FORMULATION AND EVALUATION OF SORAFENIB TOSYLATE IMMEDIATE RELEASE TABLETS

A Dissertation Submitted to

The Tamil Nadu Dr. M.G.R. Medical University

Chennai - 600 032

In partial fulfillment for the award of Degree of

MASTER OF PHARMACY

(Pharmaceutics)

Submitted by

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OCTOBER- 2012

CERTIFICATE

This is to certify that the dissertation entitled "FORMULATION AND EVALUATION OF SORAFENIB TOSYLATE IMMEDIATE RELEASE TABLETS" submitted to The Tamil Nadu Dr. M.G.R. Medical University in partial fulfillment for the award of the Degree of the Master of Pharmacy (Pharmaceutics) was carried out by CHAN SULTHANA S.M (Register No. 26106012) in the Department of Pharmaceutics under my direct guidance and supervision during the academic year 2011-2012.

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CERTIFICATE

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ACKNOWLEDGEMENT

First and foremost I wish to express my deep sense of gratitude to His Holiness **ARULTHIRU AMMA** for his ever blessing in each step of study. I am grateful to **THIRUMATHI LAKSHMI BANGARU ADIGALAR**, Vice President, ACMEC trust, Melmaruvathur for having given me an opportunity and encouragement all the way in completing the study.

With great respect and honor, I extent my thanks to our Managing truste **Mr.B.ANBALAGAN**, Adhiparasakthi Hospital and Research Institute, Melmaruvathur for his excellence in providing skillful and compassionate spirit of unstinted support to our department for carrying out research work.

I received initiation and inspiration to undergo experimental investigation in modern analytical methods entitled as "**FORMULATION AND EVALVATION OF SORAFENIB TOSYLATE IMMEDIATE RELEASE TABLET"** to this extent, I wish to sincerely record my deepest gratitude and thanks to **Dr. S. SHANMUGAM, M. Pharm.,Ph.D.,** Professor, Department of Pharmaceutics, Adhiparasakthi College of Pharmacy, Melmaruvathur for his kind cooperation and initiative guidance, constructive criticism with enthusiastic encouragement which enabling me to complete this project work successfully.

On a personal note I wish to avail my deep sense of thanks

Prof. (Dr.) T. VETRICHELVAN, M. Pharm., Ph.D., Principal, Adhiparasakthi College of Pharmacy, for all the support offered by him during the period of my entire dissertation work I have great pleasure in express my sincere heartfelt thanks to **Mr.J.SRIKANTH.Manager(R&D)** and **ANANTHA RAO**, Head of

AR&D,NATCO Pharma Pvt.Ltd. Hyderabad, for encouragement and support for the successful completion of this work.

My sincere thanks to our lab technicians, **Mr. M. GOMATHI SHANKAR,** D. Pharm., and **Mrs. S. KARPAGAVALLI,** D. Pharm., for their kind help throughout this work.

My special thanks to our librarian **Mr. M. SURESH,** for providing all reference books to make this project a great success.

I am grateful to my **Classmates** for their pleasant working atmosphere and discussion during the work.

A special thanks to my ever loving **College staffs, Friends, Seniors and Juniors** for their kind support during my work.

Last but not least, with my whole heart, I would like to express my thanks to my father **D.S.ABDUL MUNAFF**, My mother Mrs. **S.GHOUSIA** for their encouragement and support which were a tower of strength during the entire course of work.

CHAN SULTHANA S.M

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ABBREVIATION AND MEANING

%	Percentage
FDA	Food and drug administration
µ	Micron
µg/ml	Microgram per milliliter
^{0}C	Degree Celsius
cm^{-1}	Centimeter inverse
C_{max}	Peak plasma concentration
DSC	Differential scanning calorimetry
SLS	Sodium lauryl sulfate
F	Formulation
F/C	Film coated
g/ml	gram per milliliter
GIT	Gastro intestinal tract
HCl	Hydrochloric acid

NCE	New Chemical Entity
RCC	Renal cell Carcicoma
ICH	International conference on harmonization
IP	Indian pharmacopoeia
kg/cm^2	kilogram per centimeter square
API	Active pharmaceutical ingredient
mg	Milligram
ml	Millilitre
ml/min	Millilitre per minute
CBC	Complete blood count
N	Normality
DDS	Drug delivery system
HCC	Hepato cellular carcicoma
nm	Nanometer
^{o}	Degree
PEG	Polyethylene glycol
HPMC	Hydroxy propyl methyl cellulose

Qs	Quantity sufficient
RH	Relative humidity
Rpm	Revolution per minute
S.No.	Serial number
SD	Standard deviation
IR	Immediate release
$t_{1/2}$	Biological half life
TBD	Tapped bulk density
T_{max}	Time of peak concentration
USP	United states pharmacopoeia
UV	Ultraviolet
HPLC	High performance liquid chromatography
CT	Computer tomography

INTRODUCTION

1. INTRODUCTION

1.1 ORAL SOLID DOSAGE FORMS: *(Lachman, L., et al., 1990)*

A solid dosage form is drug delivery system that includes tablets, capsules, sachets and pills as well as a bulk or unit-dose powders and granules. Among the various dosage forms oral solid dosage forms have greater importance and occupy a prime role in the pharmaceutical market. Oral route of drug administration is widely acceptable and drugs administered orally as solid dosage form represents the preferred class of products. Over 90% of drugs formulated to produce systemic effects are produced as solid dosage forms. Because of these reason whenever New chemical entity (NCE) has discovered, which shows a sufficient pharmacological action, first the pharmaceutical company asks whether the drug is successfully administered by oral route or not. The oral route of administration still continues to be the most preferred route due to its manifold advantages including:

Tablets and capsules represent unit dosage forms in which the accurate dose of drug to show sufficient pharmacological action can be administered. In case of liquid oral dosage forms such as Syrups, Suspensions, Emulsions, Solutions and Elixirs the patient is asked to administer the medication of 5-30 ml. Such dosage measurements are typically error by factor ranging from 20-50 %, when the drug is self administered by patient.

Solid dosage forms are less expensive to shipping and less prone for the degradation when compared to liquid dosage forms.

1.1.1 **Tablets:**

"In 1843, the first patent for a hand operated device used to form a tablet was granted." Tablets are defined as solid preparations each containing a single dose of one or more active ingredients and obtained by compressing uniform volumes of

particles. They are intended for oral administration, some are swallowed whole, some after being chewed. Some are dissolved or dispersed in water before being administered and some are retained in the mouth, where the active ingredient "liberated". Tablets are used mainly for systemic drug delivery but also for local drug action. For systemic use drug must be released from tablet that is dissolved in the fluids of mouth, stomach and intestine and then absorbed into systemic circulation by which it reaches its site of action. Tablets remain popular as a dosage form because of the advantages, afforded both to the manufacturer [e.g. simplicity and economy of preparation, stability and convenience in packing, shipping and dispensing] and the patient [e.g. accuracy of dosage, compactness, portability, blandness of taste and ease of administration].

They may differ greatly in size and weight depending on the amount of drug substance present and the intended method of administration. They may have lines or break-marks and may bear a symbol or other markings. Tablets may be coated.

1.1.1.1 Advantages of tablets:

They are a unit dosage form, and they offer the greater capabilities of all oral dosage forms for the greatest dose precision and the least content variability.

- They are the lightest and most compact of all oral dosage forms.
- Product identification is potentially the simplest and cheapest, requiring no additional processing steps when employing an embossed or monogrammed punch face.
- They are in general the easiest and cheapest to package and ship of all oral dosage forms.
- They may provide the greatest ease of swallowing with least tendency for "hang-up" above the stomach. Especially when coated, provided that tablet disintegration is not excessively rapid.

- They lend themselves to certain special release profile products, such as enteric or delayed release products.
- They are better suited to large scale production than other unit oral forms.
- They have the best-combined properties of chemical, mechanical and microbiological stability of all the oral forms.
- One of the major advantages of tablet over capsules is that the tablet is essentially "tamper proof dosage form".

1.1.1.2 Disadvantages of tablets:

- Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low-density character.
- Drugs with poor wetting, slow dissolution properties, intermediate to large dosages, optimum absorption high in the gastrointestinal tract, or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet.
- Bitter tasting drugs, drugs with objectionable odor or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation or a special type of coating which may increase the weight of the finished products

1.1.1.3 Types of tablets:

The main reasons behind formulation of different types of tablets are to create a delivery system that is relatively simple and inexpensive to manufacture, provide the dosage form that is convenient from patient's perspective and utilize an approach that is unlikely to add complexity during regulatory approval process. To understand each dosage form, tablets here are classified by their route of administration and by the type of drug delivery system they represent within that route.

A**. Tablets ingested orally:**

1. Compressed tablet, e.g. Paracetamol tablet

2. Multiple compressed tablet

3. Repeat action tablet

4. Delayed release tablet, e.g. Enteric coated Bisacodyl tablet

5. Sugar coated tablet, e.g. Multivitamin tablet

6. Film coated tablet, e.g. Metronidazole tablet

7. Chewable tablet, e.g. Antacid tablet

B. Tablets used in oral cavity:

1. Buccal tablet, e.g. Vitamin-c tablet

2. Sublingual tablet, e.g. Vicks Menthol tablet

3. Troches or lozenges

4. Dental cone

C. Tablets administered by other route:

1. Implantation tablet

2. Vaginal tablet, e.g. Clotrimazole tablet

D. Tablets used to prepare solution:

1. Effervescent tablet, e.g. tablet (Aspirin)

2. Dispensing tablet, e.g. Enzyme tablet (Digiplex)

3. Hypodermic tablet

4. Tablet triturates e.g. Enzyme tablet (Digiplex)

A. **Tablets ingested orally**:

1**. Compressed tablets*:***

Standard uncoated tablets are manufactured by compression. The general methods are by wet granulation, dry granulation or direct compression, used for rapid disintegration and drug release. Both type of action – systemic effect and local effect.

2. Multiple Compressed tablets:

For incompatible components these are formulated in two ways:

I. Layered tablet- These are either two layered (for two components) or three layered (for three components) tablets.

II. Compression Coated type- These are either tablet within a tablet or tablet within a tablet within a tablet. Tablet in this category are usually prepared for two reasons

- To separate physically or chemically incompatible ingredients.
- To produce repeat action or prolong action product.

3. Repeat action tablet:

Sugar coated or multiple compressed tablets are used for this purpose. The core tablet is usually coated with Shellac or an enteric polymer so that it will not release its drug in stomach but intestine.

4. Delayed action and Enteric-coated tablet:

This dosage form is intended to release the drug after some time delay or after the tablet has passed one part of the GIT into another. All Enteric coated tablets are type of Delayed action tablet but all Delayed action tablets are not Enteric or not intended to produce enteric action.

5. Sugar coated tablet:

Primary role of Sugar coating is to produce an elegant, glossy tablets. These are easy to swallow and multivitamin and multivitamin mineral combination. Sugar coating doubled the tablet weight. Now polymers are used with sugar solution.

6. Film Coated tablet:

One type of coated tablet in which drug is not required in coating. Polymers such as Hydroxy propyl cellulose, Hydroxy propyl methyl cellulose, and colloidal dispersion of Ethyl cellulose are commonly used. A 30% dispersion of Ethyl cellulose, is known as Aqua coat, is widely used in film coating. Advantage of film coated over sugar widely utilized in preparing coated tablets is better mechanical strength and flexibility of the coating, little increase in tablet weight.

7. Chewable tablet:

These are intended to be chewed in the mouth before swallowing. Used for large tablet of antacid. Bitter or foul testing drugs are not suitable for this type tablet.

B. Tablets used in oral cavity:

1. Buccal and sublingual tablet:

These tablets are small, flat and are intended to be held between the cheek and teeth or in cheek pouch (buccal tablet) or below the tongue (sublingual tablet). Drugs used by this route are for quick systematic action. The tablets are designed not to be disintegrated but slowly dissolve.

2. Troches and lozenges:

These are used in the oral cavity to exert local effect in mouth and throat. They are commonly used to treat sore throat or to control coughing in common cold. They may contain local anesthetics, antiseptic, antibacterial agents, demulcents, astringent and antitussive. These tablets are dissolving slowly over a period of 30 minutes.

3. Dental cone:

These tablets are designed to be placed in the empty socket remaining after tooth extraction. Main purpose is to prevent microbial growth in the socket or to reduce bleeding.

C. Tablets administered by other route:

1. Implantation tablets:

These tablets are designed for substances implantation to provide prolonged drug effect from one month to a year; tablets are usually small, cylindrical not more than 8mm length. These methods require special surgical technique for implantation and discontinuation of therapy.

2. Vaginal tablets:

These are designed to undergo slow dissolution and drug release in vaginal cavity. Tablets are wide or pear shaped, used to produce antibacterial, antiseptic and astringent effects to treat vaginal infection.

D. Tablets used to prepare solution:

1**. Effervescent tablets:**

Tablets are designed to produce a solution rapidly with the release of carbon dioxide. The tablets are prepared by compressing the active ingredient with mixture of organic acid such as Citric acid or Tartaric acid and Sodium bicarbonate.

2. Dispersing tablets:

Tablets are intended to be added to a given volume of water to produce a solution of a given drug concentration.

3. Hypodermic tablets:

These tablets are composed of one or more drugs with water-soluble ingredients. Drug is added to sterile water to prepare sterile solution, which is injectable.

4. Tablet triturates: *(Ansel., 2006)*

Usually these are made from moist materials using a triturate mold, which gives them the shape of cylinder. Generally these tablets consisting of highly potent drugs

1.1.1.4 Manufacturing defects in tablets:

Problems involved during the manufacturing of tablets include:

- Capping
- Lamination
- Chipping
- Sticking
- Picking
- Mottling
- Hardness variation
- Double impression *(Jhong, A., 2011)*

1.2 CURRENT TECHNOLOGIES IN ORAL DRUG DELIVERY:

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 drug delivery systems 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.

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

I. Immediate-release preparations.

II. Controlled-release preparations.

III. Targeted- release preparations.

I. Immediate-Release Preparations:

Immediate release drug delivery system is also conventional type of drug delivery system and it is defined as immediate release of drug without any special rate controlling features such as special coatings and other techniques.

These preparations are primarily intended to achieve faster onset of action for drugs such as analgesics, antipyretics, and coronary vasodilators. Other advantages include enhanced oral bioavailability through transmucosal delivery and pre-gastric 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, crosscarmellose sodium, and crosspovidone. Current technologies in fast-dispersing dosage forms include modified tabulating systems, floss or Shear form technology, which employs application of centrifugal force and controlled temperature, and freeze-drying.

II. Controlled-Release (CR) Preparations:

The currently employed CR technologies for oral drug delivery are diffusion-controlled systems; solvent activated systems, and chemically controlled systems.

Diffusion-controlled systems include monolithic and reservoir devices in which diffusion of the drug is the rate-limiting step, respectively, through a polymer matrix or a polymeric membrane.

Solvent-activated systems may be either osmotically controlled or controlled by polymer swelling.

Chemically controlled systems release drugs via polymeric degradation (surface or bulk matrix erosion) or cleavage of drug from a polymer chain. It is worth mentioning here that the so-called programmed-release (‘‘tailored-release’’) profile of a final CR product is rarely the outcome of a single pharmaceutical principle. Depending on the specific physicochemical properties of the drug in question and desired therapeutic objectives, different formulation and CR principles may be proportionally combined within the same dosage form. This task appears to be simpler when realized in terms of appropriate selection of polymers and excipients that incorporate desired principles.

III. Targeted-Release Preparations: (*Saltzman, W., et al., 2008)*

Targeted drug delivery, sometimes called smart drug delivery. Targeted drug delivery systems have been developed to optimize regenerative techniques. The system is based on a method that delivers a certain amount of a therapeutic agent for a prolonged period of time to a targeted diseased area within the body. This helps maintain the required plasma and tissue drug levels in the body. Therefore, avoiding any damage to the healthy tissue via the drug. The drug delivery system is highly integrated and requires various disciplines, such as chemists, biologist and engineers, to join forces to optimize this system

1.3 METHODS USED IN TABLET MANUFACTURING: *(Lieberman H.A. and Lachman L., 1999; Ansel H.C., 2009; http://www.pharmainfo.net)*

Granulation:

Granulation may be defined as a size enlargement process which converts small particles into physically stronger & larger agglomerates.

The reason for granulation:

- Become the pharmaceutical ingredient are free flowing
- Increase the denseness of ingredient
- We can formulate uniform granular size that does not existing apart
- Produce better compression characteristic of drug
- Controlling the rate of drug release from the dosage form
- Reduce dust in granulation technique
- The appearance of tablet can be achieved

Methods:

1. Direct compression
2. Wet granulation
3. Dry granulation

1.3.1. Direct compression:

In early days, most of the tablets require granulation of the powdered Active Pharmaceutical Ingredient (API) and Excipients. At the availability of new excipients or modified form of old excipients and the invention of new tablet machinery or modification of old tablet machinery provides an ease in manufacturing of tablets by simple procedure of direct compression.

Amongst the techniques used to prepare tablets, direct compression is the most advanced technology. It involves only blending and compression. Thus offering

advantage particularly in terms of speedy production. Because it requires fewer unit operations, less machinery, reduced number of personnel and considerably less processing time along with increased product stability.

1.3.1.1. Definition:

The term "direct compression" is defined as the process by which tablets are compressed directly from powder mixture of API and suitable excipients. No pretreatment of the powder blend by wet or dry granulation procedure is required.

1.3.1.2. The events that motivates the industry people to use direct compression technique:

I. Commercial availability of the directly compressible excipients possessing both good compressibility and good flow ability. For example, Spray dried lactose, Anhydrous lactose, Starch-1500, microcrystalline cellulose, sorbitol.

II. Major advances in tablet compression machinery:

i) Improved positive die feeding,

ii) Precompression of powder blend.

1.3.1.3 Merits:

i) Direct compression is more efficient and economical process as compared to other processes, because it involves only dry blending and compaction of API and necessary excipients.

ii) The most important advantage of direct compression is economical process. Reduced processing time, reduced labor costs, fewer manufacturing steps, and less number of equipments are required, less process validation, reduced consumption of power.

iii) Elimination of heat and moisture, thus increasing not only the stability but also the suitability of the process for thermolabile and moisture sensitive API's.

iv) Particle size uniformity.

v) Prime particle dissolution.

In case of directly compressed tablets after disintegration, each primary drug particle is liberated. While in the case of tablets prepared by compression of granules, small drug particles with a larger surface area adhere together into larger agglomerates; thus decreasing the surface area available for dissolution.

vi) The chances of batch-to-batch variation are negligible, because the unit operations required for manufacturing processes is fewer.

vii) Chemical stability problems for API and excipient would be avoided.

viii) Provides stability against the effect of aging which affects the dissolution rates.

1.3.1.4. Merits over wet granulation process:

The variables faced in the processing of the granules can lead to significant tableting problems. Properties of granules formed can be affected by viscosity of granulating solution, the rate of addition of granulating solution, type of mixer used and duration of mixing, method and rate of dry and wet blending. The above variables can change the density and the particle size of the resulting granules and may have a major influence on fill weight and compaction qualities. Drying can lead to unblending as soluble API migrates to the surface of the drying granules.

1.3.1.5. Demerits:

Excipients Related:

i) Problems in the uniform distribution of low dose drugs.

ii) High dose drugs having high bulk volume, poor compressibility and poor flowability are not suitable for direct compression.

iii) The choice of excipients for direct compression is extremely critical. Direct compression diluents and binders must possess both good compressibility and good flow ability.

iv) Many active ingredients are not compressible either in crystalline or amorphous forms.

v) Direct compression blends may lead to unblending because of difference in particle size or density of drug and excipients. Similarly the lack of moisture may give rise to static charges, which may lead to unblending.

vi) Non-uniform distribution of colour, especially in tablets of deep colours.

Process Related:

i) Capping, lamination, splitting, or layering of tablets is sometimes related to air entrapment during direct compression. When air is trapped, the resulting tablets expand when the pressure of tablet is released, resulting in splits or layers in the tablet.

ii) In some cases require greater sophistication in blending and compression equipments.

iii) Direct compression equipments are expensive.

1.3.1.6 Manufacturing steps for direct compression:

Direct compression involves comparatively few steps:

- Milling of drug and excipients.
- Mixing of drug and excipients.
- Tablet compression.

