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Formulation and Evaluation of Controlled Release Imatinib Mesylate Tablets

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1. INTRODUCTION

Cancer is a term encompassing a wide range of diseases that can affect any part of the body. It is characterized by the rapid development of abnormal cells that grow beyond their usual boundaries, invading neighboring tissues and potentially spreading to other organs through metastasis. The devastating impact of widespread metastases makes cancer one of the leading causes of death globally, accounting for nearly 10 million deaths in 2020, or approximately one in six deaths. Among the most common types of cancer are breast, lung, colon and rectum, and prostate cancers. However, skin, ovarian, pancreatic, and cervical cancers are also frequently diagnosed. The causes of cancer are diverse, ranging from genetic factors and exposure to harmful substances like tobacco and radiation to infectious agents and unhealthy lifestyles[1]. Early diagnosis and timely treatment are pivotal in improving survival rates for cancer patients. A variety of treatment options are available, including surgery, radiation therapy, chemotherapy, immunotherapy, targeted therapy, and hormone therapy. Ongoing research and advancements in the prevention, diagnosis, and treatment of cancer continue to make significant progress in combatting this complex disease.

Controlled drug delivery systems play a crucial role in the treatment of cancer. They offer several significant advantages in addressing the unique challenges associated with cancer therapy. Firstly, controlled drug delivery systems allow for targeted drug delivery directly to the tumor site. Traditional systemic chemotherapy often leads to systemic toxicity, causing adverse effects on healthy cells and tissues. By encapsulating or conjugating drugs within targeted delivery systems, such as nanoparticles or liposomes, the drug can be directed specifically to the tumor site, minimizing damage to healthy cells and reducing side effects.

Controlled drug delivery systems offer several advantages for cancer therapy:

Targeted Delivery, Sustained Drug Release, Improved Drug Stability and Solubility, Overcoming Drug Resistance ,Reduced Side Effects

Numerous methods have been devised for the development of controlled release drug delivery systems, and among them, certain techniques have gained noteworthy prominence in terms of their commercial viability.

a) Matrix based drug delivery system

b) Reservoir type delivery system

c) Gastro retentive delivery system

d) Osmotic pump delivery system

e) Multi unit particulate system

Matrix based drug delivery system

The use of matrix-based drug delivery systems, which involve readily available polymers or matrix-forming agents, is the predominant and commercially viable technique. These systems, comprising natural or synthetic materials, are favoured due to their affordability and ease of large-scale production.

Advantages of Matrix based drug delivery system

Unlike reservoir and osmotic systems, the development and manufacturing of drug delivery products based on matrix design can be carried out using existing processes and equipment without requiring additional investments. This makes matrix systems highly advantageous from a practical and cost-effective standpoint.

Limitations of matrix-based drug delivery system

Similar to other technologies, matrix systems have their own limitations. One limitation is their lack of flexibility in adjusting to varying dosage levels based on clinical study results. This often results in the need for developing a new formulation and additional resources.

There are two categories of matrix systems, which are determined by the type of materials used to form the matrix. In the case of the hydrophobic matrix system, the main components responsible for controlling the drug release rate are water-insoluble. These components include waxes, glycerides, long chain fatty acids, as well as polymers like ethyl cellulose, methyl cellulose, and acrylate copolymer. By incorporating these insoluble ingredients in the formulation, the hydrophobic matrix retains its physical structure during the release of the drug.

Hydrophilic matrix system

The matrix system can be classified into two groups based on the type of materials utilized to create the matrix. In the hydrophobic matrix system, the main components responsible for regulating the release rate of the drug are those that are insoluble in water. These components include waxes, glycerides, long chain fatty acids, and polymers like ethyl cellulose, methyl cellulose, and acrylate copolymer.

Drug release mechanism from matrix systems

The predominant factors that govern the drug release mechanism from a matrix system are primarily characterized by two phenomena.

Polymer swelling and drug release

The release mechanism in swelling-controlled release systems is greatly influenced by the design, including the composition and shape, of the delivery system. Initially, when an aqueous solution comes into contact with the matrix, the surface wets, and this wetting gradually progresses into the matrix through tiny pores.

Reservoir type delivery system

The release mechanism in swelling-controlled delivery systems heavily relies on the design, including the composition and geometry, of the system. When the matrix comes into contact with an aqueous solution, it initially becomes damp at the surface and gradually permeates the entire matrix through microscopic pores.

Swelling-controlled release systems depend greatly on the design aspects such as composition and geometry. When in contact with an aqueous solution, the matrix gradually becomes wet from the surface and permeates through microscopic pores. Liquid penetration into the matrix requires a driving force derived from pressure difference.

