drug release at the end of 10,20 30 and 45 minutes was found to be 54.2%,78.8%,91.2%,98.7% respectively. Hence the drug release values

of reproducibility batch are similar to the optimized formulation. Results are shown in **Table:18**

7.11 Comparision between optimized batch and Innovator:

The optimized batch F8 is compared with Xeloda. The drug release profile of optimized batch and marketed product was found to be 98.7% and 97.2% at the end of 45 minutes.. **Table: 18** shows that the formulation F-8 was close to the Xeloda release profile. Then similarity factor (f_2) was calculated between formulation F-8 and Xeloda. Similarity factor was (85); therefore, formulation F-8 has similar release profile to the Xeloda release.**Table 27.**The dissolution efficiency of all the formulations and innovator product are determined.Dissolution Efficiency values are in the range of 72% to 73%.The Dissolution Efficiency of optimized formulation is 72.6% and that of the innovator is 72.22%

7.12 Stability studies:

Stability studies were conducted for the formulation F8. The stability study was performed at 40±2^{0}C /75±5 % RH for 1 to 3 months. The tablets were analysed for appearance, moisture content, drug content,impurities and *in vitro* drug release. The overall results showed that the formulation is stable at the end of 1st,2nd and 3rd months. Results were depicted in **Table: 29.**

8. Summary :

Chapter 1 begins with a general introduction presenting an overview about Immediate Release formulations, advantages, methods of granulation, coating technique, mechanism of drug release. An introduction about cancer treatment and types are discussed. A brief description about breast and colorectal cancer is discussed.

Chapter 2 described the literature review carried out for carried out for selected drug, super disintegrant, other excipients and formulation are reviewed.

Chapter 3 gives information about Aim and Objective of the formulation

Chapter 4 Describes schematic diagram of plan of work.

Chapter 5 gives detailed information about the drug and excipients used in the formulation.

Chapter 6 deals with raw material analysis, drug excipient compatibility, procedure for flow properties of lubricated blend and procedure for evaluation of tablets are described.

Chapter 7 shows the results and discussion of all formulations. The raw material analysis results meet the specifications of IP. The FTIR studies show that there are no interactions between drug and excipients. The flow properties of lubricated blend was observed and evaluation of tablets was done. The *in vitro* drug release of formulations from F2 to F9 was observed compared and discussed. Effect of super disintegrant SSG when taken as extragranular agent was studied. Maximum drug release was observed at the end of 45 min for F8 and F9 formulations Stability studies were carried out for F8 formulation by keeping the tablets at $40^0C \pm 2^0C$, 75% ± 5% RH for 3 months. The physical appearance, moisture content, assay values, impurities and dissolution values were not altered much at the end of 1^{st}, 2nd and3^{rd} months. So the tablets are stable.

9. Conclusion*:*

In the present work efforts have been made to develop Capecitabine Immediate Release (IR) tablets by direct compression and wet granulation technique. The drug release profile enhanced using SSG and compared with innovator drug product. The results showed that the release of the drug was depended on Sodium starch glycolate, super disinttegrant used at intra-granular and extra-granular state.

All the parametric evaluations were satisfactory with F8-batch when compared with Innovator product. Hence, the Bio-equivalence study under progress in our lab for optimized Batch Formulation(F8).

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