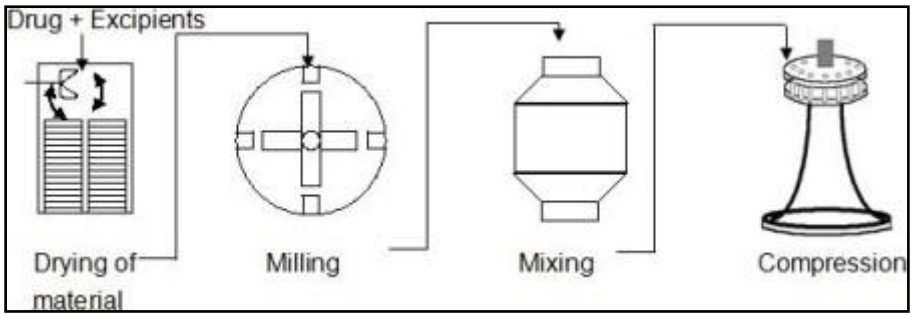


Figure 1.1: Manufacturing Steps for Direct Compression.

1.3.1.7. Direct compression Excipients:

Direct compression excipients mainly include diluents, binders and disintegrants. Generally these are common materials that have been modified during the chemical manufacturing process, in such a way to improve compressibility and flowability of the material.

The physicochemical properties of the ingredients such as particle size, flowability and moisture are critical in direct compression tableting. The success of direct compression formulation is highly dependent on functional behavior of excipients.

1.3.1.7.1. An ideal direct compression excipient should possess the following attributes:

i) It should have good compressibility.

ii) It should possess good hardness after compression, that is material should not possess any deformational properties; otherwise this may lead to capping and lamination of tablets.

iii) It should have good flow ability.

iv) It should be physiologically inert.

v) It should be compatible with wide range of API.

vi) It should be stable to various environmental conditions (air, moisture, heat, etc.).

vii) It should not show any physical or chemical change in its properties on aging.

viii) It should have high dilution potential i.e. able to incorporate high amount of API.

ix) It should be colourless, odorless and tasteless.

x) It should accept colourants uniformity.

xi) It should possess suitable organoleptic properties according to formulation type, that is in case of chewable tablet diluent should have suitable taste and flavor. For example, mannitol produces cooling sensation in mouth and also sweet test.

xii) It should not interfere with bioavailability and biological activity of active ingredients.

xiii) It should be easily available and economical in cost.

Granulation method can be broadly classified into two types:

- Wet granulation and
- Dry granulation.

1.3.2. Wet granulation:

The most widely used process of agglomeration in pharmaceutical industry is wet granulation. Wet granulation process simply involves wet massing of the powder blend with a granulating liquid, wet sizing and drying.

1.3.2.1. Important steps involved in the wet granulation:

i) Mixing of the drugs and excipients

ii) Preparation of binder solution

iii) Mixing of binder solution with powder mixture to form wet mass.

iv) Coarse screening of wet mass using a suitable sieve (6-12 # screens).

v) Drying of moist granules.

vi) Screening of dry granules through a suitable sieve (14-20 # screen).

vii) Mixing of screened granules with disintegrant, glidant, and lubricant.

1.3.2.2. Limitations of wet granulation:

i) The greatest disadvantage of wet granulation is its cost. It is an expensive process because of labor, time, equipment, energy and space requirements.

ii) Loss of material during various stages of processing

iii) Stability may be major concern for moisture sensitive or thermo labile drugs

iv) Multiple processing steps add complexity and make validation and control difficult.

v) An inherent limitation of wet granulation is that any incompatibility between formulation components is aggravated.

1.3.3. Dry granulation:

In dry granulation process the powder mixture is compressed without the use of heat and solvent. It is the least desirable of all methods of granulation. The two basic procedures are to form a compact of material by compression and then to mill the compact to obtain a granules. Two methods are used for dry granulation. The more widely used method is slugging, where the powder is pre-compressed and the resulting tablet or slug are milled to yield the granules.

The other method is to pre-compress the powder with pressure rolls using a machine such as Chilosonator.

1.3.3.1. Advantages:

The main advantages of dry granulation or slugging are that it uses less equipments and space. It eliminates the need for binder solution, heavy mixing equipment and the costly and time consuming drying step required for wet granulation. Slugging can be used for advantages in the following situations:

i) For moisture sensitive material

ii) For heat sensitive material

iii) For improved disintegration since powder particles are not bonded together by a binder

1.3.3.2. Disadvantages:

i) It requires a specialized heavy duty tablet press to form slug

ii) It does not permit uniform colour distribution

iii) Achieved with wet granulation where the dye can be incorporated into binder liquid.

iv) The process tends to create more dust than wet granulation, increasing the potential contamination.

1.4. INTRODUCTION TO TABLET COATING:

Coated tablets are covered with one/more layers of mixtures of various substances such as natural waxes authorized colouring materials. Substances used for coating are usually applied as solution/suspension under condition where vehicle evaporates. In the past sugar coating was mostly borrowed from the confectionary industry. But in now a days it is replaced with film coating.

Tablet film coating is performed by two types, one is aqueous film coating (generally water is used as a solvent) and non aqueous film coating (generally organic solvent are used). Some problems are associated with the non aqueous film coating like employee safety (it's dangerous, it smells, and it's not good to breathe) atmosphere pollution etc. But key problem is with the approval of the regulatory authority. High quality aqueous film coating must be smooth, uniform and adhere satisfactorily to the tablet surface and ensure chemical stability of a drug.

- **1.4.1. Reasons for Tablet Coating:** *(Cole, G., et al., 1998)*
- The core contains a material which has a bitter taste in the mouth or has an unpleasant odour.
- Coating will protect the drug from the surroundings with a view to improve its stability.
- The core contains a substance which is incompatible in the presence of light and subject to atmospheric oxidation, i.e. a coating is added to improve stability.
- The active substance is coloured and migrates easily to stain hands and clothes.
- The coated tablets can be packed on high-speed packaging machine. Coating reduces friction and increases packaging rate.
- Coating can modify the drug release profile, e.g., enteric coating, osmotic pump, pulsatile delivery2.
- **1.4.2. Film Coating Materials:**

  A film coating is a thin polymer-based coat applied to a solid dosage form such as a tablet. The thickness of such a coating is usually between 20-100 µm.

  Film coating formulations usually contain the following components:

  1. Polymer
  2. Plasticizer
  3. Colourants / Opacifiers
  4. Solvent / Vehicle.

  1. Polymer

  Among the vast majority of the polymers used in film coating are cellulose derivatives or acrylic polymers and copolymers.

i. Non-enteric polymers:

Hypromellose, Hydroxy ethyl cellulose, Hydroxy ethyl methyl cellulose, Carboxy methyl cellulose sodium, Hydroxy propyl cellulose, Polyethylene glycol, Ethylcellulose

ii. Enteric polymers:

Hypromellose phthalate, Polyvinyl acetate phthalate, Cellulose acetate phthalate, Polymethacrylates, Shellac

2. Plasticizers

The capacity to alter the physical properties of the polymer to render it more useful in performing its function as a film coating material. It is generally considered to be mechanism of plasticizer molecule to interpose themselves between individual polymer strands thus breaking down polymer-polymer interactions. Thus polymer is converted in to more pliable materials. Plasticizers are classified in three groups. Polyos type contains glycerol, propylene glycol, PEG (Polyethyleneglycol). Organic esters contain phthalate esters, dibutyl sebacetate, citrate esters, triacetin. Oils/glycerides contain castor oil, acetylated, monoglycerides, and fractionated coconut oil.

3. Solvents/Vehicles

The key function of a solvent system is to dissolve or disperse the polymers and other additives. All major manufactures of polymers for coating give basic physicochemical data on their polymers. These data are usually helpful to a formulator.

The major classes of solvents being used are

•Water

•Alcohols

•Ketones

•Esters

•Chlorinated hydrocarbons

Because of environmental and economic considerations, water is the solvent of choice; however organic coating is totally cannot be avoided.

4. Colourants / Opacquants:

These materials are generally used as ingredients in film-coating formulae to contribute to the visual appeal of the product, but they also improve the product in other ways:

- Identification of the product by the manufacturer and therefore act as an aid for existing GMP procedures.
- Reinforcement of brand imaging and reduction in product counterfeiting.
- Identification of the product by patients by using colourants.

Colourants for film coating are having, more or less amount and property of pacifier. So they would give protection to active ingredients in presence of light. Colourants are mainly classified in to three parts. Sunset yellow, Tartrazine, Erythrosine are examples of Organic dyes and their lakes. Iron oxide yellow, red and black, Titanium dioxide, Talc are the examples of Inorganic colours. Anthrocyanins, Ribofloavine and Carmine are the examples of natural colours.

1.4.3. Miscellaneous coating solution components:

Flavours and sweeteners are added to mask unpleasant odours or to develop the desired taste.

For example Aspartame, various fruit spirits (organic solvent), water soluble pineapple flavor (aqueous solvent) etc.

Surfactants are supplementary to solubilize immiscible or insoluble ingredients in the coating.

For example : Spans, Tweens etc.

Antioxidants are incorporated to stabilize a dye system from oxidation and colour change.

For example : Oximes, Phenols etc.

Antimicrobials are added to put off microbial growth in the coating composition. Some aqueous cellulosic coating solutions are mainly prone to microbial growth, and long-lasting storage of the coating composition should be avoided.

For example : Alkyl iso thiazloinone, Carbamates, Benzothiazoles etc

(Hogan, J., 1998)

1.4.4. Coating Process:

Film-coating of tablets is a multivariate process, with many different factors, such as coating equipment, coating liquid, and process parameters which affect the pharmaceutical quality of the final product.

1.4.4.1. Coating equipment: *(Heinamaki, J., et al., 1997)*

Before few years different types of coating pans are used for coating like conventional coating pans, manesty accelacota, Driam (Driacoater), butterfly coater etc. Now a days the side-vented, perforated pan-coater is the most commonly used coating device of tablets. In equipment spray nozzle, number of spray nozzle, pan size, etc may also affect the quality of final product. Its air flow system through a perforated pan ensures rapid and continuous drying conditions.

1.4.4.2. Coating liquid:

Coating liquid may affect the final quality of the tablets. Different film former have different chemical nature and different characteristics. Viscosity may

affect the spreading of coating liquid across surface of substrate. Surface tension may affect in wetting of surface. % Solid content generally affects the tablet surface and coating efficiency.

1.4.5. Process parameters:

1.4.5.1. Spray rate *(Obara, S., et al., 1995)*

The spray rate is an significant parameter since it impacts the moisture content of the formed coating and, subsequently, the quality and uniformity of the film. A low coating liquid spray rate causes incomplete coalescence of polymer due to insufficient wetting, which could effect in brittle films. A high coating liquid spray rate may result in over wetting of the tablet surface and subsequent problems such as picking and sticking. If the spray rate is high and the tablet surface temperature is low, films are not formed during the spraying but the post drying phase and rapid drying often produces cracks in the films.

1.4.5.2 Atomizing air pressure (*Tobiska, S., et al., 2003)*

In general, increasing the spraying air pressure decreases the surface roughness of coated tablets and produces denser and thinner films. If spraying air pressure is excessive, the spray loss is great, the formed droplets are very fine and could spray-dry before reaching the tablet bed, resulting in inadequate droplet spreading and coalescence. If spraying air pressure is inadequate, the film thickness and thickness variation are greater possibly due to change in the film density and smaller spray loss. In addition, with low spraying air pressure big droplets could locally over wet the tablet surface and cause tablets to stick to each other

1.4.5.3. Inlet air temperature. (*Okutgen, E., et al., 1991)*

The inlet air temperature affects the drying efficiency (i.e. water evaporation) of the coating pan and the uniformity of coatings. High inlet air

temperature increases the drying efficiency of the aqueous film coating process and a decrease in the water penetration into the tablet core decreases the core tablet porosity, tensile strength and residual moisture content of coated tablets. Too much air temperature increases the premature drying of the spray during application and, subsequently, decreases the coating efficiency. Measuring the pan air temperature helps to manage the optimum conditions during the coating process and, consequently, enables predicting possible drying or over wetting problems which may result in poor appearance of the film or may have unfavorable effects on the moisture and heat sensitive tablet cores

1.4.5.4. Rotating speed of pan *(Wilson, K., et al., 1997)*

It is well documented that increasing the rotating speed of the pan improves the mixing of tablets. The pan speed affects the time the tablets spend on the spraying zone and, subsequently, the homogeneous distribution of the coating solution on the surface of each tablet throughout the batch. Increasing the pan speed decreases the thickness variation and increase the uniformity of coatings. Too much rotating speed of the pan will cause the tablet to undergo unnecessary attrition and breakage

1.5. INTRODUCTION TO CANCER:

Cancer is a class of diseases characterized by out-of-control cell growth. There are over 100 different types of cancer, and each is classified by the type of cell that is initially affected.

1.5.1. Renal Cell Carcinoma*:* *(Rini, B.I., et al., 2008)*

Renal cell carcinoma (RCC, also known as Hyper nephroma) is a kidney cancer that originates in the lining of the proximal convoluted tubule, the very small tubes in the kidney that filter the blood and remove waste products. RCC is the most common type of kidney cancer in adults, responsible for approximately 80% of cases.

It is also known to be the most lethal of all the genitourinary tumors. The metastatic stage of renal cell carcinoma occurs when the disease invades and spreads to other organs. It is most likely to spread to neighboring lymph nodes, the lungs, the liver, the bones, or the brain. Metastatic renal cell carcinoma presents a special challenge to oncologists, as about 70% of patients develop metastases during the course of their disease

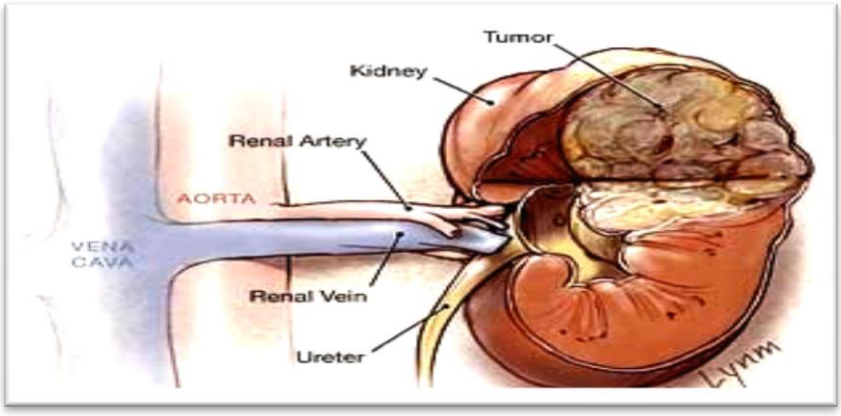


Figure: 1.2. Renal cell carcicoma

1.5.2. Diagnosis:

Physicians use information from symptoms and several other procedures to diagnose cancer. Imaging techniques such as X-rays, CT scans, MRI scans, PET scans, and ultrasound scans are used regularly in order to detect where a tumor is located and what organs may be affected by it. Doctors may also conduct an endoscopy, which is a procedure that uses a thin tube with a camera and light at one end, to look for abnormalities inside the body.

Extracting cancer cells and looking at them under a microscope is the only absolute way to diagnose cancer. This procedure is called a biopsy. Physicians will analyze body's sugars, fats, proteins, and DNA at the molecular level. For example, cancerous prostate cells release a higher level of a chemical called PSA (prostate-specific antigen) into the bloodstream that can be detected by a blood test.

1.5.3. Epidemiology: *(McLaughlin, J.K., et al., 2000)*

From 1975 to 2006, the incidence of kidney cancer rose 2% annually in the United States. The American Cancer Society estimated that in 2009 there would be 57,760 cases (35,430 in males and 22,330 in females) of malignant tumors of the kidney diagnosed, with 12,890 deaths (8,160 in males and 4,820 in females); renal cell cancer (RCC) accounted for 80% of this incidence and mortality. Renal cell carcinoma is more common in people of Northern European ancestry (Scandinavians) and North Americans than in those of Asian or African descent. In addition, the incidence in men is greater than in women (1.6:1).

1.5.4. Etiology:

Cigarette smoking, Obesity, Hypertension, Phenacetin-containing analgesia taken in large amounts.

1.5.5. Risk factors include:

Dialysis treatment, Family history of the disease, High blood pressure, Horseshoe kidney, Smoking, Von Hippel-Lindau disease (a hereditary disease that affects the capillaries of the brain, eyes, and other body parts)

1.5.6. Symptoms:

Abdominal pain, Back pain, Blood in the urine, Enlargement of the veins around a testicle (varicocele), Swelling or enlargement of the abdomen, Unintentional weight loss.

1.5.7. Signs and tests

Examination of the abdomen may show a mass or organ enlargement, particularly of the kidney or liver. Men may have a varicocele in the scrotum (a varicocele that is only on the right side is especially suspicious).

Tests include:

- Abdominal CT scan
- Blood chemistry
- Complete blood count (CBC)
- Intravenous pyelogram (IVP)
- Liver function tests
- Renal arteriography
- Ultrasound of the abdomen and kidney
- Urinalysis and urine cytology.

1.5.8. Treatment (*Novick, A.C., 1998)*

Surgical removal of all or part of the kidney (nephrectomy) is recommended. This may include removing the bladder or surrounding tissues or lymph nodes. Radiation therapy usually does not work for renal cell carcinoma so it is not often used. Hormone treatments may reduce the growth of the tumor in some cases. Chemotherapy is generally not effective for treating renal cell carcinoma. The drug interleukin-2 (IL-2), which works by helping the body's own immune system kill the cancer cells, may help a small number of patients, but it is very toxic. Other chemotherapy drugs have been used, but patients generally do not live long once the disease has spread outside the kidneyNewer therapies include sorafenib (Nexavar), sunitinib (Sutent), and temsirolimus (Torisel). The biologic drug bevacizumab (Avastin) has also been used. A cure is unlikely unless all of the cancer is removed with surgery.

1.5.9. Hepatocellular Carcinoma: (*Kumar, V., et al., 2003)*

Hepatocellular carcinoma (HCC, also called malignant hepatoma) is the most common type of liver cancer. Most cases of HCC are secondary to either a

viral hepatitide infection (hepatitis B or C) or cirrhosis (alcoholism being the most common cause of hepatic cirrhosis). Compared to other cancers, HCC is quite a rare tumor in the United States. Treatment options of HCC and prognosis are dependent on many factors but especially on tumor size and staging. Tumor grade is also important. High-grade tumors will have a poor prognosis, while low-grade tumors may go unnoticed for many years, as is the case in many other organs, such as the breast .

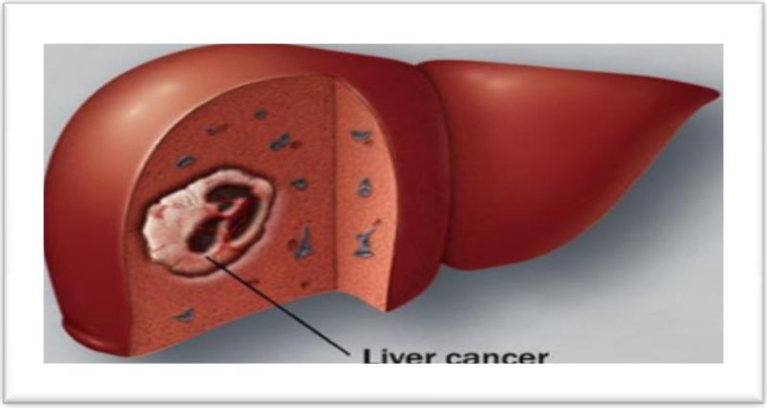


Figure:1.3.Hepato cellular carcicoma

1.5.9.1. Diagnosis:

Hepatocellular carcinoma (HCC) most commonly appears in a patient with chronic viral hepatitis (hepatitis B or hepatitis C, 20%) or/and with cirrhosis (about 80%). These patients commonly undergo surveillance with ultrasound due to the cost-effectiveness. CT scans use contrast agents, which are typically iodine or barium based.Mostly the radiologists are using MRIs to do a secondary study to look at an area where a tumor has already been detected.

1.5.9.2. Epidemiology:

HCC is one of the most common tumors worldwide. The epidemiology of HCC exhibits two main patterns, one in North America and Western Europe and another in non-Western countries, such as those in sub-Saharan Africa, central and Southeast Asia, and the Amazon basin. Males are affected more

than females usually and it is most common between the age of 30 to 50. Hepatocellular carcinoma causes 662,000 deaths worldwide per year about half of them in China.

1.5.9.3. Signs/Symptoms

Abdominal swelling, Vague pain upper right abdomen and back, Fatigue, Fever, Weight loss, Jaundice , Loss of appetite.

1.5.9.4. Risk Factors

Occupational exposure to chemicals, e.g. vinyl chloride, Cirrhosis, Alcohol abuse combined with heavy tobacco use, Hepatitis B or C, Poor nutrition.