Gastric retention of dosage forms can be achieved through various methods, such as floatation, muco-adhesion, swellable systems, hydrodynamically balanced systems, sedimentation, and expansion modified shape systems. Among these techniques, floatation is considered the most convenient and effective approach for prolonging gastric retention. By utilizing floatation, the dosage form releases the drug at a constant rate, leading to an extended gastric residence time. Some well-known commercial products that utilize this gastric retention technology include CifranOD (Ciprofloxacin extended-release tablet), OflinOD (Ofloxacin extended-release tablet), and Glumetza (Metformin extended-release tablet).Osmotic pump delivery system.

Oral osmotically controlled release delivery systems rely on the principle of osmotic pressure to achieve controlled drug release. These systems are not influenced by factors such as pH or physiological conditions and can be tailored by optimizing the drug and system properties. Osmotic drug delivery devices consist of a drug core that is osmotically active and is surrounded by a semipermeable membrane to control the release rate.

Multiunit particulate systems

Multiunit particulate systems (MUPS) have emerged as an innovative technique for controlled and modified drug delivery, aiming to overcome certain drawbacks associated with matrix systems. MUPS offer several advantages compared to other systems, including a reduced risk of local irritation and toxicity, minimized chances of dose dumping, and the ability to administer high dose strengths. Multiparticulate systems also exhibit more consistent pharmacokinetic behavior.

Pelletization process

Each discrete particle of any MUPS is prepared as pellets using different techniques such as

a) Drug suspension layering on inert substrate

b) Drug powder layering on inert substrate

c) Direct pelletization

d) Drug powder compaction/milling

e) Extrusion spheronization

MUPS (multiunit particulate systems) have emerged as a novel technique for controlled and modified drug delivery, offering advantages over matrix systems. These advantages include reduced risk of local irritation and toxicity, decreased likelihood of dose dumping, and the ability to administer high doses. MUPS also exhibit more consistent pharmacokinetic behavior compared to other systems.

Drug suspension layering on inert substrate

During the layering process, successive layers of drug entities are applied onto nuclei, which can be crystals or inert starter seeds. This can be done using a solution, suspension, or dry powder. In solution/suspension layering, the drug particles are mixed with a binding liquid.

Drug powder layering on inert substrate

In the powder drug layering technique, a binder solution is sprayed onto pre-prepared inert seeds, and then powder is added. This process has been traditionally carried out using conventional pan coaters since the early stages of drug layering pelletization.

Direct pelletization

The process of powder drug layering entails applying a binder solution onto inert seeds that have been prepared beforehand, and subsequently adding powder. This technique has been commonly executed using conventional pan coaters since the inception of drug layering pelletization.

Drug powder compaction/milling

This compaction technique is utilized to produce pellets with specific sizes and shapes. It involves applying pressure to a mixture of active ingredients and excipients to form the pellets. The quality of the resulting pellets is controlled by similar factors used in tablet manufacturing, including formulation and process variables.

Extrusion and spheronization

The manufacturing of pharmaceutical pellets typically involves the use of extrusion spheronization, a process introduced in the late 1960s. This three-step process produces spherical granules with a diameter of around 1 mm. Wet mass extrusion spheronization, commonly referred to as cold-mass extrusion spheronization, is the preferred method. It allows for the creation of uniform and dense spherical pellets through a series of specific steps.

Dry mixing

Homogeneous dispersion of powdered ingredients is achieved by utilizing suitable blenders or mixers for the process of dry mixing.

Wet massing

In order to create a sufficiently cohesive mass for extrusion, the technique of wet massing is employed. This involves using standard equipment and processes typically utilized in wet granulation. The planetary mixer, Hobart mixer, sigma blade mixer, or high shear granulator are commonly employed for this purpose.

Extrusion

To create a sufficiently malleable mass for extrusion, wet massing is carried out using conventional equipment and procedures used in wet granulation. Planetary mixers, Hobart mixers, sigma blade mixers, and high shear granulators are commonly utilized as granulators during the wet massing process.

Spheronization

Extrusion, as the third step in the process, involves transforming the wet mass into cylindrical particles with a consistent diameter. This is achieved by forcing the wet mass through dies, shaping it into long rod-like structures called "extrudate." The extrudate particles are then fractured into similar lengths by their own weight.

Drying

In order to reach the targeted moisture content, it is essential to include a drying stage. The drying rate plays a crucial role, as a higher rate can lead to more porous pellets by minimizing pellet densification during the drying process. The pellets can be dried either at room temperature or at an elevated temperature using equipment such as a tray dryer, oven, or fluidized bed dryer.

Screening

Sieving is performed to achieve the desired size distribution of pellets, thus avoiding high polydispersity index. This is achieved by using sieves. Alongside the conventional techniques mentioned earlier, there are also a few other methods utilized in pharmaceutical pellet production, albeit on a limited scale. These alternative methods include melt pelletization, globulation, balling, and compression.

2. MATERIALS AND METHODS

DRUG PROFILE:

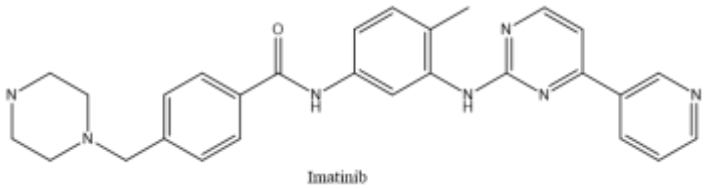

Fig-4.1: Structure of Imatinib mesylate

IUPAC NAME:

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

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

Molecular Weight: 493.6

Melting Point: 221 228 °C

Boiling Point: 754.9 °C

log P: 4.38

pKa: 1.52 ,2.56 ,3.73 ,8.07

Solubility: Soluble in water, DMSO and sparingly soluble in ethanol.

Trade name: Gleevec

Dose: 100 – 400mg per day

Half Life: 18 – 40 hours

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

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

Mechanism of action: Imatinib works by binding close to the ATP binding site, locking it in a closed or self-inhibited conformation, therefore, inhibiting the enzyme activity of the protein semi competitively.

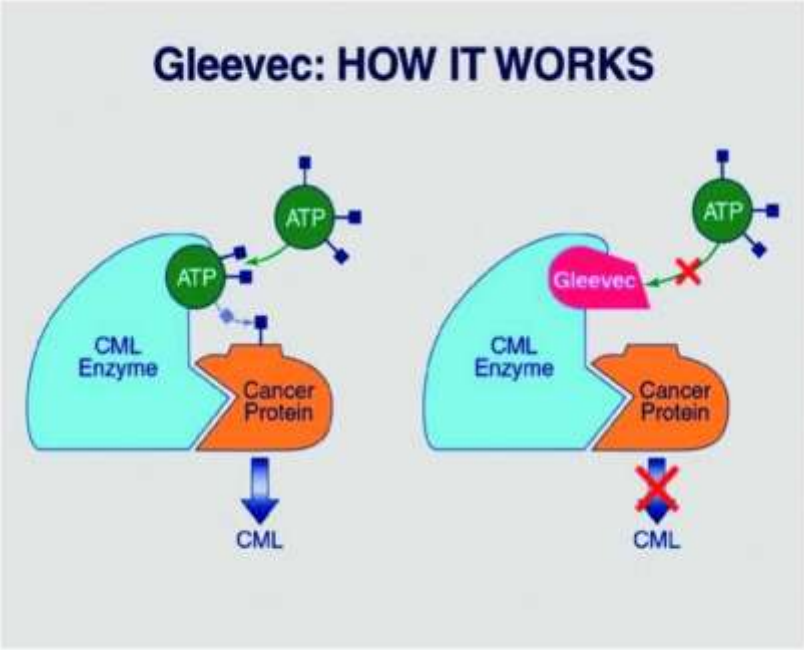

Fig-4.2: Mechanism of action of of Imatinib mesylate

METHODOLOGY

1. DETERMINATION OF λ MAX :

A solution of imatinib mesylate with a concentration of 10 µg/ml using 0.1N HCl, the UV spectrum of the solution was examined using a UV carywin (UV-1800) double beam spectrophotometer. The spectrophotometer was set up correctly, and a quartz cell containing the imatinib mesylate solution was positioned in the sample holder. By initiating the spectrophotometer software, the scanning process was carried out, resulting in a UV spectrum data file that was subsequently analysed. The wavelength associated with the highest absorbance was determined, and the intensity of absorbance at that wavelength was recorded. To validate the obtained UV spectrum, it was compared to a reference spectrum or literature data[15]. Additionally, any notable characteristics or deviations in the UV spectrum were observed and documented. The adherence to Beer-Lambert's Law, the linearity of the spectrum, and the presence of potential interference or impurities were also considered. All observations and findings resulting from this UV spectrum analysis were documented, providing valuable information about the imatinib mesylate solution for further analysis purposes.

STANDARD CALIBRATION OF IMATINIB MESYLATE:

To construct a standard curve for imatinib mesylate, a series of steps were followed. Initially, 100mg of imatinib mesylate was precisely weighed using an accurate balance. The imatinib mesylate was then dissolved in a solution of 0.1N HCl, resulting in a stock solution with a concentration of 1000 µg/ml. Thorough mixing ensured complete dissolution of the compound. From the stock solution, a solution with a concentration of 100 µg/ml was prepared by diluting the appropriate volume with a 0.1N HCl. Subsequently, dilutions were prepared from the 100 µg/ml solution to obtain concentrations of 2, 4, 6, 8, and 10 µg/ml. Using a UV-spectrophotometer set at a wavelength of 210nm and a pH 6.8 phosphate buffer as a reference blank, the absorbance of each diluted solution was measured and recorded. By plotting a standard curve with concentrations on the x-axis and absorbance on the y-axis, a functional relationship between concentration and absorbance was established. This standard curve can now be utilized to determine the concentration of imatinib mesylate in unknown samples by measuring their absorbance and aligning it with the curve. Throughout the process, caution was exercised in handling imatinib mesylate and operating the spectrophotometer in adherence to safety guidelines and relevant safety data sheets (SDSs).