1.5.9.5. Treatment: *(Kelley, R.K., et al., 2008)*

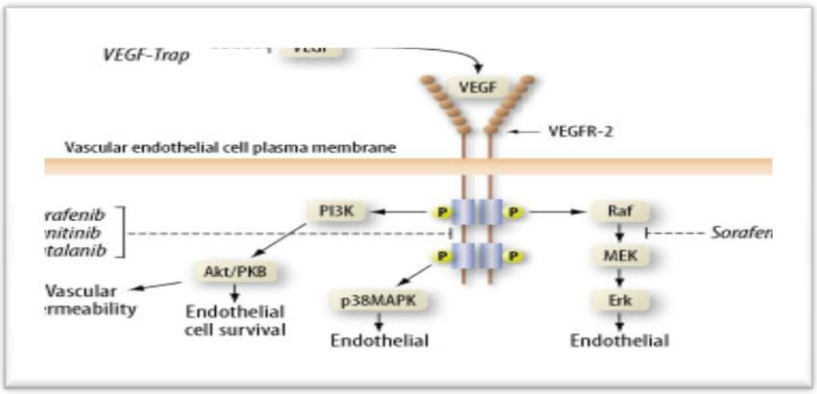


Figure:1.4.Treatment of Hepatocellular carcicoma by sorafenib

Treatment of liver cancer depends on the type of tumor and the stage of the disease, the condition of the liver, and the patient's age and overall health. The three main treatment methods include surgery, chemotherapy, and radiation therapy. Surgery to remove a tumor, called surgical resection, is the only way to cure liver cancer. Unfortunately, in the majority of liver cancers, complete removal of the cancer is not possible, either because the cancer has already spread beyond the liver or because the tumor is too large, or several tumors are present in different parts of the liver. Chemotherapy, the use of cancer-killing drugs, is also used to treat liver cancer.

Chemotherapy can be administered systemically by injection into a vein (IV) or by mouth. In systemic chemotherapy, the anticancer drugs enter the bloodstream and travel throughout the whole body, attacking cancer cells found beyond the liver.

The targeted therapy Nexavar (Sorafenib) is the first systemic therapy to improve survival in hepatocellular carcinoma, and is now a standard approach to treatment among patients with advanced hepatocellular carcinoma

AIM

AND

OBJECTIVE

2. AIM & OBJECTIVE

2.1. Aim of the study:

The aim of present work is to develop a solid oral dosage form of Sorafenib tosylate and it's comparision with innovator drug (Nexavar). The formulation of tablets were done to match the in-vitro drug release with respect to the reference drug and carry out the stability studies as per the ICH guidelines.

2.2. Objectives:

2.2.1. Primary Objective:

1. To formulate and evaluate immediate release Sorafenib tosylate film coated tablets 200mg.

2.2.2. Secondary Objectives:

1. To perform preformulation studies including drug – excipient compatibility study.
2. To develop various formulations with different excipients.
3. To study the effect of excipient concentrations on the tablet characteristics.
4. To establish the invitro release compliance with the established criteria.
5. To achieve immediate release profile for the developed formulation.
6. To establish the stability of the formulation.

PLAN OF WORK

3. PLAN OF WORK

The present research work was planned as per the following experimental protocol

- **Literature survey:**

  Literature survey on the various works carried out on this topic is reviewed.

- **Procurement of chemicals:**

  Procurement of drug and other ingredients required for the study.

- **Preformulation:**

a. Physical observation

b. Bulk density

c. Tapped density

d. Hausner‘s Ratio

e. Car‘s index

f. Compatibility studies of drug with various excipients.

- **Formulation:**

Tablets will be prepared by compression method using various grades of excipients in different ratios.

- **Film coating tablets:**

  Film coating will be done to prepare tablets by using film coating polymer like HPMC, Advantia prime pink

- **Evaluation of tablets:**

a. Tablet appearance

b. Thickness

c. Hardness

d. Disintegration test

e. % Friability

f. Invitro dissolution testing

g. Stability Studies

LITERATURE REVIEW

4. LITERATURE REVIEW

Anton, S., et al. (2011) This research work was aimed to formulate film coated tablets of secnidazole by wet granulation method and granules are compressed for tablets and they are coated with polymers by using Hydroxypropyl methyl cellulose and advatia prime pink. The resulted tablets were evaluated for different parameter and concluded that the coating has not shown any effect on the dissolution of the drug.

Kane, R.C. (2010) This report describes the U.S. Food and Drug Administration (FDA) review and approval of Sorafenib (Nexavar, BAY43-9006), a new small-molecule, oral, multi-kinaseinhibitor for the treatment of patients with advanced renal cell carcinoma (RCC). Sorafenib received FDA regular approval on December 20, 2005 for the treatment of advanced RCC. The recommended dose is 400 mg (two 200-mg tablets) twice daily taken either 1 h before or 2 h after meals. Adverse events were accommodated by temporary dose interruptions or reductions.

Li.Y., et al. (2010) report the more evidence sources to the standard treatment for patients with advanced hepatocellular carcinoma, the writer analyze patients' time to progression (TTP) and overall survival (OS) after patients receiving Transcatheter Arterial Chemo Embolization (TACE) combined with Sorafenib as a treatment of advanced hepatocellular carcinoma (HCC); observe the healing effect embolization combined with anti-angiogenic treatment for advanced hepatocellular carcinoma; and also analyze treatment of security. Combined with sorafenib treatment may give patients with advanced hepatocellular carcinoma a longer longevity and keep the disease in a steady state. This therapy can be added into the treatments to patients with advanced hepatocellular carcinoma.

Benjamin, H., et al. (2010) reported that there are multiple reports on Sorafenib-induced hand foot skin reaction, this case report details a patient presenting with an unusually severe and painful skin reaction. As the armamentarium of anti- neoplastic kinase inhibitors continues to increase, clinicians must be aware of the array of skin reactions these drugs can induce. A 66 years old Caucasian male with metastatic renal cell carcinoma presented with flu-like symptoms, rash, and painful bullous lesions of his fingertips. After empiric coverage with antibiotics and an infectious workup that turned up negative, it was determined that the patient's presentation was due to a severe and painful hand skin reaction to sorafenib. While most patients taking sorafenib will experience a cutaneous side effect, the hand foot skin reaction can be extremely debilitating and occurs frequently. Oncologists and dermatologists must be informed about the array of adverse effects o f kinase inhibitors. In the case report, the bullous skin reaction, debilitating hand pain, and absence of foot involvement were the interesting features.

Mila, P., et al. (2010) reported that medullary thyroid cancer (MTC) is a rare and only surgically treatable disease with early development of metastases and bad prognosis. Due to the lack of efficient systemic treatment, new strategies and approaches are needed to better the patients' outcome. One of the most promising treatment options is the use of tyrosine multikinase inhibitors, which appear to have some effect on the disease progression with tolerable toxicity. They reported a case of a young patient with metastatic MTC treated successfully for two months with sorafenib.

Tejash, S., et al. (2010) Orodispersible tablets of pheniramine maleate were prepared by direct compression method using various superdisintegrants like Crospovidone, croscarmellose sodium, sodium starch glycolate, low substituted

hydroxypropyl cellulose, pregelatinized starch. The prepared tablets were evaluated for uniformity of weight, hardness, friability, wetting time, in-vitro disintegration time, in-vitro dispersion time and drug release study. All the formulation exhibited hardness between 3.3 – 3.6 kg/cm2. The tablets were disintegrating in–vitro within 20 to 51 sec. Dissolution studies revealed that formulations containing 10% Crospovidone and formulation containing 10% croscarmellose sodium showed 100% of drug release, at the end of six min.

Thomas, S., et al. (2010) Sorafenib, an oral multitargeted tyrosine kinase inhibitor, is licensed for the treatment of hepatocellular carcinoma. Rash is one of the most common side effects of its use, generally appearing within days to a few weeks of commencing treatment. They reported the first case of rash appearing nine months after starting treatment with sorafenib. Sorafenib is a drug of choice in Barcelona Clinic Liver Cancer stage B hepatocellular carcinoma. It can cause protracted rash quite late into treatment. Successful management of the rash could contribute to achieving stable disease in hepatocellular carcinoma over a significant period of time.

Thomas, E., et al. **(2010)** The phase III Treatment Approaches in Renal cancer Global Evaluation Trial (TARGET) indicated that sorafenib is effective and well tolerated in advanced renal cell carcinoma patients. However, few data have been published on the safety of long-term sorafenib treatment. A retrospective subgroup analysis was performed to evaluate the efficacy and safety of sorafenib in patients in TARGET who received treatment for >1 year. Results of this subgroup analysis of patients enrolled in TARGET who received treatment for >1 year indicate that long-term treatment with sorafenib is associated with continued efficacy and a well-tolerated safety profile.

Dok, H. Y., et al. (2010) Sorafenib is the only drug that has shown a survival benefit in patients with hepatocellular carcinoma in randomized Phase 3 trials. The efficacy and safety of sorafenib in the treatment of recurrent hepatocellular carcinoma after liver transplantation, however, has not been determined. These findings suggest that sorafenib may be a feasible treatment option regarding its efficacy and safety for recurrent hepatocellular carcinoma after liver transplantation.

Jeng, F.C., et al. (2009) Sorafenib is a newly established cancer drug found to be an effective systemic treatment for advanced hepatocellular carcinoma (HCC). However, little is known about any potential effectors that modify tumor cell sensitivity towards sorafenib. The first evidence that glucose-regulated protein 78 (GRP78) is intimately associated with acquisition of resistance towards sorafenib. RNA interference in cancer cells was applied to determine the influence of GRP78 expression on sensitivity to sorafenib treatment.GRP78 is a positive modifier for sorafenib resistance acquisition in HCC and represents a prime target for overcoming sorafenib resistance.

Lettieri, J.T., et al. (2009) reported that Sorafenib is a multikinase inhibitor currently approved by the FDA for the treatment of advanced renal-cell carcinoma (RCC) and unresectable hepatocellular carcinoma (HCC). Sorafenib is available as a tablet formulation. Some patients who are unable to swallow tablets have suspended sorafenib tablets in a liquid for ease of administration. He performed a study to assess whether this process alters the bioavailability of sorafenib. The pharmacokinetics of sorafenib, when administered as a liquid suspension of tablets in water, were similar to the pharmacokinetics of tablets swallowed whole.

Ann, L.C., et al. (2009) cases of hepatocellular carcinoma occur in the Asia-Pacific region, where chronic hepatitis B infection is an important aetiological factor. Assessing the efficacy and safety of new therapeutic options in an Asia-Pacific population is thus important. A multinational phase III, randomised, double-blind, placebo-controlled trial to assess the efficacy and safety of sorafenib in patients from the Asia-Pacific region with advanced (unresectable or metastatic) hepatocellular carcinoma. Sorafenib is effective for the treatment of advanced hepatocellular carcinoma in patients from the Asia-Pacific region, and is well tolerated. Taken together with data from the Sorafenib Hepatocellular Carcinoma Assessment Randomised Protocol (SHARP) trial, sorafenib seems to be an appropriate option for the treatment of advanced hepatocellular carcinoma.

Rajarajan, R. (2009) To develop film coated tablets of B-complex vitamins with amino acids and minerals with various polymers by trial and error method. The excipients were selected to control of moisture uptake from environment; film coating approach was used seal coat followed film coating using commercially available OPADRY AMB as a coating polymer. Selected formulations were subjected to accelerated stability study. Trial batch formulations were having better release which is having excipients of less-hygroscopicity. Formulation was found stable by using less hygroscopic excipients with super disintegrents. The film coating was effective with initial seal coat followed by film coating with OPADRY AMB as a film coating polymer. The accelerated stability of the formulation was found satisfactory.

Ambrosini, G., et al. (2008) report Tumor cells were treated with Sorafenib and examined for growth inhibition, inhibition of phosphor kinases, cell cycle arrest. A review of this literature confirms the minimum concentration of Sorafenib required inhibiting the growth of tumours.

Preetha, B., et al. (2008) The effect of mode of incorporation of superdisintegrants like croscarmellose sodium, sodium starch glycolate and crospovidone (polyplasdone XL and XL-10) on dissolution of three model drugs with varying aqueous solubility, like carbamazepine (poorly soluble), acetaminophen (sparingly soluble) and cetrizine HCl (Soluble) from their respective tablet formulations prepared by wet granulation was studied. The disintegrants were incorporated extragranularly or intragranularly or distributed equally between the two phases. The results indicated that Crospovidone in general was effective in improving the dissolution of the drugs used in the study and generally extragranular mode of addition seemed to be the best mode of incorporation, irrespective of the solubility of the main tablet component.

Sebastien, H. (2007) report a case of adult clear-cell RCC with extensive rhabdoid features treated with the tyrosine kinase inhibitor Sorafenib. A review of the literature summarizes important aspects of this malignancy. They discussed clinical and histological findings as well as the patient's response to Sorafenib therapy. A review of the literature confirms that adult rhabdoid RCC is a rare but aggressive tumour with a distinctly poor prognosis. In patient, Sorafenib appeared to confer prolonged disease stabilization.

Sanghvi, P., et al. (2003) Investigate the effect of sodium lauryl sulfate (SLS) as an ingredient of dissolution media on the disintegration and dissolution of immediate release (IR) tablets containing cellulose derivative disintegrants using USP dissolution apparatus 2 tester. To develop alternative dissolution test methods for such tablets by employing different surfactants and dissolution apparatus. Conclusion was Dissolution media containing SLS can significantly hinder the disintegration of tablets containing cellulose-based disintegrants resulting in a very slow dissolution rate. Other surfactants, ionic and nonionic, did not exhibit this effect.

DRUG AND EXCIPIENTS PROFILE

5. DRUG AND EXCIPIENTS PROFILE

5.1. DRUG PROFILE:

(http://en.wikipedia.org/wiki/sorafenib)

Name of the drug : Sorafenib

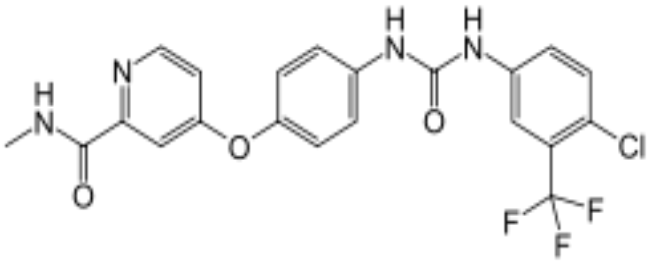
Description : White to pale yellow in colour

State : Solid

Molecular formula : $C_{21}H_{16}ClF_3N_4O_3$

Molecular Weight : 464.825

Chemical Structure :



IUPAC Name : 4-[4-[[4-chloro-3-(trifluoromethyl) phenyl] carbamoylamino] Phenoxy –N-methyl pyridine-2-carboximide

Solubility : Soluble in PEG,Slightly soluble in ethanol and Insoluble in water

Melting Point : 230ºC

Taste & Odour **:** Tasteless , Odourless

Absorption : Absorbed through GI tract

Protein binding : 99.5 %

Half life : 25-48 hrs

Clearance : 1280 ±67 ml/min.

Cmax : 12.5 µ mol/l

Tmax : 4 hrs

Bioavailability : 29-49 %

5.1.1. Pharmacological Nature of Sorafenib

Indication: It is a kinase inhibitor indicated for the treatment of

- Hepatocellular carcinoma.
- Advanced renal cell carcinoma.

5.1.2. Mechanism of action: *(Ahmad, T., et al., 2004)*

Sorafenib is a kinase inhibitor that decreases tumor cell proliferation in vitro. Sorafenib was shown to inhibit multiple intracellular (CRAF, BRAF and mutant BRAF) and cell surface kinases (VEGFR-1, VEGFR-2, VEGFR-3, and PDGFR-ß). Several of these kinases are thought to be involved in tumor cell signaling, angiogenesis, and apoptosis. Sorafenib inhibited tumor growth and angiogenesis of human hepatocellular carcinoma and renal cell carcinoma

5.1.3. Pharmacokinetic Nature of Sorafenib

5.1.3.1. Absorption

Following oral administration, sorafenib reaches peak plasma levels in approximately 3 hours. When given with a moderate-fat meal, bioavailability was similar to that in the fasted state. With a high-fat meal, sorafenib bioavailability was reduced by 29% compared to administration in the fasted state. It is recommended that NEXAVAR be administered without food (at least 1 hour before or 2 hours after eating) Mean Cmax and AUC increased less than proportionally beyond doses of 400 mg administered orally twice daily.

5.1.3.2. Distribution

In vitro binding of Sorafenib to human plasma proteins is 99.5%. Human serum albumin, α-globulin and the low density lipoproteinare the main binding proteins. Sorafenib was equally distributed between plasma and blood cells.The

binding of Sorafenib to plasma dependant on pH. The fraction unbound decreased to 0.165% at pH7.99 and increased to 1.80% at acidic pH 6.78.

5.1.3.3. Metabolism

Sorafenib is metabolized primarily in the liver, undergoing oxidative metabolism, mediated by CYP3A4, as well as glucuronidation mediated by UGT1A9. Sorafenib accounts for approximately 70-85% of the circulating analytes in plasma at steady-state. Eight metabolites of sorafenib have been identified, of which five have been detected in plas N-oxide, shows in vitro potency similar to that of sorafenib. This metabolite comprises approximately 9-16% of circulating analytes at steady-state.

5.1.3.4. Excretion

Following oral administration of a 100 mg dose of a solution formulation of sorafenib, 96% of the dose was recovered within 14 days, with 77% of the dose excreted in feces, and 19% of the dose excreted in urine as glucuronidated metabolites. Unchanged sorafenib, accounting for 51% of the dose, was found in feces but not in urine.

5.1.4. Drug Interactions:

• Docetaxel : Caution, Docetaxel AUC increases when co-administered with Nexavar.

•Doxorubicin:Caution,doxorubicin AUC increases when co-administered with Nexavar.

•Fluorouracil:Caution,fluorouracil AUC changes when co-administered with Nexavar.

5.1.5. Side effects:

- Diarrhoea
- Rash/Desquamation
- Fatigue
- Anemia

- Hand/Foot Skin Reaction
- Alopecia
- Nausea
- Pruritus
- Anorexia
- Hemorrhage

5.1.6. Dosing and administration:

400 mg (2 tablets) orally twice daily without food. Treatment interruption and/or dose reduction may be needed to manage suspected adverse drug reactions. Dose may be reduced to 400 mg once daily or to 400 mg every other day.

5.2. EXCIPIENTS PROFILE

5.2.1. Excipients:

Substances, other than the active ingredient, which have been appropriately evaluated for safety and are included in a drug delivery system to provide support. The excipients used must have following characteristics-

1. They must be stable both physically, chemically and biologically inactive.

2. It must be free from microbial contamination

3. Excipients used in tablet formulation must be accepted by regulatory agencies and should meet the entire current regulatory requirement.

5.2.1.1. Types of excipients:

Binders:

Binders hold the ingredients in a tablet together. Binders ensure that tablets and granules can be formed with required mechanical strength, and give volume to low active dose tablets.

Example: microcrystalline cellulose, sucrose, lactose

Fillers and diluents:

Fillers fill out the size of a tablet or capsule, making it practical to produce and convenient for the consumer to use. By increasing the bulk volume, the fillers make it possible for the final product to have the proper volume for patient handling.

Example: mannitol, sorbitol, calcium carbonate,

Lubricants:

Lubricants prevent ingredients from clumping together and from sticking to the tablet punches or capsule filling machine. Lubricants also ensure that tablet formation and ejection can occur with low friction between the solid and die wall

Example: magnesium stearate

Colours:

Colours are added to improve the appearance of a formulation. Colour consistency is important as it allows easy identification of a medication.

Glidants:

Glidants are used to promote powder flow by reducing interparticle friction and cohesion. These are used in combination with lubricants as they have no ability to reduce die wall friction.

Example: talc and magnesium carbonate

Flavours:

Flavours can be used to mask unpleasant tasting active ingredients and improve the likelihood that the patient will complete a course of medication.

Disintegrants:

Disintegrants expand and dissolve when wet causing the tablet to break apart in the digestive tract, releasing the active ingredients for absorption.

Example: sodium starch glycolate, croscarmellose sodium

Antiadherents:

Antiadherents are used to reduce the adhesion between the powder (granules) and the punch faces and thus prevent sticking to tablet punches.

Example: magnesium stearate

I. Microcrystalline Cellulose

1 **Nonproprietary Names:**

BP: Microcrystalline cellulose

IP: Microcrystalline cellulose

PhEur: Cellulosum microcristallinum

USPNF: Microcrystalline cellulose

2.Synonyms:

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

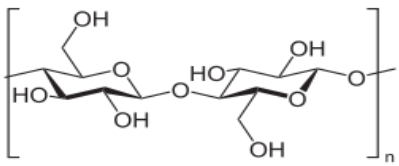
3.Description:

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

4.**Empirical Formula and**

Molecular Weight : $(C_6H_{10}O_5)n \approx 36\,000$ where $n \approx 220$.