MANUFACTURING PROCEDURE

Table-4.1: FORMULATION DEVELOPMENT TRIALS OF IMATINIB MESYLATE CONTROLLED RELEASE TABLETS

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Imatinib Mesylate IP	100	100	100	100	100	100	100	100	100	100
Microcrystalline Cellulose (101) USP/Ph. Eur.	92	72	52	32	92	72	52	32	32	32
Hydroxy propyl methyl cellulose (E-15) USP/Ph. Eur.	20	40	60	80					40	20
Hydroxy propyl methyl cellulose (K-100)					20	40	60	80	40	60
Purified water 1H	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Colloidal silicon dioxide Ph.Eur/BP/USP	3	3	3	3	3	3	3	3	3	3
Magnesium Stearate Ph. Eur./BP/USP	2	2	2	2	2	2	2	2	2	2
Opadry Brown	33	33	33	33	33	33	33	33	33	33

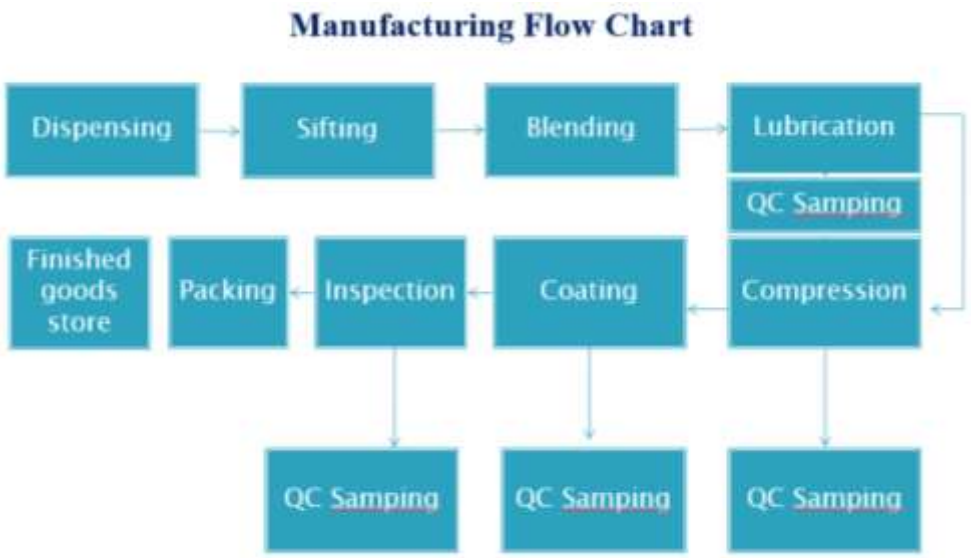

Fig-4.3: Manufacturing Process

Dispensing:

Dispense all the ingredients needed for the lubricated blend as per the requirements of the batch size and record the weights and other details, follow these steps:

1. Review the batch size and requirements specified in the formulation or production plan.

2. Collect all necessary ingredients for the lubricated blend, including lubricant(s) and base material(s).

3. Set up the weighing scale and ensure it is calibrated and accurate.

4. Obtain the appropriate containers or bags to hold the lubricated blend.

5. Weigh the empty container or bag and record its tare weight.

6. Place the container or bag on the weighing scale and set the scale to zero to account for the tare weight.

7. Add the required amount of ingredients to the container or bag, ensuring accuracy by checking the weight on the scale.

Sifting

1. Prepare the sifting equipment, ensuring it is clean and in proper working condition. This may include using a vibrating sieve or a mechanical sifter, depending on the specific requirements of the lubricated blend.

2. Transfer the lubricated blend to the sieve or sifter, ensuring that the quantity matches the desired batch size.

3. Start the sifting equipment and adjust the settings for optimal sifting efficiency. This may include adjusting the vibration intensity or the speed of the sifter.

4. Allow the lubricated blend to pass through the sieve or sifter, which will help remove any oversized particles, agglomerates, or foreign matter.

5. Monitor the sifting process closely to ensure that the desired particle size distribution is achieved.

6. Collect the sifted lubricated blend in a clean and suitable container for further processing or packaging.

7. Inspect the sifted lubricated blend to ensure it meets the required specifications and quality standards.

8. Label the container with necessary information, such as batch number, date, and any other relevant details.

9. Proceed with the next steps of the manufacturing process using the sifted lubricated blend as per the specific requirements.

Blending

1. The sifted lubricated blend is further mixed to get homogenous blend.

2. Ensure that the blending equipment, such as a blender or mixer, is clean and in good working condition.

3. Measure and weigh the ingredients accurately, following the specified quantities or ratios.

4. Place the ingredients into the blending equipment, taking care to add them in the correct order if applicable.

5. Start the blending equipment and adjust the speed or settings as needed for thorough mixing.

6. Allow the ingredients to blend for the specified time or until a uniform mixture is achieved.

7. Monitor the blending process to ensure that all ingredients are evenly distributed and properly incorporated.

8. If necessary, periodically stop the blending equipment to scrape down the sides of the container and ensure complete blending.

9. Once blending is complete, check the blend for any lumps, clumps, or inconsistencies. If present, remix or further blend to achieve a smooth and homogeneous mixture.

10. Transfer the blended mixture to a clean and suitable container for further processing or packaging.

11. Label the container with necessary information, such as batch number, date, and any other relevant details.

12. Store the blended mixture in a designated area, following any specific storage instructions or requirements.

13. Document the blending process, including the ingredients used, blending time, and any observations or deviations.

Fig-4.4: Rapid Granulator Mixer

Lubrication

1. Mix or blend the lubricant with the all the ingredients thoroughly, using appropriate equipment or techniques specified for the particular blend.

2. Weigh the filled container or bag, including the lubricated blend, and record its gross weight.

3. Calculate the net weight of the lubricated blend by subtracting the tare weight from the gross weight.

4. Record the net weight, along with other necessary details such as batch number, date, operator initials, and any additional relevant information specified.

5. Label the container or bag with the appropriate identification and storage instructions, if applicable.

6. Store the lubricated blend in the designated area or transfer it to the next step in the production process.

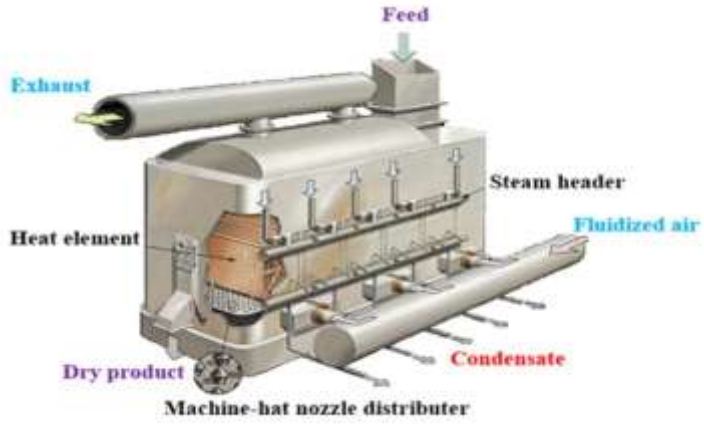

Fig-4.5: Fluidized Bed Dryer

Compression:

1. Lubricated blend has been properly checked and dispensed according to the required batch size.

2. Set up the compression machine with the designated tooling that is specifically specified for this process.

3. Refer to the provided table or documentation for the parameters required for compression. This may include information on compression force, speed, dwell time, and any other relevant settings.

4. Adjust the compression machine settings according to the specified parameters.

5. Inspect and prepare the tooling, ensuring that it is clean, in good condition, and properly aligned with the compression machine.

6. Load the lubricated blend into the compression machine using the appropriate feeding system or method. Ensure that the amount of lubricated blend loaded corresponds to the batch size and requirements.

7. Start the compression process, following the established procedures and safety protocols. Monitor the compression machine and the quality of the compression throughout the process.

8. Record the compression parameters used, including the compression force, speed, and any other relevant details.

13. Continue the compression process until the desired compression quality or tablet specifications are achieved.

14. Upon completion of the compression process, inspect and collect the compressed tablets for further processing or packaging as required. The lubricated blend was compressed by using the below specified tooling at parameters as defined in the table.

Table-4.2: Tooling Parameters

Type of Punch / Die	**Specification**
Upper Punch	19X8 mm oval shaped concave punches embossed with "SPAL' and having score line
Lower Punch	19X8 mm oval shaped concave punches embossed with “100 - 400”
Die	19X8 mm oval shape

Fill the hopper with Lubricated blend in compression machine. Adjust the machine and compress the lubricated blend and collect the tablets.

Fig-4.6: Compression Machine

Compressed tablets dedusting and Metal detection

1. Pass the compressed tablets through deduster and metal detector.
2. After completion of the dedusting and metal detection collect the compressed tablets into double layered polythene bag.

Coating

Coating suspension preparation

1. In the coating solution preparation tank, disperse the specified amount of Opadry Brown into purified water. Stir the mixture for 45 minutes or until a uniform and homogeneous solution is achieved. The dispersion should have an approximate solid content of 15% w/v.