5.Molecular structure:



6.Functional Category:

Adsorbent; Suspending agent; as a Diluent in tablets and capsules; tablet disintegrant.

7.Solubility:

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

8.Incompatibilities:

Microcrystalline cellulose is incompatible with strong oxidizing agents.

9.Stability and storage conditions*:*

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

10.Applications in Pharmaceutical Formulation or Technology*:*

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

II. Sodium Starch Glycolate (SSG)

1. **Synonyms:**

   Explotab; Primogel; Vivastar. Carboxymethyl starch, sodium salt.

2. **Chemical Name:**

   Sodium carboxymethyl starch

3. Description:

It is a white or almost white free-flowing very hygroscopic powder. The PhEur states that when examined under a microscope it is seen to consist of: granules irregularly shaped, ovoid or pear-shaped, 30–100 mm in size, or rounded,10–35 mm in size; compoundgranules consisting of 2–4 components occur occasionally; the granules have an eccentric hilum and clearly visible concentric striations. Between crossed nicol prisms, the granules show a distinct black cross intersecting at the hilum; small crystals are visible at the surface of the granules. The granules how considerable swelling in contact with water.

4. Functional Category:

Tablet and capsule disintegrate.

5. Solubility:

Practically insoluble in water and insoluble in most organic solvents.

6. Incompatibilities:

Sodium starch glycolate is incompatible with ascorbic acid.

7. Stability and Storage Conditions:

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

8. Applications in Pharmaceutical Formulation *:*

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablet prepared by either direct compression or wet granulation processes.

III. Crospovidone

1. Nonproprietary Name:

Crospovidone.

2. Synonyms:

Crospovidonum; Polyplasdone XL; Poly vinyl poly pyrrolidone.

3. Chemical Name:

1-Ethenyl-2-pyrrolidinone homopolymer

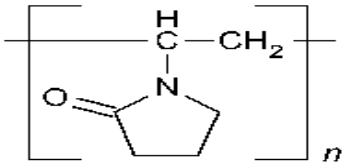
4. Description:

Crospovidone is a white to creamy-white, finely divided, free flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

5. Empirical Formula and Molecular Weight:

(C_6H_9NO) n, 2.500 - 2.5000.000 $g \cdot mol^{-1}$

6. Molecular structure:



7. Functional Category:

Tablet disintegrant

8. Solubility:

Practically insoluble in water and most common organic solvents.

9. Stability and Storage Conditions:

Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place

10. Incompatibilities:

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

11. Applications:

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2-5 % concentration in tablets prepared by direct compression or wet- and dry-granulation methods. It can also be used as a solubility enhancer.

12. Related Substances:

Crospovidone, povidone.

IV. Sodium Lauryl Sulphate (SLS)

1. Synonyms:

Dodecyl sodium sulphate; Elfan 240

2. Description:

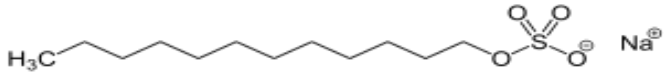
White cream to pale yellow coloured crystals, bitter in taste.

3. Empirical Formula*:* $C_{12}H_{25}NaO_4S$

4. Molecular Weight*:* 288.37

5. Functional Category: Anionic surfactant; detergent; emulsifying agent; skin penetrant; tablet and capsule lubricant; disintegrant, wetting agent.

6. Molecular structure:



7. Solubility:

Freely soluble in water forming opalescent solution, practically insoluble in chloroform, ether.

8. Incompatibilities:

Incompatible with strong oxidizing agents.

9. Applications in Pharmaceutical Formulation or Technology:

Sodium Lauryl Sulphate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used as emulsifier, detergent, topical application, tablet lubricant & wetting agent in dentifrices It is commonly used in tablet prepared by either direct compression or wet granulation processes.

10. Storage conditions:

Should be stored in well-closed container, in a cool & dry place.

V. Magnesium Stearate

1. Nonproprietary Names:

BP: Magnesium stearate

IP: Magnesium stearate

PhEur: Magnesii stearas

USPNF: Magnesium stearate

2. Synonyms:

Magnesium octadecanoate; octadecanoic acid; magnesium salt; stearic acid.

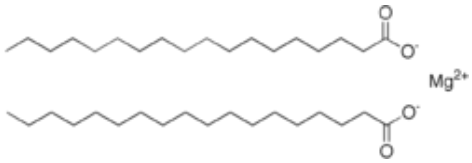
3. Chemical Name *:*

Octadecanoic acid magnesium salt

4. Empirical Formula: $Mg(C_{18}H_{35}O_2)_2$

5. Molecular Weight*:* 591.27 g/mol

6. Molecular structure*:*



7. Functional Category*:* Tablet and capsule lubricant.

8. Description:

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

9. Solubility:

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

10. Incompatibility:

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

11. Storage conditions:

Should be stored in well-closed container, in a cool & dry place.

12. Applications in Pharmaceutical Formulation or Technology:

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

VI. Croscarmellose Sodium

1. Nonproprietary Name:

Croscarmellose sodium

2. Synonyms:

Carmellosum natricum conexum; Crosslinked carboxy methyl cellulose sodium; Explocel:modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol

3. Chemical Name:

Cellulose, carboxy methyl ether, sodium salt.

4. Functional Category:

Tablet and capsule disintegrant.

5. Description:

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

6. Solubility:

Insoluble in water, although Croscarmellose sodium rapidly swells to 4-8 times its original volume on contact with water. Practically insoluble in acetone, ethanol and toluene.

7. Stability and Storage Conditions:

Croscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with Croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 300^0C for 14 months. Croscarmellose sodium should be stored in a well closed container in a cool, dry place.

8. Incompatibilities:

The efficacy of disintegrant such as Croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct compression process that contain hygroscopic excipients such as sorbitol.

Croscarmellose Sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury and zinc.

9. Applications:

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

VII. Hydroxypropyl Methyl Cellulose (HPMC)

1. Non-proprietary names:

IP: Hydroxypropylmethylcellulose

BP: Hypromellose

Ph Eur: Methylhydroxypropylcellulosum

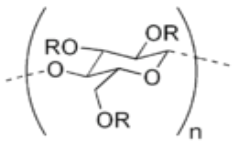
USP: Hypromellose

2. Chemical Name*:* Cellulose, 2-hydroxypropyl methyl ether

3. Synonyms:

Methyl Hydroxy Propyl cellulose; Propylene Glycol ether of methylcellulose; Culminal HPMC.

4. Structural Formula:



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

5. Molecular weight: 10,000 - 15,00,000

6. Color*:* White to creamy-white

7. Nature*:* Fibrous or granular powder

8. Solubility*:*

Soluble in cold water, practically insoluble in Chloroform, ethanol (95%) and ether but Soluble in mixture of ethanol and Dichloromethane.

9. Functional Category:

Used as Coating agent, film-forming, rate-controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent.

10. Applications:

In oral product HPMC is primarily used as tablet binder. Concentration between 2-5% w/w may be used as a binder in either wet or dry granulation process. HPMC is widely used in oral and topical pharmaceutical formulation. Concentration of 0.45-1% w/w may be added as a thickening agent to vehicle for eye drop and artificial tear solution. HPMC is used as an adhesive in plastic bandage and as a wetting agent for hard contact lenses. It is widely used in cosmetics and food products. In addition, HPMC is used as an emulsifier, suspending agent and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particle from coalescing or agglomerating thus, inhibiting the formation of sediments.

11.Stability and storage:

It is stable although it is slightly hygroscopic. The bulk material should be stored in an airtight container in a cool and dry place. Increased in temperature reduces the viscosity of the solution.

12.Safety: *.(Raymond, C.R. et al., 2009)*

It is generally regarded as a non-toxic and non-irritant material, so it is widely used in many oral and topical pharmaceutical formulations. Excessive consumption of HPMC may have laxative effect

5.3. INNOVATOR PROFILE:

(http://www.rxlist.com/nexavar-drug.hmt)

PRODUCT NAME	:	Nexavar, BAY 43-9006, Sorafenibum, Kinome-766.
LABEL CLAIM	:	Each tablet contains 200 mg of sorafenib
MANUFACTURED BY	:	Bayer health care
DESCRIPTION	:	Red in colour, debossed with bayer cross on one side and 200 on other side.
INACTIVE INGREDIENTS	:	microcrystalline cellulose, croscarmellose sodium, hydroxy propyl methyl cellulose, magnesium stearate.
THICKNESS	:	4.44 mm
WIDTH	:	7.64 mm
DIAMETER	:	10.05 mm
STORAGE	:	Store at 25˚C (77˚F)
DISSOLUTION APPARATUS	:	Paddle type(USP apparatus II)
DISSOLUTION MEDIUM	:	0.1M Hydrochloric acid with 1%SLS.
DISSOLUTION VOLUME	:	900 ml
TIME POINTS	:	5, 10, 15, 20, 30 minutes
SPEED	:	75 rpm

MATERIALS AND EQUIPMENTS

6. MATERIALS

6.1. MATERIALS USED

Table 6.1: List of raw materials used in the formulation

S.No	Ingredients	Manufacturer	Category
1.	Sorafenib tosylate	NATCO Pharma Ltd, Hyderabad.	Active pharmaceutical ingredients
2.	Micro crystalline Cellulose	FMC Bio polymer, Newyork.	Diluent
3.	Sodium Lauryl Sulfate	Ferro Corporations, USA Ferro	Surfactant
4.	CrosCarmellose sodium	Ferro Corporations,Ireland.	Disintegrant
5.	HPMC E-5	DMV Fonterra Excipients, Hyderabad.	Binder
6.	Sodium starch glycolate	DMV Fonterra Excipients, Hyderabad.	Disintegrant
7.	CrosPovidone	M/S Isp Technology , USA.	Disintegrant
8.	Magnesium Stearate	Luzenac valchisone, Italy	Lubricant
9.	Purified water	NATCO Pharma Ltd, Hydreabad.	Solvent
10.	Advantia prime pink	Ferro industriasquimicas, Portugal	Colouring agent

6.2. INSTRUMENTS

6.2 INSTRUMENTS:

Table no 6.2: List of instruments used for the formulation

S.No	**Name of instrument**	**Model no.**	**Make**
1.	Electronic Weighing Balance	PR 203	Mettler Toledo,Mumbai
2.	Tap Density Tester USP	ETD-1020	Electro lab,Mumbai
3.	Electronic Moisture Analyzer	HG 63	Mettler Toledo
4.	Tablet Compression Machine-8 Station	MINI Press - II MT	Rimek,Mumbai.
5.	Digital Hardness Tester	TH 10503	Labindia,Hyderabad
6.	Disintegration Test Apparatus USP	ED-2AL	Electro lab,Mumbai.
7.	Friabilator USP	EF-2	Electro lab,Mumbai.
8.	Mechanical Stirrer	RQT-127D	Remi Motors,Mumbai.
9.	Pharma R&D Coater	Deluxe	Ideal Cures,Mumbai.
10.	Fluid Bed Drier	UT-150	Umang Pharmatech
11.	Rapid mixture granulator	RMG 25	Anchor mark,Mumbai.
12.	Multi Mill	MM 15	Anchor mark,Mumbai.
13.	Tray Drier	PPT TD6	Platinum Pharmatech
14.	Dissolution Test Apparatus Type II	UV-Pharmaspec– 1700	DBK Instruments Ltd., Mumbai.

EXPERIMENTAL WORK

7. EXPERIMENTAL WORK

7.1. Preformulation Studies

Preformulation studies are performed to investigate the physical and chemical properties of a drug substance alone and also when combined with other substance such as excipients. It is the first step in the rational development of dosage forms.

Objective:

The overall objective of preformulation testing is to generate information useful to the formulation in developing stable and bioavailable dosage forms.

Scope:

The use of preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product and at same time provides the basis for optimization of the drug product quality.

7.1.1. Identification of Drug:

7.1.1.1. Identification of drug by HPLC method: (*Krefeld,Germany)*

In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

7.1.2. Organoleptic Properties:

The color, odor and taste of the drug were recorded using descriptive terminology.

7.1.3. Solubility Study: *(IP,2007)*

It is important to know about solubility characteristic of a drug in aqueous system, since they must possess some limited aqueous solubility to elicit a therapeutic response. The solubility of drug was recorded by using various descriptive terminology specified in Indian pharmacopoeia, 2007.

7.1.3.1. Solubility specification:

Table 7.1: The solubility specifications

Descriptive terms.	Approximate volume of solvent in milliliters per gram of solvent.
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 1 to 30
Sparingly soluble	From 30to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 100 to 10,000
Practically insoluble	More than 10,000

7.1.4. Preparation of standard curve:

7.1.4.1. Linearity:

The linearity of the response for Sorafenib tosylate was determined by preparing suitable dilutions were made 10-50µg/ml from standard stock solution. All the solutions were injected and the chromatograms were recorded at 265 nm. The above concentration range was found to be linear and obeys Beer's law. The procedure was repeated for three times. The peak areas were plotted against concentration and the calibration curve was constructed.

7.1.5. Determination of Drug-Excipient Compatibility:

A Compatibility study focuses on a binary mixture of drug substance and some selected excipients in a fixed ratio with or without added moisture. The mixture is stored at elevated temperature 40˚ C±2˚C/75%±5%RH, 25˚C± 2˚C/60%±5%RH in capped vials. The result of the interaction between the active drug and excipients is determined by HPLC.

7.1.5.1. Procedure:

- Drug and Excipients mixture shall be prepared based on the information from Physician Desk Reference (PDR).
- The Drugs and Excipients individually and in combination shall be subjected for accelerated study conditions along with control samples and study at fixed intervals.
- The recommended drug- excipients ratios for solid dosage forms are tabulated below

Table 7.2: Drug excipient ratios for solid dosage forms:

Name of Excipient	Quantity of Drug in mg					
	< 5 mg	5 ≤ 10mg	10 ≤ 50mg	50 ≤ 200mg	200 ≤ 500mg	≥500 mg
Fillers & Diluents	1:40	1:20	1:10	1:5	1:2	1:1
Disintegrates / Polymers	1:10	1:5	1:1	1:1	1:0.5	1:0.25
Binders	1:10	1:5	1:1	1:0.5	1:0.25	1:0.1
Lubricants	1:0.5	1:0.5	1:0.25	1:0.1	1:0.05	1:0.05
Coating agents	1:5	1:5	1:1	1:0.5	1:0.25	1:0.1
Colours / Sweetners	1:0.05	1:0.05	1:0.05	1:0.05	1:0.05	1:0.05

7.1.5.2 . Related Impurities (HPLC method):

Instuments: High performance liquid chromatograph equipped with UV-Detector and Data Handling system.

7.1.5.2.1. Apparatus:

- Analytical balance
- Volumetric flasks
- Pipettes
- 0.22µm membrane filter
- Filteration unit
- 0.22µm PVDF filter
- pH meter

7.1.5.2.2. Chemicals and Reagents:

- Sorafenib working standard
- Potassium dihydrogen Orthophosphate
- Orthophosphoric acid- HPLC grade
- Methonol- HPLC grade
- Tetrahydrofuran
- Acetonitrile- HPLC grade
- Purified water- Milli-Q-grade
- Impurity A working standard
- Impurity B working standard
- Impurity C working standard

7.1.5.2.3 Chromatographic conditions:

- Column- X-Terra RP- 18 (100 x 4.6mm), 5µm
- Flow rate – 2.0ml/ minute
- Wavelength- UV-293nm

- Column temperature- 30ºC
- Injection volume- 10µl
- Run time- 45 minutes

7.1.5.2.4 Preparations:

Phosphate buffer preparation:

2.72 g of potassium dihydrogen orthophosphate was weighed and transferred in to 1000 ml of purified water and mix. Adjust the solution pH to 3.0 with orthophosphoric acid.

Mobile phase-A Preparation: Buffer preparation was used as mobile phase-A ,it was filtered through 0.22µm membrane filter and degassed.

Mobile phase-B preparation:

Mixture of Acetonitrile and Tetrahydrofuran in the ratio of 90:10 v/v was prepared and the solution was filtered through 0.22µm membrane filter and degassed.

Diluent preparation:

Prepare a filtered and degassed mixture of Methanol and Acetonitrile in the ratio of 50:50 v/v respectively.

Placebo preparation:

Placebo powder equivalent to 200 mg of Sorafenib was weighed accurately and transferred into 200 ml volumetric flask and added with 160 ml of dilution medium and sonicated for 20 minutes with occasional shaking .The solution was cooled to room temperature and the volume was made and filtered through 0.22 µm membrane filter and degassed.

Peak Identification solution preparation:

About each 5.0 mg of Impurity-A ,Impuity-B, Impurity-C was accurately weighed and transferred into a 50 ml volumetric flask, added with 30 ml of dilution medium and sonicated to dissolve .The solution was cooled and the volume was made.

137.0 mg of Sorafenib tosylate working standard (equivalent to 200mg ot Sorafenib) was weighed and transferred into 200 ml volumetric flask,160 ml of dilution medium was added and sonicated for 20 mintues with occasional shaking. The resulting solution was cooled room temperature, added with 2.0 ml of peak identification solution and the volume dilute to mark diluents medium.

Standard preparation:

20mg equivalent of Sorafenib tosylate working standard was accurately weighed and transferred into 200ml of volumetric flask add about 160ml of dissolution medium and sonicated to dissolve. Solution was cooled to room temperature and volume was made to mark with dilution medium

1ml of the standard preparation transferred into a 100ml volumetric flask and made with dilution medium.

Sample preparation:

20 tablets of Sorafenib was powered and transferred an accurately weighed portion of the powder, equivalent to 200mg of Sorafenib into a 200 ml volumetric flask. Add about 160ml of dilution medium . Sonicated for 20 minutes with occasional shaking. The solution was cooled to room temperature volume was made upto 200ml and filtered through0.22µm PVDFfilter.

7.1.5.2.5 System suitability:

The standard preparation (Six replicate injections),and Peak identification solution(one injection) was chromatogramed and the peak area responses for the analyte peak and evaluate the system suitability parameters as directed.

7.1.5.2.6 Acceptance criteria:

%RSD for replicate injections of peak area response of the Sorafenib peak from the standard preparation should be not more than 10.0

The Tailing factor for Sorafenib peak should be not more than 2.0

The number of Theoretical plates for Sorafenib peak should be not less than 2000.

7.1.5.2.7. Procedure:

10µl of placebo preparation , peak identification solution preparation, diluent as blank, standard preparation and sample preparation are injected seperatly into the chromatograph, and the chromatograms recorded and % of each impurity in the portion of Sorafenib tablets was calculated using the formula

7.1.5.2.8 Calculation:

% known impurities:

$$\frac{IA}{SA} X \frac{SW}{200} X \frac{1}{100} X \frac{200}{TW} X \frac{P}{100} X \frac{464.825}{63.040} \times \frac{Avg.Wt}{LA} X 100/RRF$$

% Unknown impurities:

$$\frac{UA}{SA} X \frac{SW}{200} X \frac{1}{100} X \frac{200}{TW} X \frac{P}{100} X \frac{464.825}{63.040} \times \frac{Avg.Wt}{LA} X 100/RRF$$

Where,

UA- Peak area response due to Unknown impurity from Sample preparation

IA- Peak area response due to known impurity from Sample preparation

SA- Peak area response due to Sorafenib from Standard preparation

SW- Weight of Sorafenib working Standard taken in mg.

TW- Weight of sample taken in mg

P- Purity of Sorafenib working standard, taken on as is basis.

Avg Wt- Average weight of tablet.

LA- Label Amount

RRF-Relative response factor of respective known impurity.

7.1.6 Differential scanning calorimetry:

Any possible drug excipients interaction can be studied by thermal analysis. The DSC analysis of pure drug, drug +CCS, drug + SLS were carried out using Shimadzu to evaluate any possible drug-excipient interaction. The 2 mg sample were heated in a hermetically sealed aluminum pans in the temperature range of 25-300ºC at heating rate of 10ºC /min under nitrogen flow of 30 ml/min.

7.1.7. Loose Bulk Density (LBD) *(Lachman L.,et al.,1991)*

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced in to a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume. The loose bulk density (LBD) of powder blends was determined using the following formula.

Loose bulk density = Total weight of powder / Total volume of powder

7.1.8. Tapped bulk density (TBD) (*Lachman L.,et al.,1991)*

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume.

The tapped bulk densities (TBD) of powder blends were determined using the following formula.