2. Continuously stir the coating solution throughout the operation to ensure proper mixing and consistency.

6. Once the desired result is achieved, turn off the heaters and allow the pan to rotate for 15 minutes to cool the tablets down to room temperature.

7. Transfer the coated tablets into stainless steel containers lined with double polythene for storage or further processing.

Fig-4.7: Ganson Coater

EVALUATION OF PRECOMPRESSION PARAMETERS:

1. Angle of Repose

In preformulation studies of tablets, the angle of repose is an important parameter that is measured to assess the flowability and compressibility of the powdered materials used in tablet formulation. The angle of repose provides an indication of how easily the powder particles can flow and pack together during the tablet manufacturing process. To determine the angle of repose, a cone-shaped pile of the powdered material is formed on a flat surface. The height and base diameter of the pile are measured, and the tangent of the heap angle is calculated using these measurements. If a powder has a high angle of repose indicating poor flowability, additional measures like the addition of flow enhancers or optimization of particle size distribution may be necessary to improve flow properties and tablet manufacturing efficiency.

Angle of repose was determined by the fixed funnel and free-standing cone method. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane.

Tan θ = (h/r) ; θ = tan-1 (h/r)

Where ‟ h‟ is the height of the cone , "r‟ is the radius of the pile.

2. Bulk Density

The bulk density (ρb) of the blend is determined by pouring the blend into a graduated cylinder and calculating the weight (M) of the powder and the bulk volume (Vb). The formula $\rho b = M / Vb$ is used to determine the bulk density. This calculation allows for understanding the compactness of the powder and its flow and packing abilities.

$$\rho_b = M/V_b$$

Where,

ρb=BulkDensity

M = Sample weight in grams

Vb=Finalblendvolumeincm^3

3. Tapped Density

The tapped density is determined by measuring the ratio of the total mass of the powder to the volume of the powder after it has been tapped. This tapping process involves repeatedly tapping the powder,

100 times, to determine the tapped volume. The tapped density is calculated by dividing the total mass of the powder by the tapped volume using the provided formula. Tapped density is a valuable parameter used to evaluate the packing and compaction behavior, as well as the flow characteristics of powders in industries such as pharmaceutical formulation and tablet manufacturing.

Where,

$$\rho_t = M/V_t$$

Pt=TappedDensity

M=Sampleweightingrams

Vt=Tappedblendvolumeincm^3.

CompressibilityIndexandHausner'sRatio: The compressibility index and Hausner's ratio of a powder can be determined by measuring both its bulk density and tapped density. The compressibility index, also known as Carr's index, indicates the powder's ability to decrease in volume when subjected to pressure. It is calculated by dividing the difference between the tapped density and bulk density by the tapped density, and multiplying by 100. The lower the compressibility index, the better the powder's flowability and compressibility.

Hausner's ratio, on the other hand, is a measure of the powder's interparticulate friction and cohesion. It is calculated by dividing the tapped density by the bulk density. A lower Hausner's ratio indicates good flowability, while a higher ratio suggests poorer flow properties and increased interparticulate friction.

By assessing both the compressibility index and Hausner's ratio, valuable insights can be gathered about the powder's flow and compaction characteristics, which are crucial for industries like pharmaceuticals that heavily rely on powder processing and formulation[19].

$$\text{CompressibilityIndex} = \text{Tapped Density} - \text{Bulk Density}/\text{Tapped Density} \times 100$$

Basic methods for determining the Compressibility Index and Hausner's Ratio: The procedure for determining the compressibility index and Hausner's ratio involves measuring the initial unsettled apparent volume (Vo) and the final tapped volume (Vf) of the powder. The powder is tapped repeatedly until there are no further volume changes. Based on these measurements, the compressibility index and Hausner's ratio can be calculated.

$$\text{Hausner's Ratio} = \text{TappedDensity}/\text{BulkDensity}$$

Evaluation of Post compression parameters

Appearance: Appearance is a critical organoleptic property that refers to the visual characteristics of a product. It encompasses various aspects that can influence consumer perception and purchasing decisions. When evaluating the appearance of a product, several factors are typically considered:

1. Color

2. Shape

3. Texture

4. Surface characteristics

5. Clarity and transparency

6. Packaging:

7. Visual defects

%Weight Variation:

To assess the weight variation of tablets, a representative sample of 20 tablets from each formulation is randomly selected. Each tablet is weighed individually to determine its weight. The US Pharmacopeia (USP) sets specific guidelines for acceptable weight variation in tablets. These guidelines aim to ensure consistency and uniformity in tablet manufacturing. The USP limits for weight variation vary depending on the tablet strength and weight. It defines different maximum allowable ranges of variation based on the tablet's label claim. The percentage weight variation calculation involves comparing the individual tablet weights to the average weight of the sample.