Tapped bulk density= Total weight of powder / Total volume of tapped powder

7.1.9. Hausner's Ratio: *(Lachman L.,et al.,1991)*

Hausner's ratio was determined by following equation,

$$\text{Hausner's Ratio} = \text{Tapped bulk density}/\text{Loose bulk density}$$

A hausner ratio less than 1.25 indicates good flow while greater than 1.5 indicates poor flow.

7.1.10. Carr's Compressibility Index: *(Lachman L.,et al.,1991)*

It is a simple index that can be determined on small quantities of powder. In theory, the less compressible a material the more flowable it is. The compressibility indices of the powder blends was determined using formula,

Carr's Compressibility Index (%) = [(TBD-LBD)/ TBD] x100

Relationship between % compressibility and flowability is shown in the table 7.2.

Table 7.3: Standard values of Carr's index

S. No.	Carr's index	Type of flow
1	5-15	Excellent
2	12-16	Good
3	18-21	Fair to passable
4	23-35	Poor*
5	33-38	Very poor*
6	>40	Extremely poor*

* May be improved by glidant

7.1.11. Angle of repose *(LachmanL.,et al.,1991)*

The angle of repose was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured. The angle of repose was calculated using the following equation.

$$\tan(\theta) = \frac{h}{r}$$

Where 'h' and 'r' are the height and radius respectively of the powder cone

Table 7.4: Standard values of angle of repose (θ)

S. No.	Flowability	Angle of repose
1	Excellent	<25
2	Good	25-30
3	Passable*	30-40
4	Poor	37-45
5	Very poor	>45

* Adding glidant for improving flow

7.2. METHODOLGY

7.2.1. Formulation of Sorafenib Tosylate 200 mg tablets

7.2.1.1. Formulation Planning:

The immediate release tablets containing 200mg sorafenib tosylate were prepared with a total tablet weight of 400mg.

7.2.1.2. Manufacturing Procedure:

• Micro crystalline cellulose, cross Carmellose sodium, sodium lauryl Sulphate were weighed and sifted through 40 mesh.

• To the above blend sorafenib tosylate was added and sifted through 18 mesh.

• The sifted material was placed in cantabin blender and mixed for 8, 10, 12 min.

• Dry mix samples were taken at respective time points for content uniformity.

• Hypromellose E5 was dissolved in purified water and above was granulated

• The wet mass passed through 12 mesh and dried in tray dryer at 60^0C.

• The dried granules were passed through 18 mesh.

• Crosscarmellose, magnesium Stearate were weighed and sifted through 40 mesh.

• To the dried granules lubricated blend was added and placed in cantabin blender.

• The lubricated blend was compressed using 10 mm round punches.

Film coating:

10% coating solution is used .weight gain is 10 mg / tablet.

Coating solution composition*:*

Advantia prime pink, Hypromellose, Titanium dioxide, Ferric oxide, poly ethylene glycol.

7.2.1.3. Formulation of Sorafenib tosylate immediate release tablets

Table 7.5: Composition of sorafenib tosylate immediate release tablets

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Sorafenib Tosylate	274	274	274	274	274	274	274	274	274
Microcrstalline cellulose	75.3	65.3	61.4	57.5	57.5	53.6	49.7	64.5	48.5
Sodium lauryl sulphate	-	-	3.9	7.8	7.8	11.7	15.6	7.8	7.8
CrosCarmellose sodium	39.0	39.0	39.0	-	39.0	39.0	39.0	32.0	48.0
Sodium starch glycolate	-	-	-	39.0	-	-	-	-	-
Hypromellose E5	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8
Magnesium Stearate	3.90	3.90	3.90	3.90	3.90	3.90	3.90	3.90	3.90
Purified Water	-	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Advantia prime pink	-	10	10	10	10	10	10	10	10
Total (mg)	400	400	400	400	400	400	400	400	400

7.3. EVALUATION PARAMETERS:

Tablet evaluation in immediate release dosage forms may be divided conveniently in to following categories

7.3.1. Appearance: (*Lachman L.,et al.,1991; Bankar G.S. and Rhodes C.T.,1996)*

The tablets were visually observed for capping, chipping, and lamination.

7.3.2. Physicochemical characteristics:

7.3.2.1. Dimension (Thickness) *(Lachman L.,et al.,1991)*

The thickness of tablets were important for uniformity of tablet size. The thickness of the tablets was determined using a Vernier caliper. Three tablets from each type of formulation were used and average values were calculated.

7.3.2.2. Tablet Hardness: *(Lachman L.,et al.,1991; Bankar G.S. and Rhodes C.T., 1996)*

For each formulation, the hardness of 6 tablets was determined using the Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm2. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in kg/cm2.

7.3.2.3. Percent Friability: *(Lachman L.,et al.,1991; Bankar G.S. and Rhodes C.T., 1996)*

Friability is the measure of tablet strength. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of pre weighed tablets was placed in Roche friabilator which

was then operated for 100 revolutions. The tablets were then de dusted and reweighed. A loss of less than 1 % in weight is generally considered acceptable. Percent friability (% F) was calculated as follows,

$$\%F = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

7.3.2.4. Weight Variation *(IP, 2007; Lachman L.,et al.,1991*

To find out weight variation 20 tablets of each formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight compared with average value to find the deviation in weight.

Table 7.6: Specifications of % weight variation allowed in tablets as per Indian Pharmacopoeia

S. No.	Average weight of tablets (mg)	Maximum percent deviation allowed (%)
1	80 or less	10
2	More than 80 but less than 250	7.5
3	More than 250	5

7.3.3 In-vitro disintegration test

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 palable mass remaining in the apparatus was measured.

Table 7.7: Specifications

Tablet Type	Time limit and Specifications
1. BP	
❖ Uncoated	<15min
❖ Coated	
Film	<30min
Sugar	<60min, repeat in 0.1MHCl
❖ Gastro resistant, enteric	>120min in 0.1MHCl
	<60min in pH 6.8(Phosphate)
❖ Effervescent	<5min in 200ml, water, 20°C
❖ Soluble	<3min
❖ Dispersible	<3min, 2 tablets in 100ml water dispersed
,	
USP	
❖ Uncoated	<15min
❖ Plain coated	<30 min
❖ Enteric coated	60min
❖ Buccal	<4hour

7.3.4. Dissolution:

Dissolution is the process by which a solid solute enters a solution. In the pharmaceutical industry, it may be defined as the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition. Dissolution is considered one of the most

important quality control tests performed on pharmaceutical dosage forms and is now developing into a tool for predicting bioavailability.

7.3.4.1. Dissolution (by HPLC method):

7.3.4.2. Instrument(LC 10): High performance liquid chromatography equipped with UV-Detector.

7.3.4.3. Apparatus:

- Analytical balance
- Volumetric flasks
- Pipettes
- 0.22µm membrane filter
- Syringes
- Dissolution apparatus
- pH meter

7.3.4.4. Chemicals and Reagents:

- Sorafenib working standard
- Potassium dihydrogen phosphate
- Orthophosphoric acid- HPLC grade
- Methonol- HPLC grade
- Tetrahydrofuran
- Acetonitrile- HPLC grade
- Purified water- Milli-Q-grade

7.3.4.5. Dissolution conditions:

- Medium 0.1 M HCl with 1% SLS.
- Volume: 900ml
- Temperature : $37^0C \pm 0.5^0C$

- Apparatus: USP type –II (paddle)
- RPM: 75 rpm
- Time interval : 5, 10, 15, 20, &30 min

7.3.4.6. Preparation of Dissolution medium (0.1M HCl solution):

8.5ml of hydrochloric acid was pipetted and dissolved in 1000ml of distilled water

7.3.4.7. Chromatographic conditions:

- Column- X-Terra RP- 18 (100 x 4.6mm), 5µm
- Flow rate – 2.0ml/ minute
- Detector Wavelength- UV-293nm
- Column temperature- Ambient
- Injection volume- 10µl
- Run time- 15 minutes

7.3.4.8. Preparations:

Mobile phase preparation:

A mixture of phosphate buffer, Acetonitrile and Tetrahydrofuran was prepared in the ratio of 530:395:75 V/V respectively. Filtered through 0.22µm membrane filter and degassed.

Standard preparation:

Accurately weighed and transferred about 20 mg of Sorafenib tosylate working standard into 100ml of volumetric flask and added about 60ml of dissolution medium and sonicated to dissolve. Cooled the solution to room temperature and diluted to volume with dissolution medium.Transferred 5.0ml of the standard stock preparation into a 100ml volumetric flask and diluted to volume with dissolution medium.

Sample preparation:

One tablet equivalent to 200mg in each of six dissolution flasks containing 1000ml of dissolution medium, previously maintained at 37ºC, taking care to exclude air bubbles from the surface of each dosage unit and immediately operated the apparatus for specified time intervals. After completion of each specified time interval, withdraw a portion of solution from zone midway between the surface of the dissolution medium and top of the rotating blade, not less than 1cm from vessel wall and filtered through 0.22µm membrane filter. Transferred 5.0ml of the above solution into a 100ml volumetric flask and diluted to volume with dissolution medium.

7.3.4.9. System suitability:

Chromatograph the standard preparation (Six replicate injections), measure the peak area responses for the analyte peak and evaluate the system suitability parameters as directed.

7.3.4.10. Acceptance criteria:

%RSD for replicate injections of peak area response of Sorafenib peak from the standard preparation should not be more than 2.0.

The Tailing factor for Sorafenib peak should be not more than 2.0.

The number of Theoretical plates for Sorafenib peak should be not less than 2000.

7.3.4.11. Procedure:

Separately injected equal volumes (about 10µl) of the dissolution medium as blank,12.5µg/ml standard preparation and sample preparation into chromatograph, and recorded the chromatograms and measured the peak area responses for the analyte peak. Calculated the % of drug dissolved of Sorafenib in the portion of Sorafenib tablets by the formula.

7.3.4.12. Calculation:

% of Labeled amount of Sorafenib tosylte dissolved:

$$\frac{TA}{SA} X \frac{SW}{200} X \frac{5}{20} X \frac{900}{1} X \frac{P}{100} X \frac{100}{200}$$

Where,

TA- Peak area response due to sorafenib from sample preparation

SA- Peak area response due to sorafenib from standard preparation

SW- Weight of sorafenib working standard taken in mg

P- Purity of sorafenib working standard, taken on as is basis

.

7.3.5. ASSAY: (By HPLC method)

7.3.5.1. Instrument(LC 10):

High performance liquid chromatograph equipped with UV-Detector and data handling system

7.3.5.2. Apparatus:

- Analytical balance
- Volumetric flasks
- Pipettes
- 0.45µm membrane filter
- Filtration unit
- pH meter

7.3.5.3. Chemicals and Reagents:

- Sorafenib working standard
- Potassium dihydrogen phosphate
- Orthophosphoric acid- HPLC grade
- Methonol- HPLC grade

- Tetrahydrofuran
- Acetonitrile- HPLC grade
- Purified water- Milli-Q-grade

7.3.5.4. Chromatographic conditions:

- Column- X-Terra RP- 18 (100 x 4.6mm), 5µm
- Flow rate – 2.0ml/ minute
- Wavelength- UV-265 nm
- Column temperature- Ambient
- Injection volume- 20µl
- Run time- 15 minutes

7.3.5.5. Preparations:

Phosphate buffer preparation:

2.72g of potassium dihydrogen orthophosphate was weighed and transferred in to 1000ml of purified water and mixed. Adjusted the solution pH to 3.0 with orthophosphoric acid.

Mobile phase preparation:

A mixture of phosphate buffer, Acetonitrile and Tetrahydrofuran were prepared in the ratio of 530:395:75 v/v respectively. Filtered through 0.22µm membrane filter and degassed.

Diluent preparation:

A mixture of Methanol and Acetonitrile was prepared in the ratio of 50:50 v/v respectively. Filtered and degassed.

Standard preparation:

50 mg equivalent of Sorafenib tosylate working standard was weighed and taken into 100ml of volumetric flask add about 60ml of dissolution medium and

sonicated to dissolved. Cool the solution to room temperature and dilute to volume with dissolution medium.Transferred 5.0ml of the standard stock preparation into a 100ml volumetric flask and dilute to volume with dissolution medium.

Sample preparation:

Weighed and finely powdered not fewer than 20 tablets.Transferred an accurately weighed portion of the powder, equivalent to 200mg of Sorafenib into a 250 ml volumetric flask. Added about 160ml of dissolution medium .Shaken for 15 minutes on orbital shaker and sonicated for 30 minutes with occasional shaking.cool the solution to room temperature and diluted to volume with dissolution medium. Filtered the solution through 0.22µm membrane filter.Transferred 1.5 ml of the above filtered solution in to a 50ml volumetric flask, diluted to volume with diluent.

7.3.5.6. System suitability:

Chromatograph the standard preparation (Six replicate injections), measure the peak area responses for the analyte peak and evaluate the system suitability parameters as directed.

7.3.5.7. Acceptance criteria:

%RSD for replicate injections of peak area response of the Sorafenib peak from the standard preparation should be not more than 2.0

The Tailing factor for Sorafenib peak should be not more than 2.0

The number of Theoretical plates for Sorafenib peak should be not less than 2000.

7.3.5.8. Procedure:

Separately injected the equal volumes (about 20µl) of the diluent as blank, standard preparation and sample preparation into the chromatograph, and recorded the chromatograms and measured the peak area responses for the analyte peak. Calculate the % content of Sorafenib in the portion of Sorafenib tablets taken by the formula.

7.3.5.9. Calculation:

% Content of sorafenib:

$$\frac{TA}{SA} X \frac{SW}{Std.wt} X \frac{100}{25} X \frac{100}{5} X \frac{250}{TW} X \frac{200}{3} X \frac{P}{100} X Avg.wt$$

Where,

TA- Peak area response due to Sorafenib from Sample preparation

SA- Peak area response due to Sorafenib from Standard preparation

SW- Sample weight of Sorafenib mg.

TW- Weight of sample taken in mg

P- Purity of Sorafenib working standard, taken on as is basis.

Avg Wt- Average weight of tablet.

Std.wt-Standard weight.

7.3.6. STABILITY STUDY *(Manavalan R. and Ramasamy S., 2004; Suresh V.K., et al.,2010)*

7.3.6.1. Introduction

In any rational drug design or evaluation of dosage forms for drugs, the stability of the active component must be a major criterion in determining their acceptance or rejection. Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation, until its chemical or biological activity is not less than a predetermined level of labelled potency and its physical characteristics have not changed appreciably or deleteriously.

7.3.6.2. Objective of the study

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. Generally, the

observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted. The International Conference on Harmonization (ICH) Guidelines titled "Stability testing of New Drug Substances and Products (QIA) describes the stability test requirements for drug registration application in the European Union, Japan and the States of America.

ICH specifies the length of study and storage conditions

7.3.6.3. Study specifications:

Table 7.8: ICH Specifications to study the storage conditions

S.NO.	STUDY	STORAGE CONDITION	MINIMUM TIME PERIOD
1.	Long term	25ºC+ 2ºC/60 %RH+ 5ºC (or) 30C+2ºC/ 65%RH+5%RH	12 months
2.	Intermediate	30ºC+2ºC/65%RH+5%RH	6months
3.	Accelerated	40ºC +2ºC / 75% RH +5 % RH	6months

RESULTS AND DISCUSSION

8. RESULTS AND DISCUSSION

8.1. PREFORMULATION PARAMETERS

8.1.1. Identification of drug

8.1.1.1. Identification by HPLC Chromatographic method:

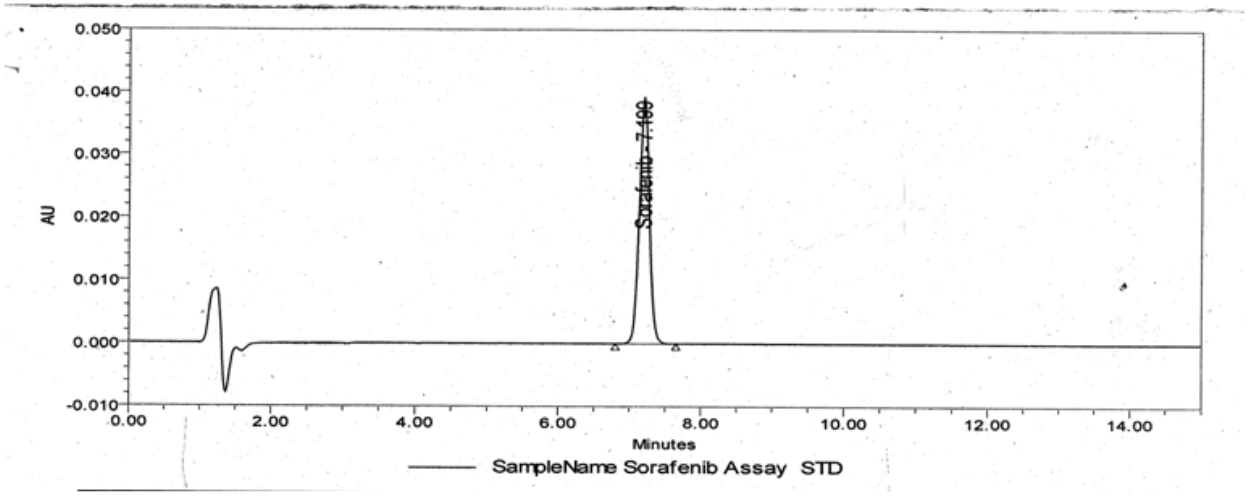


Figure 8.1: The HPLC Chromatogram of assay of Sorafenib Tosylate (Standard)

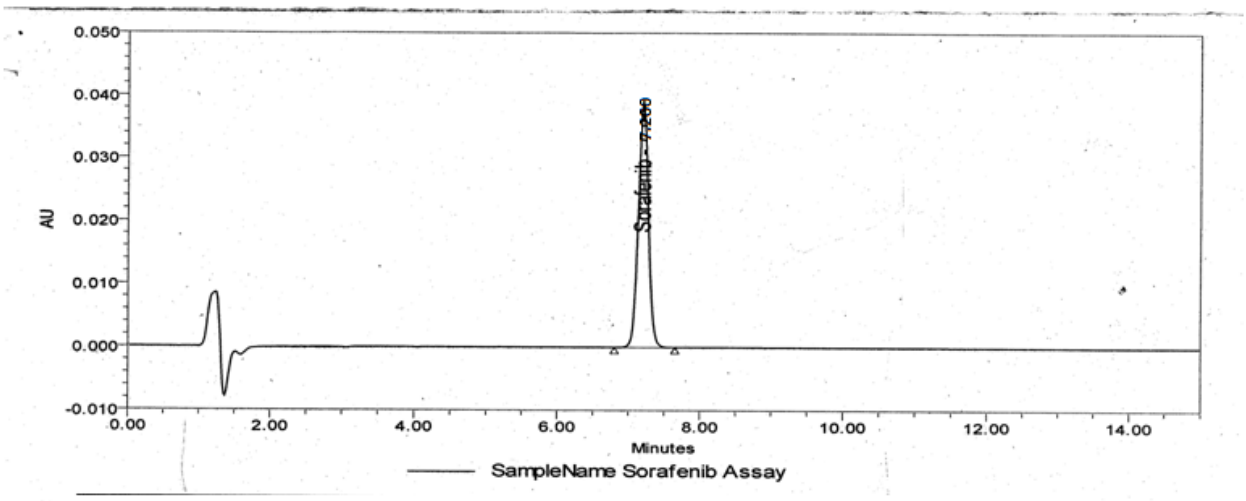


Figure 8.2: The HPLC Chromatogram of assay of Sorafenib Tosylate (Sample)

8.1.1.2. Melting point:

Melting point of Sorafenib Tosylate sample was found to be 230^0C.Hence, experimental value are in good agreement with official values.

8.1.2. Physicochemical parameters of drug:

8.1.2.1. Organoleptic properties:

Odour : Charecteristic odour

Colour : A White to yellowish powder

Nature : Crystalline powder

8.1.2.2. Solubility study:

Table 8.1: Solubility of Sorafenib in different solvents

Name of solvents	Solubility
Poly ethylene glycol	Soluble
Methanol	Soluble
0.1N HCl	Soluble
Distilled water	Practically insoluble

Table .8.2: FLOW PROPERTIES OF API

S.No	Flow Properties	Result
1.	Bulk density (g/ml)	0.206
2.	Tapped density (g/ml)	0.360
3.	Carr's index (%)	9
4.	Hausner's ratio	1.7
5.	Angle of repose(˚)	24°.4

8.1.3. Analytical methods

8.1.3.1. Preparation of standard graph of Sorafenib tosylate:

The drug obeys Beer- Lambert's law in the range of 10–50µg /ml.