The formula for calculating the percentage weight variation is:

% Weight Variation = ((Individual Tablet Weight - Average Tablet Weight) / Average Tablet Weight) × 100

If the individual tablet weights fall within the specified USP limits, the weight variation is considered acceptable. However, if the weights deviate beyond the allowed ranges, further investigation and corrective measures might be required to rectify the issue and ensure compliance with the USP guidelines.

Table-4.3:%Weight variation limits for Tablets(USP)

Average weight of a Tablet (USP Standards)	**Percentage deviation**
130mg(or)less	10
Morethan130mg andlessthan324mg	7.5
324mg(or)more	5

Uniformity of Thickness:

PharmaG automatic thickness tester to measure the thickness of six tablets randomly selected from each formulation. The measurements were taken in millimeters and the standard deviation was calculated. This allowed us to assess the variability in tablet thickness within each formulation. The standard deviation helps determine how much the thickness measurements deviated from the average thickness, indicating the level of variation among the tablets in each formulation. This analysis helps ensure the uniformity and consistency of tablet thickness, meeting quality control requirements.

Hardness:

The hardness of tablets, which indicates their resistance to mechanical shocks during handling, was assessed using a PharmaG Automatic Hardness tester. Measured in Kp (kiloPascal), the hardness values of six randomly chosen tablets from each formulation were determined by the hardness tester.

Friability:

The Roche friabilator was employed to measure the friability of tablets, with the results expressed as a percentage. Tablets weighing less than 650mg were treated as intact tablets, initially weighed (Winitial) to be approximately 6.5g, and then placed into the friabilator according to the USP guidelines. The friabilator functioned at a speed of 25rpm for a duration of 4 minutes, resulting in approximately 100 revolutions. Following this process, the tablets' final weight (Wfinal) was documented[21].

By comparing the initial and final weights, the extent of tablet friability can be determined. This data plays a crucial role in evaluating the tablets' ability to endure abrasion and potential damage during various stages such as handling, transportation, and packaging. It ensures that the tablets retain their integrity and quality throughout their shelflife.

The percentage friability was then determined as:

$$\%Friability=Winitial–Wfinal/Winitial*100$$

Disintegration time:

Disintegration refers to the process of breaking down a tablet into smaller particles. To determine the in-vitro disintegration time of a tablet, an I.P-specified disintegration test apparatus was used. In this test, one tablet was placed in each of the six tubes of the apparatus. The tubes were filled with a disc and the apparatus was operated using a pH 6.8 phosphate buffer as the immersion liquid. The temperature of the buffer was maintained at 37±2ºC throughout the test. During the test, the assembly of the apparatus was raised and lowered 30 times per minute in the pH 6.8 phosphate buffer. This continuous movement and immersion ensured consistent conditions for disintegration.

The time, measured in seconds, that it took for the tablet to completely disintegrate with no noticeable mass remaining in the apparatus was recorded. This measurement provides valuable information about the tablet's ability to break down effectively and release its active ingredients within a specific time[22].

Invitro Dissolution testing

In vitro dissolution testing is used to determine the dissolution characteristics of controlled-release tablets. It is conducted using dissolution apparatus and media that mimic the conditions in the gastrointestinal tract.

1. Equipment and materials required:

- Dissolution apparatus USP apparatus II

- Dissolution vessels

- Dissolution media (e.g., simulated gastric fluid, simulated intestinal fluid)

- Temperature-controlled water bath

- Paddles

- Sampling tools

- Analytical instruments (e.g., UV spectrophotometer, HPLC system) for drug quantification

2. Preparing dissolution media:

Prepare the appropriate dissolution media according to the specified compendial or regulatory guidelines. Adjust the pH, temperature, and other parameters as required.

3. Testing procedure:

Place the tablets in the dissolution vessels, ensuring proper positioning and avoiding any agglomeration.Start the dissolution apparatus and adjust the stirring speed as recommended in the compendial or regulatory guidelines (typically between 50-100 rpm). Maintain the dissolution media at the specified temperature (e.g., 37°C) throughout the testing. Obtain samples at predetermined time intervals (e.g., 15 minutes, 30 minutes, 1 hour, etc.) for drug release analysis. Replace the withdrawn samples with an equal volume of fresh dissolution media to maintain sink conditions and ensure accurate drug release determination. Continue the dissolution testing for the required duration (following compendial or regulatory guidelines).

4. Drug release analysis:

Analyze the collected samples using an appropriate analytical technique (e.g., UV spectrophotometry, HPLC). Calculate the cumulative drug release at each time interval and plot a dissolution profile.