Table 8.3: Data of concentration and Area of the peak for Sorafenib tosylate in 0.1N HCl

S. No.	Concentration (µg/ml)	Area of the peak
1	10	127750
2	20	255500
3	30	383250
4	40	511000
5	50	638750

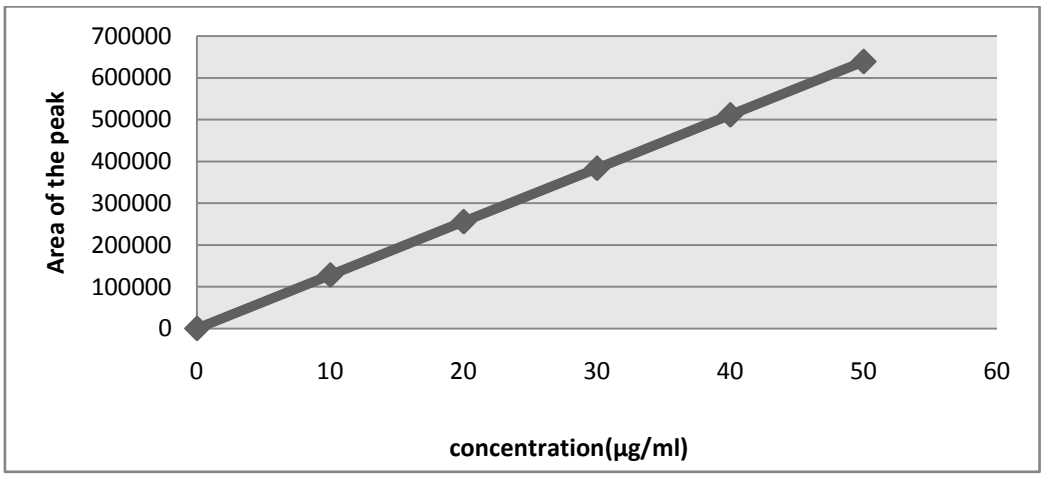


Figure 8.3: Standard graph of Sorafenib tosylate

Table 8.4: Calibration parameter values in 0.1 N HCl

S. No.	Parameters	Values
1	Correlation coefficient (r)	0.9999
2	Slope (m)	12774.99
3	Intercept (c)	0.75

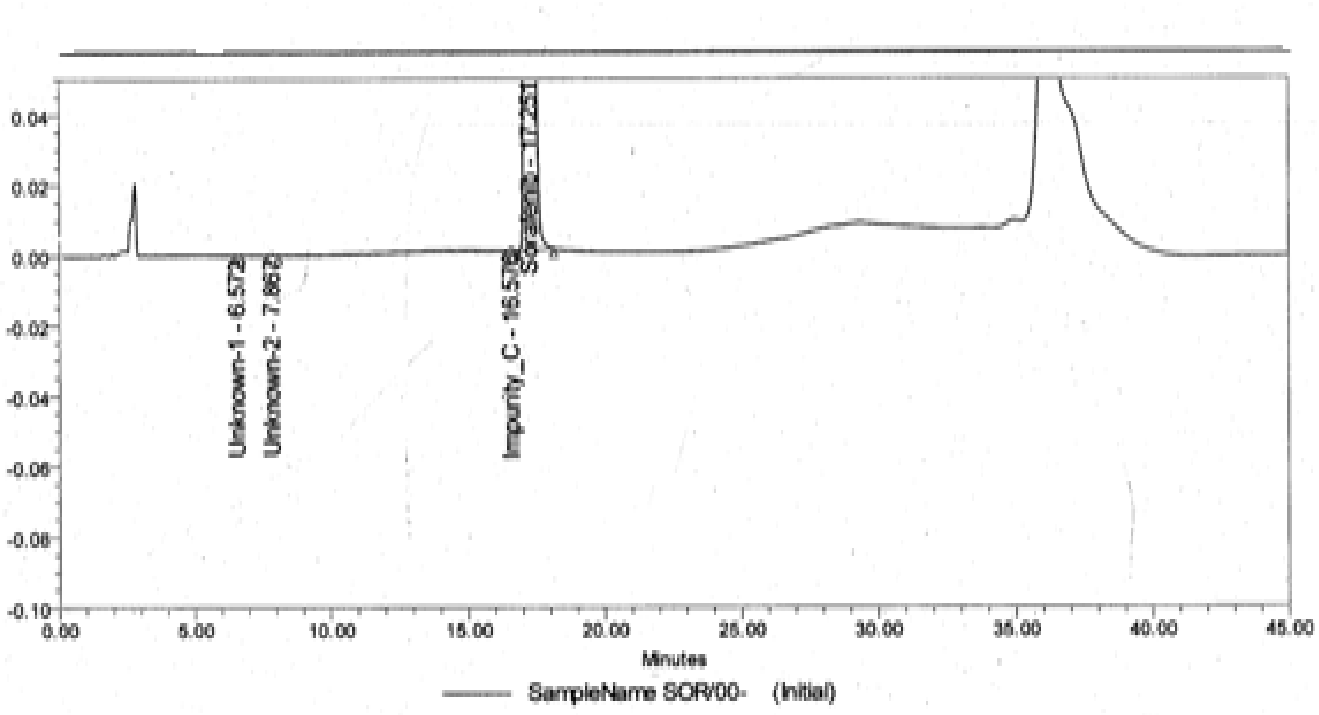


Figure 8.4: Determination of compatibility for drug with polymer

By HPLC Chromatographic method

Table 8.6: The HPLC chromatogram of Sorafenib(intial)

Impurities present in Sorafenib tosylate

S.no	Peak name	RT	Area	%Area
1	Unknown-1	6.572	507	0.00
2	Unknown-2	7.867	3375	0.01
3	Impurity-C	16.576	8315	0.02
4	Sorafenib	17.251	37000085	99.97

Impurity A: 4-(2-(N-methyl carbonyl)-4-pyrydyloxy) aniline.

Impurity B: 1, 3-Bis (4-chloro-3-di floro phenyl) phenyl urea

Impurity C: 4 (- 4 ((((2-chloro-3-tri floro methyl) phenyl) amino) carbonyl) amino)- phenyl)-N-methyl-2-pyridine carboxamide tosylate.

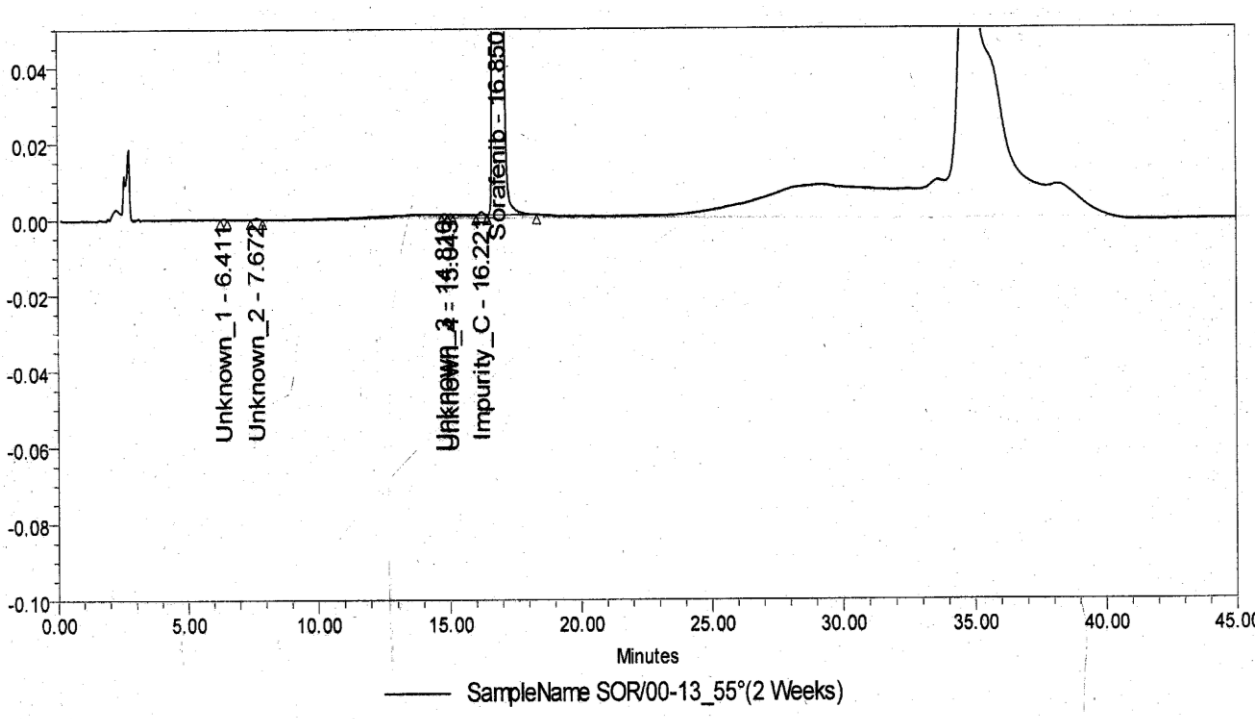


Figure 8.5: The HPLC Chromatogram of Sorafenib Impurities (2 weeks)

Table 8.7: Impurities that are present in Sorafenib(2 weeks)

S .no	Peak name	RT	Area	%Area
1	Unknown-1	6.411	511	0.00
2	Unknown-2	7.672	3867	0.01
3	Unknown-3	14.810	492	0.00
4	Unknown-4	15.043	416	0.00
5	Impurity-C	16.221	8290	0.02
6	Sorafenib	16.850	35791516	99.96

Table 8.8: compatibility study specifications

RERLATIVE SUBSTANCE	SPECIFICATIONS (%)
Impurity A	NMT 0.15
Impurity B	NMT 0.15
Impurity C	NMT 0.15
Highest unknown impurity	NMT 0.10
Total impurity	NMT 0.5

Table 8.9: Sorafenib tosylate compatibility studies (Initial)

RERLATIVE SUBSTANCE	Impurity A	Impurity B	Impurity C	Single max unknown impurity	Total Impurity
Sorafenib tosylate	0.016	ND	0.056	0.013	0.079
Sorafenib+ microcrystalline Cellulose	0.014	ND	0.043	0.09	0.071
Sorafenib + croscarmellose Sodium	0.014	ND	0.045	0.013	0.072
Sorafenib+ sodium lauryl Sulphate	0.017	ND	0.042	0.013	0.072
Sorafenib+HPMC E5	0.014	ND	0.045	0.011	0.070
Sorafenib+ magnesium State	0.015	ND	0.055	0.012	0.084
Sorafenib+ advantia prime Pink	0.018	ND	0.052	0.012	0.082
Sorafenib+ povidone	0.32	ND	0.40	0.013	0.73
Sorafenib+cross povidone	0.28	ND	0.20	0.20	0.68

Table 8.10: Sorafenib tosylate compatibility studies (2 weeks) at 55^0C

RERLATIVE SUBSTANCE	Impurity A	Impurity B	Impurity C	Single max unknown impurity	Total Impurity
Sorafenib tosylate	0.016	ND	0.056	0.012	0.084
Sorafenib+ microcrystalline cellulose	0.017	ND	0.043	0.011	0.009
Sorafenib+croscarmellose Sodium	0.015	ND	0.045	0.011	0.074
Sorafenib+ sodium lauryl Sulphate	0.019	ND	0.049	0.011	0.083
Sorafenib+HPMC E5	0.021	ND	0.049	0.012	0.086
Sorafenib+ magnesium State	0.020	ND	0.053	0.012	0.081
Sorafenib+ advantia prime Pink	0.015	ND	0.052	0.013	0.012
Sorafenib+ povidone	0.35	ND	0.43	0.012	0.12
Sorafenib+cross povidone	0.82	ND	0.20	0.14	0.75

Table 8.11: Sorafenib tosylate compatibility studies (28days) at 40^0C$\pm 2^0$C/75$\pm$5%RH

RERLATIVE SUBSTANCE	Impurity A	Impurity B	Impurity C	Single max unknown impurity	Total Impurity
Sorafenib tosylate	0.028	ND	0.056	0.012	0.091
Sorafenib+ microcrystalline Cellulose	0.015	ND	0.041	0.009	0.065
Sorafenib+croscarmellose Sodium	0.016	ND	0.043	0.010	0.069
Sorafenib+ sodium lauryl Sulphate	0.019	ND	0.067	0.011	0.097
Sorafenib+HPMC E5	0.020	ND	0.051	0.012	0.083
Sorafenib+ magnesium State	0.020	ND	0.052	0.012	0.083
Sorafenib+ advantia prime Pink	0.019	ND	0.050	0.012	0.081
Sorafenib+ povidone	0.39	ND	0.40	0.012	0.73
Sorafenib+cross povidone	0.64	ND	0.20	0.016	0.74

Impurity A: 4-(2-(N-methyl carbonyl)-4-pyrydyloxy) aniline.
Impurity B: 1, 3-Bis (4-chloro-3-di floro phenyl) phenyl urea
Impurity C: 4 (- 4 ((((2-chloro-3-tri floro methyl) phenyl) amino) carbonyl) amino)-phenyl)-N-methyl-2-pyridine carboxamide tosylate.

The increase in impurities at the initial stage is found in Povidone and Cross Povidone. So these are incompatible with active ingredient. Hence, it is recommended that the above excipients (Povidone, Cross Povidone) cannot be used in further formulation development trials.

8.1.4. Differential scanning calorimetry:

The compatibility and interactions between drug and excipients like SLS and CCS were studied using differential scanning calorimetry and the results were shown in figure 8.6,8.7,8.8.

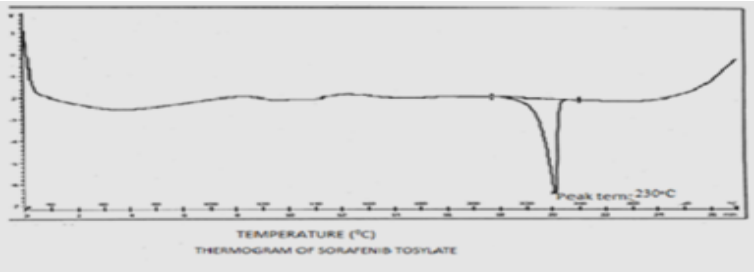


Figure:8.6.DSC Thermal analysis of Sorafenib tosylate

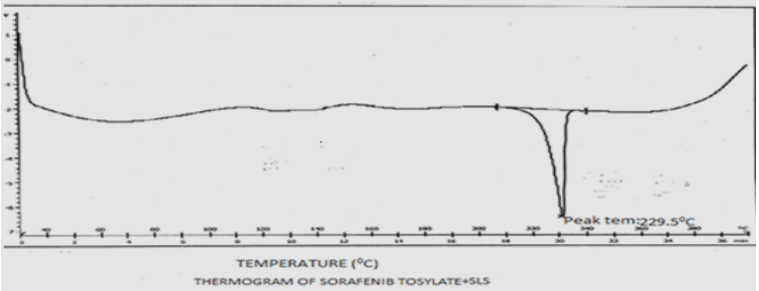


Figure:8.7.DSC Thermal analysis of Sorafenib tosylate + SLS

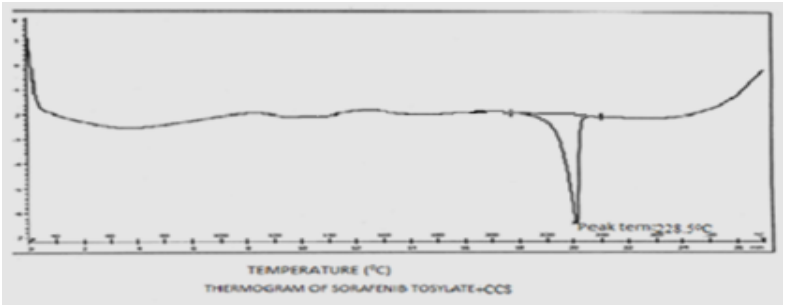


Figure :8.8. DSC Thermal analysis of Sorafenib Tosylate + CCS

From the above thermogram, it can selected that there is no change in the peak. Hence, no interaction between drug and excipients.

8.2. Evaluation of powder blends:

The blended powders of different formulations were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and Hausner ratio. The results of these evaluations were as follows: -

Table 8.12: Flow characteristics of powder blends

Formulation Code	Angle of repose (^{o})	Loose bulk density (g/ml)	Tapped bulk density (g/ml)	Hausner ratio	Carr's index (%)
F1	32.0±0.173	0.158±0.00	0.731±0.00	1.44±0.00	29.05±0.049
F2	27.51±0.05	0.434±0.00	0.500±0.00	1.14±0.00	12.3±0.11
F3	26.34±0.005	0.427±0.00	0.495±0.00	1.14±0.00	13.6±0.05
F4	25.45±0.005	0.445±0.00	0.505±0.00	1.13±0.00	11.8±0.05
F5	26.65±0.005	0.400±0.00	0.471±0.00	1.17±0.00	14.8±0.05
F6	27.04±0.005	0.416±0.00	0.482±0.00	1.15±0.00	13.4±0.05
F7	26.45±0.005	0.394±0.00	0.461±0.00	1.17±0.00	14.4±0.05
F8	26.28±0.005	0.427±0.00	0.490±0.00	1.14±0.00	12.6±0.05
F9	27.15±0.005	0.416±0.00	0.485±0.00	1.16±0.00	14.1±0.05

*All the values were expressed as mean± SD, n=3

8.2.1. Angle of repose:

Angle of repose ranged from25.45±0.005 to 32.0±0.1. The results were found to be 25º to 35º and hence the blend was found to have excellent flowability.

8.2.2. Loose bulk density and tapped bulk density: Bulk and tapped densities are used for the measurement of Compressibility index. The LBD and TBD ranged from 0.158 ± 0.00 to 0.445± 0.00 g/ml; and 0.461 ± 0.00 to 0.731± 0.00 g/ml respectively

8.2.3. Compressibility index (Carr's index):

The compressibility index ranged from 11.8± 0.11to 29.05± 0.049 .The blend was found to have good flowing property as the result were found to be below 20

8.2.4. Hausner ratio:

The Hausner ratio ranged from 0.13± 0.00 to 1.17 ± 0.00. The result indicates the free flowing properties of the powders.

8.3. Evaluation of Immediate release tablets

8.3.1. Appearance:

Surface nature of tablets was observed visually and it was concluded they did not show any defects such as capping, chipping and lamination.

8.3.2. Physico-chemical characteristics:

The physical characteristics of Sorafenib tosylate tablets (F1 toF9) such as thickness, hardness, friability, weight variation and drug content were determined.

Table 8.13: Physico-chemical parameters of Sorafenib tosylate tablets

F. Code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation	Drugcontent (%w/w)
F1	5.50±0.00	6.9±0.05	0.12	400.40±1.50	95±0.115
F2	4.63±0.01	7.3±0.05	0.06	402.15±2.94	97.3±0.05
F3	4.87±0.00	7.3±0.05	0.17	400.90±2.73	94.2±0.115
F4	4.90±0.00	7.4±0.05	0.17	401.25±3.57	97.8±0,05
F5	5.43±0.00	7.5±0.01	0.15	402.20±3.61	99.9±0.05
F6	5.82±0.00	7.8±0.05	0.18	401.75±2.22	97.4±0.05
F7	5.07±0.00	7.8±0.05	0.09	400.80±3.24	98.3±0.05
F8	4.67±0.00	7.9±0.05	0.16	403.05±3.12	92.4±0.05
F9	5.42±0.00	7.5±0.05	0.16	402.95±2.28	97.6±0.05

All the values were expressed as mean ± SD, n=3

8.3.2.1. Thickness

The thickness ranged between 4.63 ± 0.00 to 4.87 ± 0.00 mm.

8.3.2.2. Tablet hardness:

The hardness of tablets was found to be in the range from 6.9± 0.65 kg/cm^2 to 7.9 ± 0.05kg/cm^2. This indicates good mechanical strength of tablet.

8.3.2.3. Percent friability:

Percentage friability of all the formulations was found to be in the range from 0.06 to 0.18 %. This indicates good handling property of the tablet.

8.3.2.4. Weight variation:

A tablet is designed to contain a specific amount of drug. When the average weight of the tablet is 400 mg, the pharmacopoeial limit for percentage deviation is ± 5%. The percentage deviation from average tablet weight for all the tablet was found to be within the specified limits and hence all formulations complied with the test for weight variation according to the pharmacopoeial specifications IP 2007.

8.3.3. Drug content:

The drug content of all the formulation was found to be in the range from 92.4 ± 0.05 to 99.9 ± 0.05 % w/w, which was within the specified limit as per IP 2007.

8.3.4. In-vitro disintegration studies:

Table 8.14: Disintegration time of formulations (F1toF9)

Code	Disintegration time(min)
F1	29±0.57
F2	9.0±0.05
F3	8.5±0.05
F4	5.8±0.05
F5	5.5±0.05
F6	5.1±0.05
F7	8.29±0.05
F8	20±0.05
F9	5.7±0.05

8.3.5. *In-vitro* Dissolution Studies:

Table 8.15: Dissolution data of formulation F1

S.No	Dissolution Medium	Time (min)	Drug released* (%)
1	0.1N HCl	0	0.00
2		5	42.1±0.057
3		10	62.1±0.115
4		15	73.2±0.208
5		20	79.2±0.15
6		30	81.1±0.057

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

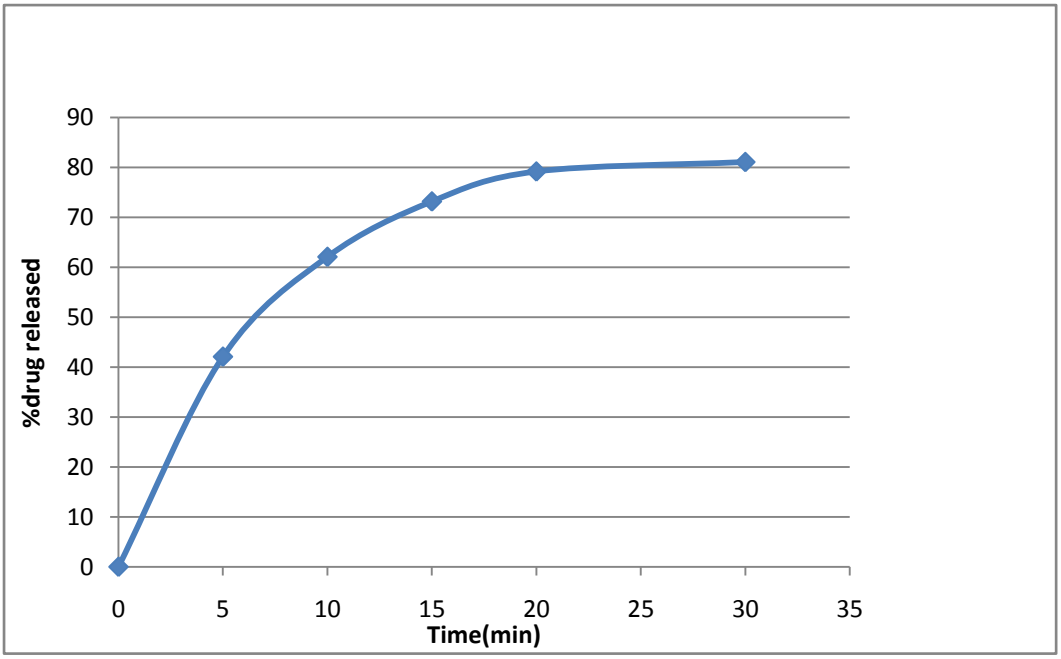


Figure 8.9*: Invitro* drug release of formulation F1

Table 8.16: dissolution data of formulation F2

S.No	Dissolution medium	Time (min)	Drug released* (%)
1	0.1N HCl	0	0.00
2		5	44.2±0.057
3		10	56.1±0.208
4		15	69.0±0.152
5		20	74.2±0.208
6		30	85.2±0.1

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

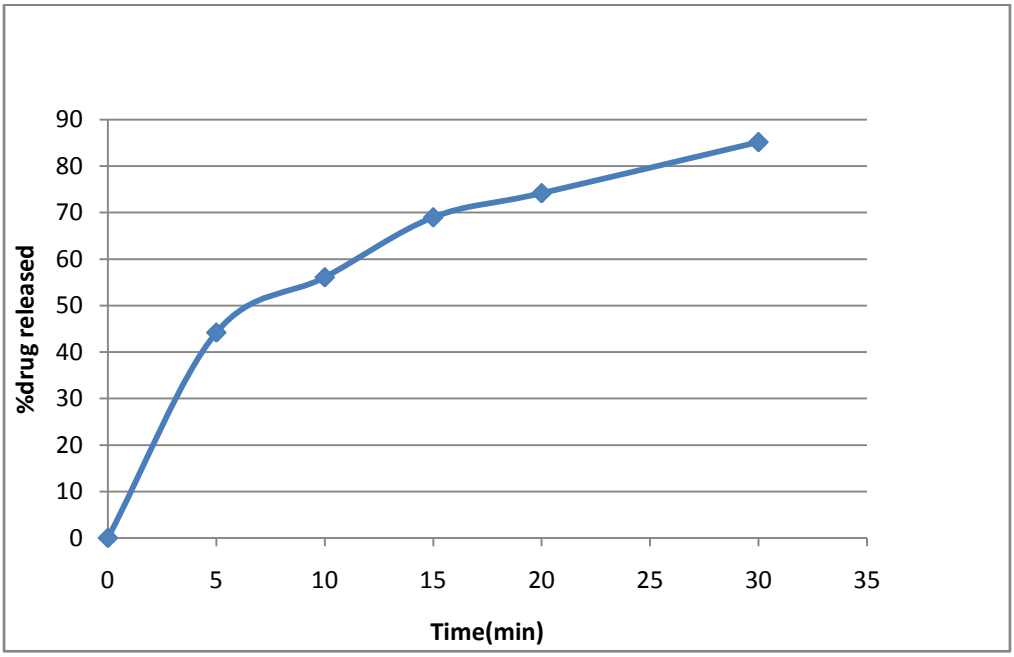


Figure 8.10: *InVitro* drug release profile of formulation F2

Table 8.17: Dissolution data of formulation F3

S.No	Dissolution medium	Time (min)	Drug released* (%)
1	0.1N HCl	0	0.00
2		5	50.6±0.55
3		10	55.2±0.057
4		15	70.5±0.585
5		20	75.1±0.781
6		30	85.2±0.057

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

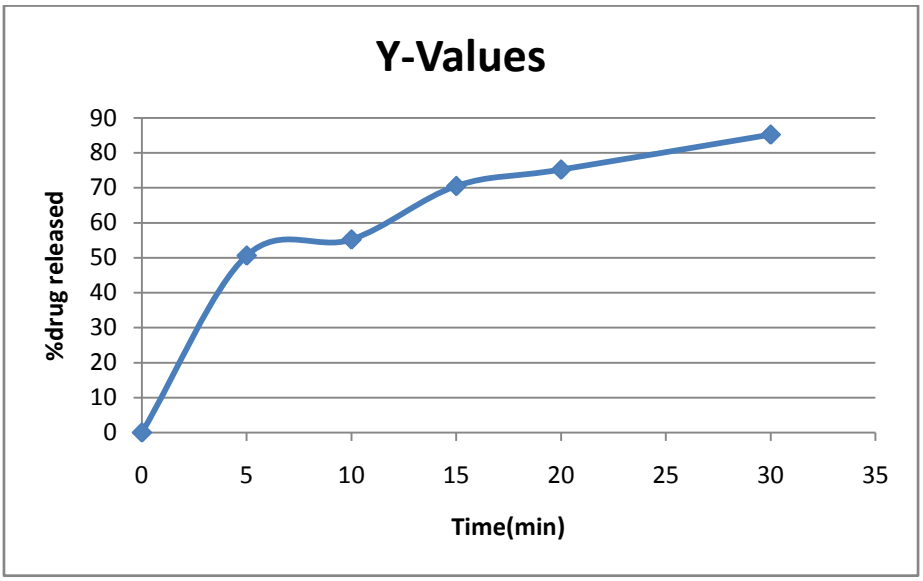


Figure 8.11: *InVitro* drug release profile of formulation F3

Table 8.18: Dissolution data of formulation F4

S.No	Dissolution medium	Time (min)	Drug released (%)
1	0.1N HCl	0	0.00
2		5	42.1±0.057
3		10	54.0±0.208
4		15	62.1±0.115
5		20	74.2±0.208
6		30	82.1±0.057

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

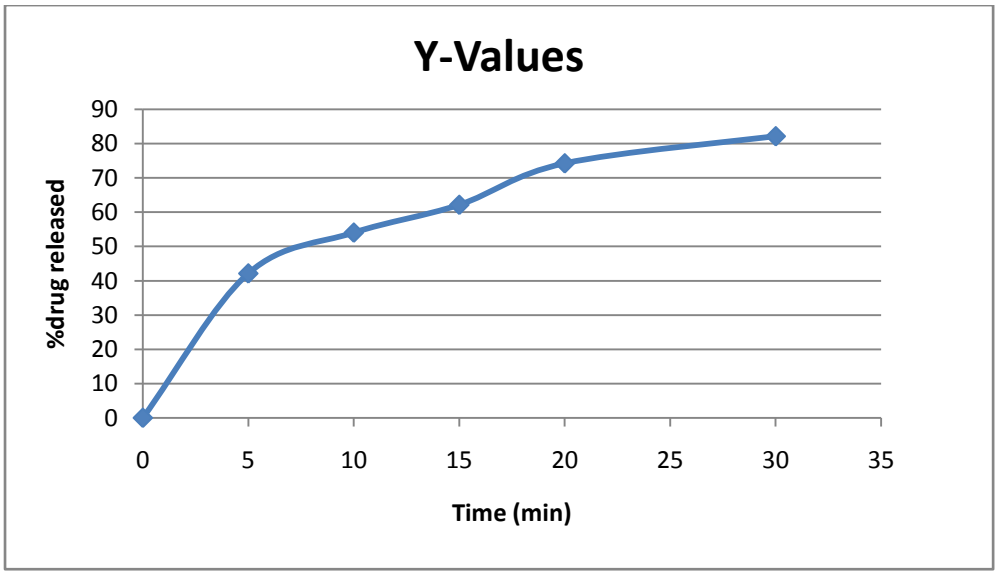


Figure 8.12: *InVitro* drug release profile of formulation F4

Table 8.19: Dissolution data of formulation F5

S.No	Dissolution medium	Time (min)	Drug released* (%)
1	0.1NHCl	0	0.00
2		5	55.3±0.208
3		10	72.6±0.351
4		15	83.5±0.10
5		20	94.6±0.450
6		30	100.1±0.1

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

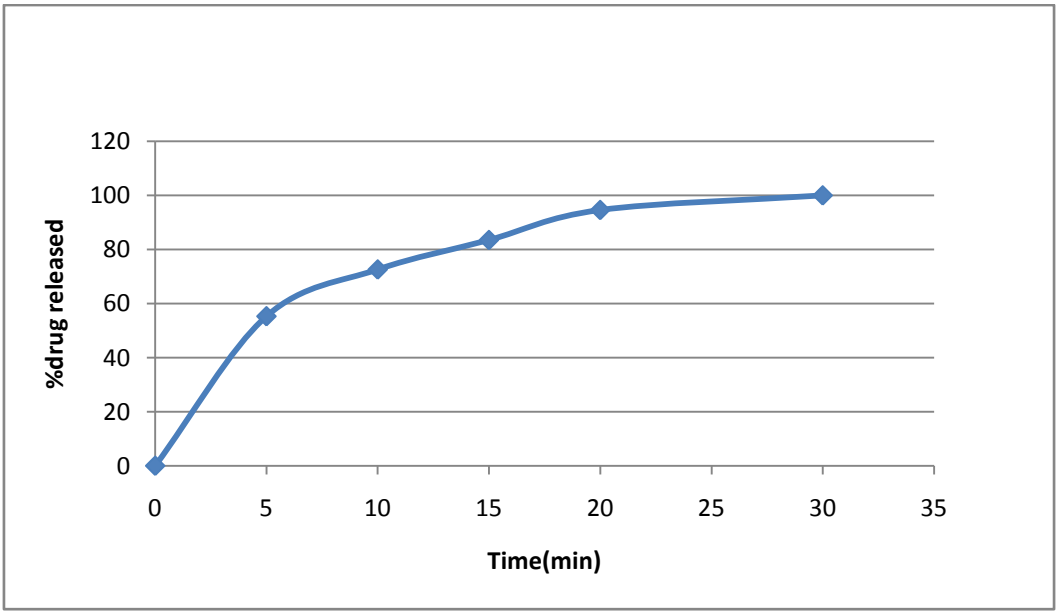


Figure 8.13: *InVitro* drug release profile of formulation F5

Table 8.20: Dissolution data of formulation F6

S.No	Dissolution medium	Time (min)	Drug released* (%)
1	0.1NHCl	0	0.00
2		5	49.1±0.152
3		10	62.2±0.152
4		15	76.1±0.208
5		20	84.2±0.057
6		30	96.9±0.493

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

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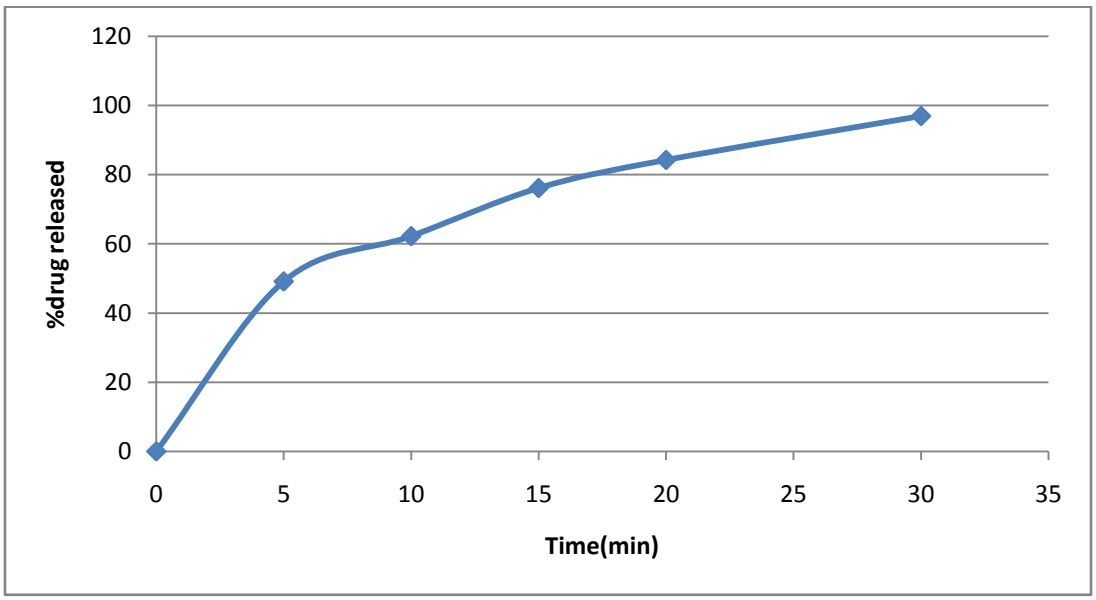

Figure 8.14: *InVitro* drug release profile of formulation F6

Table.8.21: Dissolution data of formulation F7

S.No	Dissolution medium	Time (min)	Drug released* (%)
1	0.1NHCl	0	0.00
2		5	56.2±0.208
3		10	69.1±0.152
4		15	73.1±0.208
5		20	82.1±0.057
6		30	97.1±0.115

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

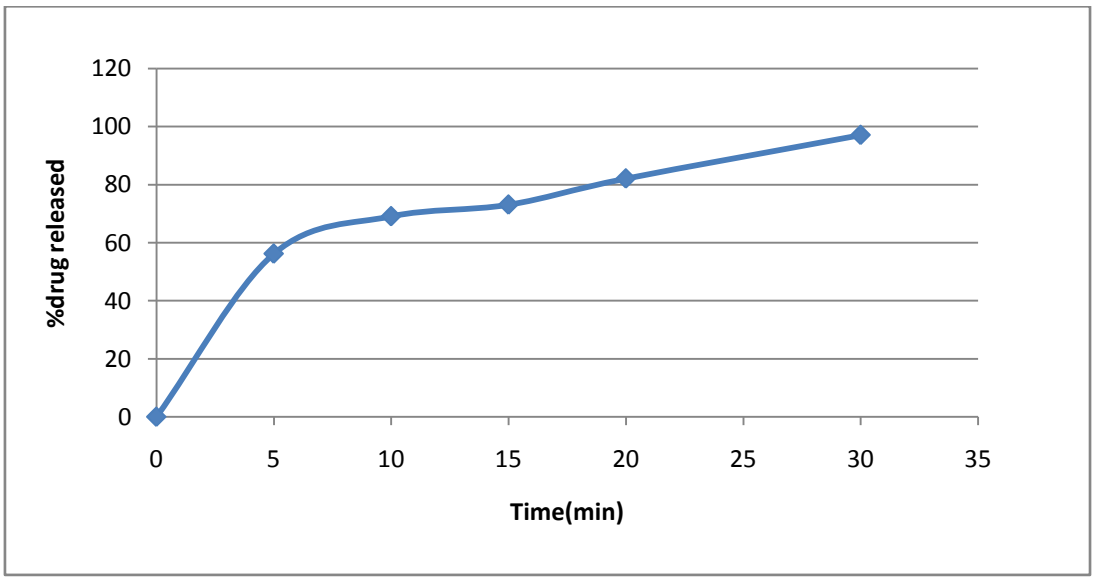

Figure 8.15: *InVitro* drug release profile of formulation F7

Table 8.22: Dissolution data of formulation F8

S.No	Dissolution medium	Time (min)	Drug released* (%)
1	0.1NHCl	0	0.00
2		5	51.2±0.057
3		10	62.2±0.152
4		15	70.5±0.152
5		20	75.2±0.057
6		30	78.3±0.152

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

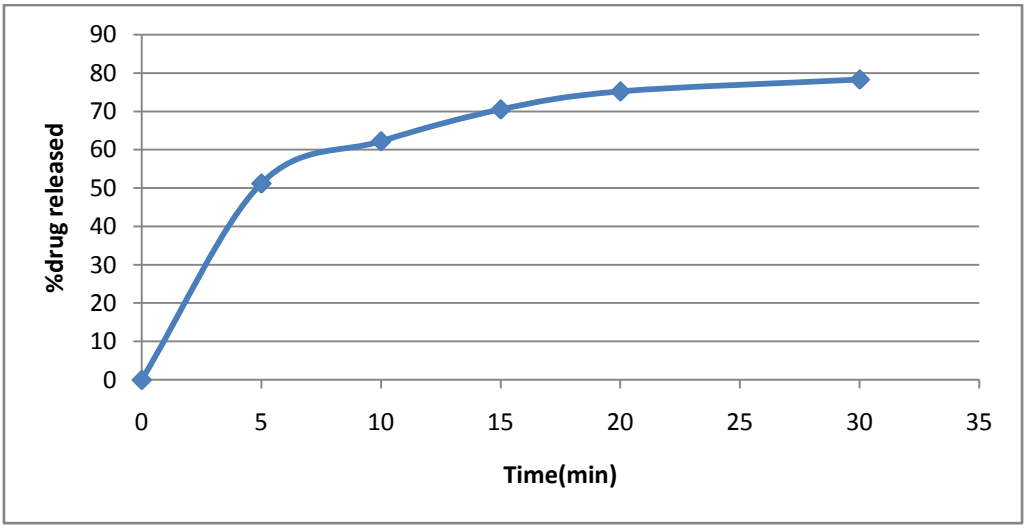

Figure 8.16: *InVitro* drug release profile of formulation F8

Table 8.23: Dissolution data of formulation F9

S.No	Dissolution medium	Time (min)	Drug released* (%)
1	0.1NHCl	0	0.00
2		5	62.1±0.115
3		10	78.1±0.115
4		15	86.1±0.1
5		20	90.1±0.057
6		30	98.1±0.1

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

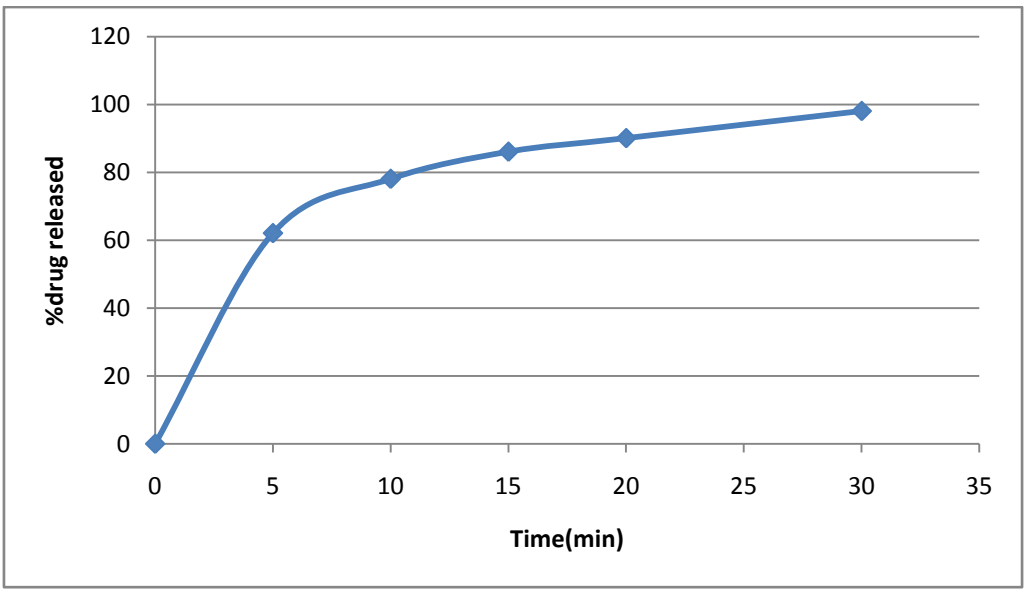

Figure 8.17: *InVitro* drug release profile of formulation F9

Table 8.24: Dissolution data of Innovater

S.No	Dissolution medium	Time (min)	Drug released* (%)
1	0.1NHCl	0	0.00
2		5	58.2±0.20
3		10	72.2±0.35
4		15	86.1±0.10
5		20	97.2±0.11
6		30	100.3±0.10

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

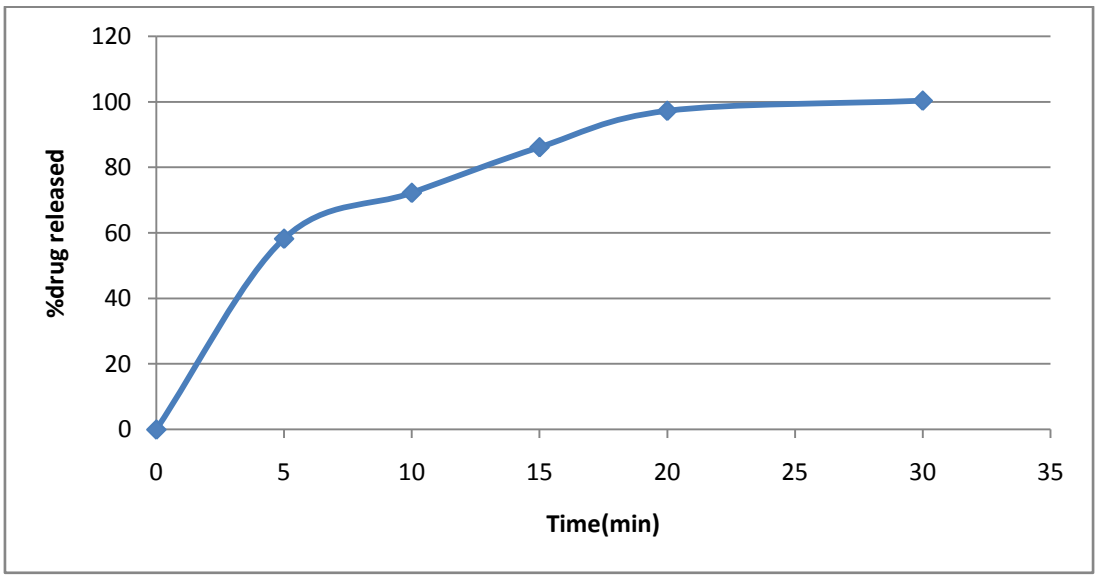

Figure 8.18: *InVitro* dissolution of innovator

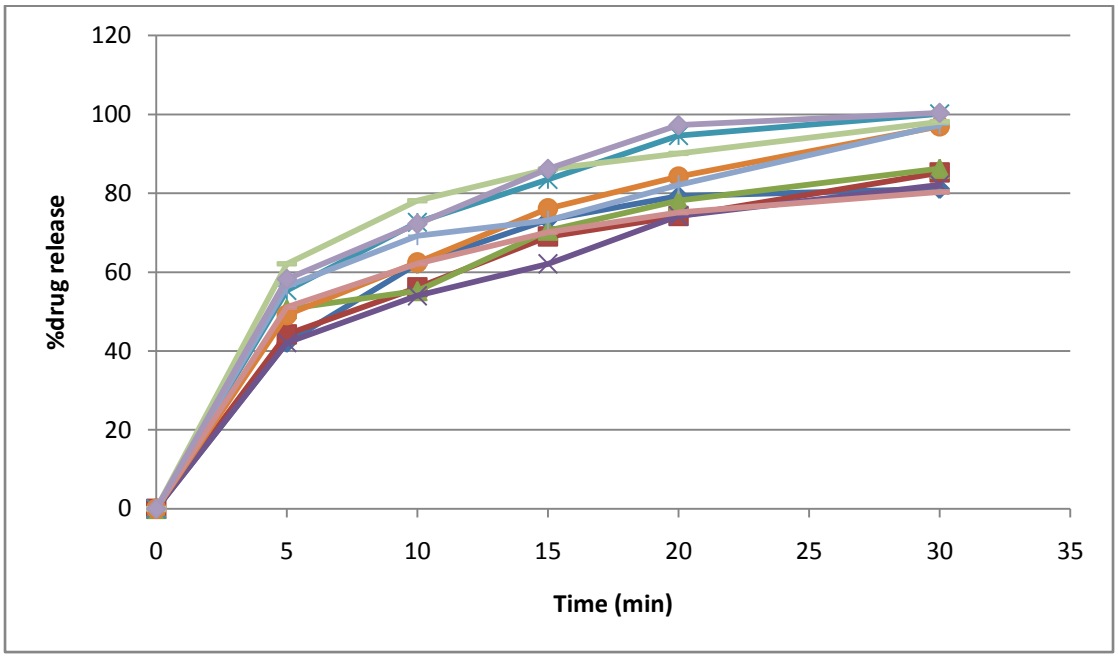

Figure 8.19: Comparision of *invitro* drug release (F1-F9)

Table 8.25**:** Time of drug release values of t_{25} , t_{50} and t_{90} for formulations (F1 to F9).

Formulation code	**Time of %Drug release(min)**		
	t25%	**t50%**	**t90%**
F1	2.96	8.05	-
F2	2.82	8.91	-
F3	2.47	9.05	-
F4	2.96	9.25	-
F5	2.26	4.52	19.02
F6	2.25	8.01	27.86
F7	2.21	7.22	27.77
F8	2.44	8.05	-
F9	2.01	8.05	27.52

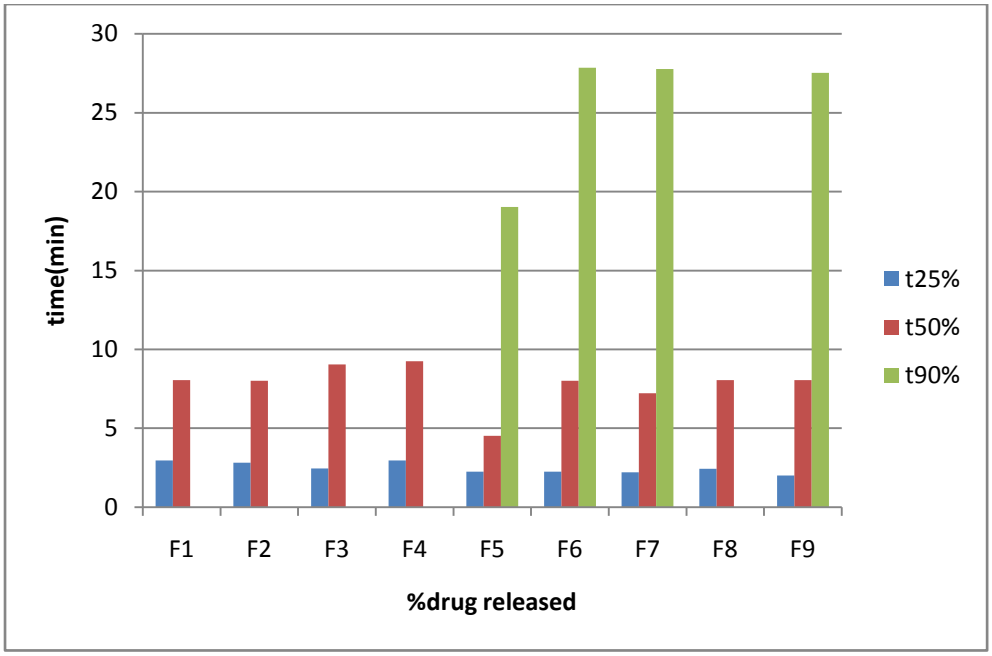

Figure 8.20:Time of drug release values of t_{25},t_{50} and t_{90} for formulations (F1 to F9).

8.4. STABILITY STUDY

After exposure to accelerated stability conditions the formulation was analyzed for various evaluation parameters.

Table 8.26:Stability studies of optimized formulation (F5).

Parameter	Initials	1 Month	2 Month	3 Month
Description	Pink coloured round shaped film coated tablet	complies	complies	Complies
Assay(%w/w)	99.9±0.05	99.6±0.01	98.6±1.02	98.1±0.98
Dissolution(%w/v)	100.1±0.95	99±0.75	97.5±1.23	96.2±1.72
Hardness(kg/cm²)	7.5±0.01	7.2±1.0	6.6±0.5	6.1±1.0
Disintegration time(min)	5.5±0.05	5.32±0.30	5.25±0.26	5.20±0.8

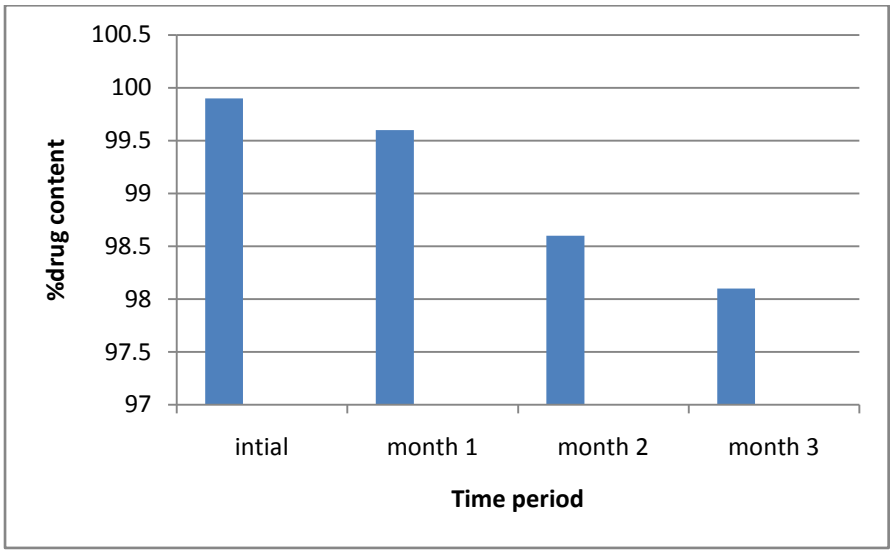

Figure 8.21:Comparision of %drug content of before and after stability studies of formulation f5

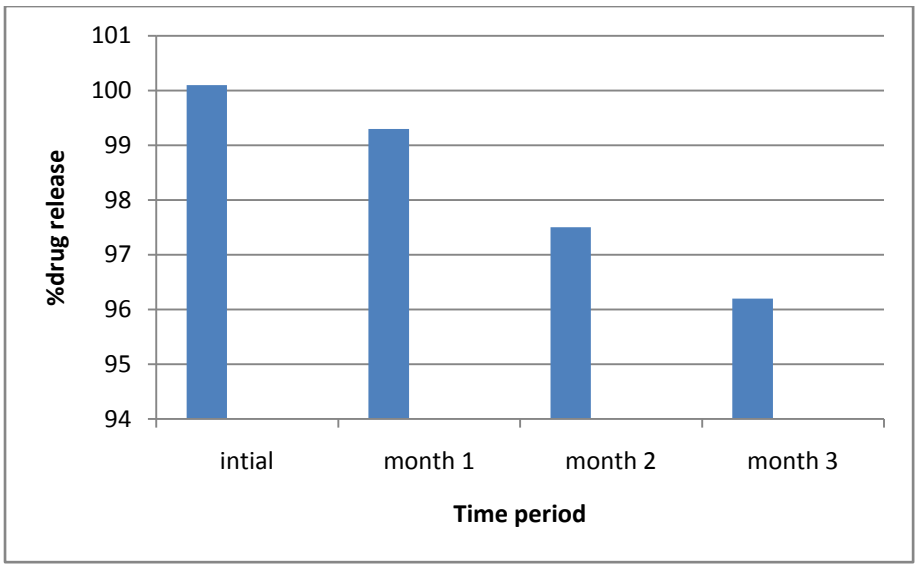

Figure 8.21:Comparision of in-vitro drug release profile of before and after stability studies of formulation f5

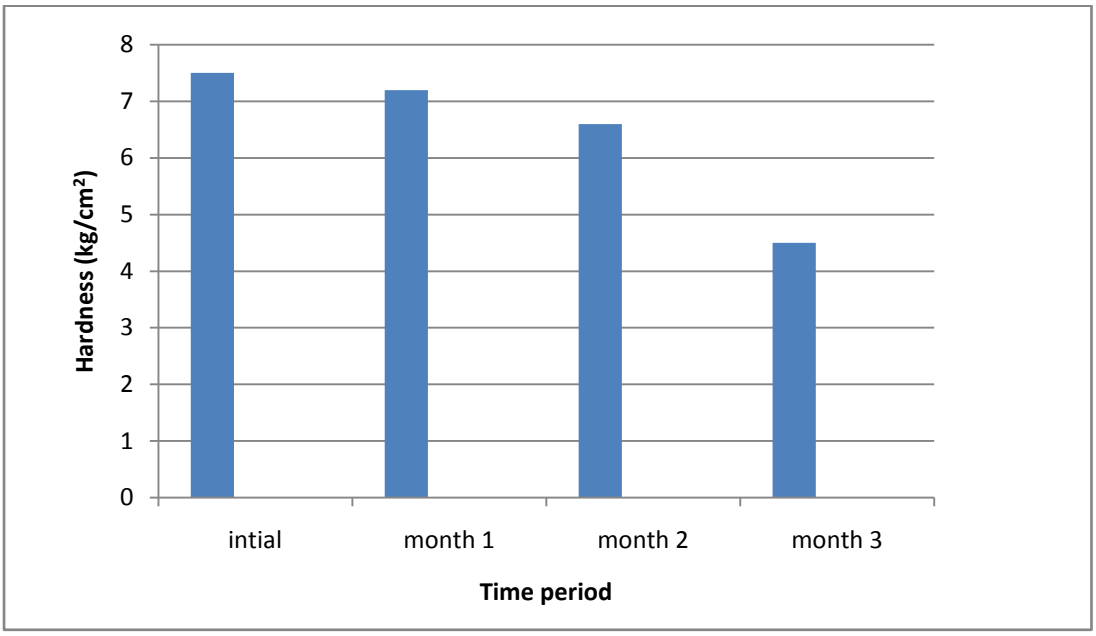

Figure 8.22:Comparision of hardness of the tablet before and after stability studies of formulation f5

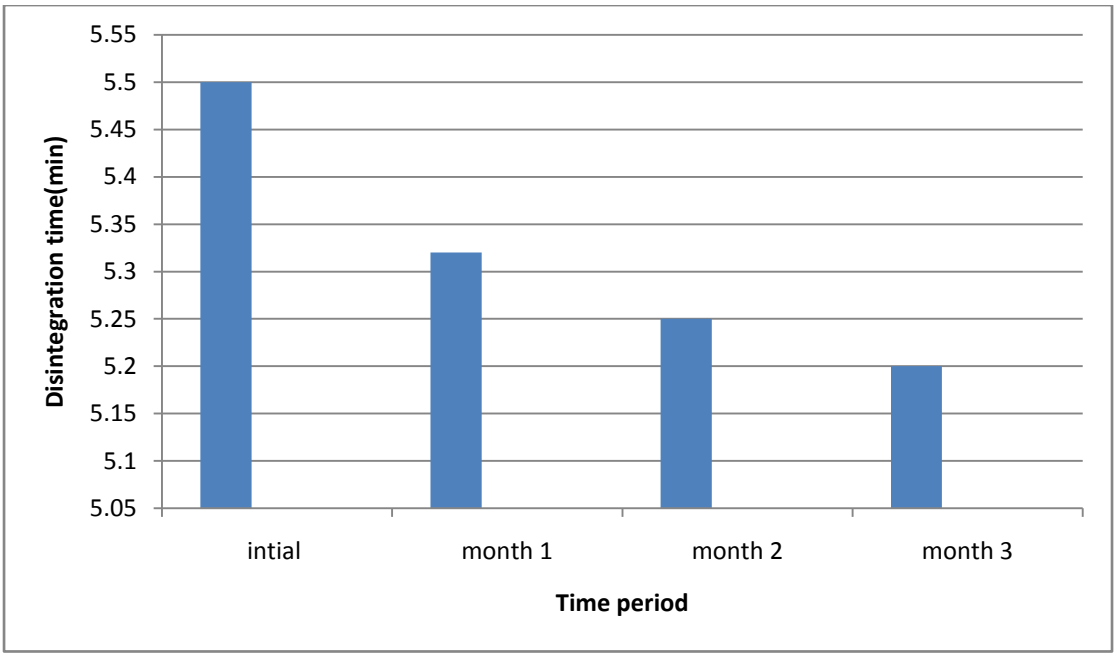

Figure 8.23:Comparision of disitntigration time of the tablet after and before stability studies of formulation f5

From the above studies there was no significant difference was initiate between the evaluated data from initial and after stability studies and all the values were found in worth accepting limit .The best formulation was showed adequate physical stability at 40 º±2ºC at 75%±5% relative humidity.

SUMMARY AND CONCLUSION

9. SUMMARY AND CONCLUSION

A Succesful immediate drug delivery system was prepared with immediate release mechanism that gives immediate on set of action, and compared with that of marketed product.

Sorafenib tosylate posses Longer half life and hence it was a good candidate for Immediate release drug delivery system. The identification of drug was carried out by HPLC and melting point. The physicochemical parameters such as appearance, solubility study were performed by suitable methods. The analytical profile of drug was evaluated for development of standard curve and percentage purity of drug. Compatibility of drug and ingredients was done by performing HPLC and DSC study. It was concluded that there was no interaction between the drug and disintegrants as the Impurities present in the drug were found unaltered in the HPLC chromatogram and peaks in the DSC thermogram of drug disintegrant physical mixture. The powder blend was prepared by blending the various ingredients in mortar and pestle for 20 min and evaluated for bulk density, tapped density, carr's index, hausner's ratio and angle of repose.

Immediate release tablet of Sorafenib tosylate was obtained by wet granulation and dry granulation method for all the formulations F1 to F9. Formulations prepared composed of , croscarmellose sodium,and sodium starch glycolate as disintegrants with other excipients like micro crystalline cellulose as diluent, HPMC E-5 as a binder, microcrystalline cellulose pH 102 as a Filler, magnesium stearate as a lubricant. The all formulations were evaluated for the appearance, hardness, percent friability, weight variation, drug content, and *In-Vitro* drug released. On the performance with respect to disintegration time and the drug release characteristics, the formulation F5 was selected as the best formulation as it is

showed a 10% disintegration time and high release as compared to marketed product. This formulation showed a Immediate release rate. And the formulation shows 100.1% release in 30 minutes.

In the present study the effect of superdisintegrants studied on *In-Vitro* disintegration time and *In-Vitro* drug release. It shows that immediate release was achieved by absorbing the water in to the tablet By the action of superdisintegrants.

The study has revealed that by interchanging the disintegrant, release rate of drug was improved and results confirmed that the release rate from tablets depends on type of disintigrant.

According to stability study it was found that there was no significant change in hardness, drug content and *In-Vitro* dissolution of optimized formulation F5.

It may be concluded that the immediate release tablets of Sorafenib tosylate was feasible and may be manufactured with reproducible characteristics with the aid of Croscarmellose sodium as super disintegrants. From the above all trials we conclude that formulation-5 obeys all the results within the Standard limits as that of innovator product. However it needs further in depth animal studies on suitable animal models with statistical clinical data for a dependable and successful pharmaceutical marketing formulation.

FUTURE PROSPECTS

10. FUTURE PROSPECTS

In the present work, the immediate release tablets of Sorafenib tosylate were prepared by wet granulation technique using different ratios disintegrants and surfactants.

In this work, only physiochemical characterization such as angle of repose, Carr's index, hausner ratio, weight variation, hardness, thickness, friability, drug content and *in vitro* evaluation of Sorafenib tosylate of immediate release tablet was performed. Along with *in vitro* studies, *in vivo* studies of drug are most important.

In future *in vivo* studies are required to set the *in vitro* - *in vivo* correlation (IVIVC) which is necessary for development of successful formulation and also long term stability studies are necessary.

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