Table-4.4:Dissolution Parameters for Acid Stage

Medium	0.1NHCl
Volume	300mL
Apparatus	USP TypeII(Paddle)
RPM	100
Time	120 minutes
Temperature	37ºC±0.5ºC

Table-4.5:Dissolution Parameters for Buffer Stage

Medium	DibasicSodiumphosphate,Buffer,pH6.8
Volume	To300mLof0.1N HCladd700mLofBuffermedium
Apparatus	USP TypeII(Paddle)
RPM	100
Time	60 minutes
Temperature	37ºC±0.5ºC

Preparation of Acid Stage Medium(0.1NHCl):

Mix 8.5 mL of hydrochloric acid with water and dilute the mixture to a final volume of 1000 mL. Ensure thorough mixing of the solution.

Preparation of Buffer Stage Medium(0.086M Sodium phosphate):

Precisely measure and add 12.2g of dibasic sodium phosphate into 1000mL of water. Mix the solution thoroughly. In a separate container, combine 300mL of 0.1N hydrochloric acid (HCl) with 700mL of buffer medium consisting of 0.086 M dibasic sodium phosphate. The pH of this solution should be maintained at 6.80 ± 0.05. If required, adjust the pH by adding 2N hydrochloric acid (HCl) or 2N sodium hydroxide (NaOH).

Preparation of Imatinib Mesylate Standard Stock Solution (about 1000 ppm):

Weigh and transfer about 25 mg of Imatinib Mesylate standard into a 25 mL volumetric flask, add about 10 mL of diluent, sonicate for 5 minutes and make up the volume with diluent.

Preparation of Imatinib Mesylate Standard Solution (about 100 ppm):

Pipette out 2 mL of Imatinib Mesylate standard stock solution in a 20 mL volumetric flask, and make up the volume with diluent and mix well.

Test preparation:

- Weigh and transfer 5 tablets and crush to a fine powder in a motor with pestle.
- Weigh powder containing equivalent to 500 mg of Imatinib Mesylate and transfer to a 250 mL volumetric flask, add 190 mL of diluent and sonicate for 1hour 30 min. Then make up the volume with diluent and mix well. Centrifuge the above solution at 5000 rpm for 5 minutes.
- Pipette out 5 mL of above supernatant liquid and transfer to a 100 mL volumetric flask, make up the volume with diluent and mix well. Filter through 0.45 µm nylon syringe filter.

Procedure:

Inject separately blank, standard solution (six times) and sample solution into the chromatographic system, record the chromatograms and measure the areas of Imatinib Mesylate peaks.

Dissolution method

Instrument:

High Performance liquid chromatography equipped with UV-detector and data handling system.

Chromatographic Parameters:

Column : Zorbax Eclipse XDB-C_8 (150 x 4.6), 5µm

Wavelength : 260 nm

Flow Rate : 0.8 mL / min

Column Temperature : 40°C

Sample temperature : 25°C

Injection Volume : 50 µL

Run Time : 30 minutes

Elution : Gradient

Standard Solution Preparation:

Preparation of Imatinib Mesylate standard in Acid stage

- Weigh accurately and transfer about 13.00 mg of Imatinib Mesylate into 2000 mL volumetric flask.
- Add 100 mL of Methanol and sonicate for 10 minutes.
- Then, add 1000 mL of 0.01 N HCl and sonicate for 15 minutes.
- Then add about 800 mL of 0.01 N HCl
- Keep on water bath for 30 minutes at 90 °C and cool to room temperature.
- Make up to the volume with 0.01 N HCl + 0.5 % Tween 80.
- Mix well and filter through 10 µ membrane filter.

Preparation of Imatinib Mesylate standard in Buffer Stage

- Measure 750 mL of Imatinib Mesylate Standard in acid stage-1 and transfer into 1000 mL volumetric flask.
- Add 250 mL of pH 6.9 phosphate buffer solution to it and mix well.
- Filter through 10 µ membrane filter.

Stability Studies:

Ensuring the stability of pharmaceutical dosage forms is critical for preserving their effectiveness and safety. This involves subjecting them to various storage conditions, including normal and extreme temperatures, and conducting formal stability studies on both the drug substance and the final product. By understanding the behavior and properties of the drug substance and evaluating its stability over time, we can design storage conditions and shelf-life specifications that ensure consistent drug absorption rates.

Table-4.6: StorageconditionsforStability samples

Accelerated	40± 2ºC/75±5%RH
Intermediate	30± 2ºC/65±5%RH
Longterm	25± 2ºC/60±5%RH

Table-4.7:TestingintervalsforStabilitysamples

Accelerated	Initial,1,2,3&6 months.
Intermediate	Initial,3,6,9,12,18,24&36months.
Longterm	Initial,3,6,9&12 months.

3.RESULTS AND DISCUSSION

5.1. Standard Graph of Imatinib Mesylate by UV-Spectrophotmetry:

The calibration curve followed Beer's law within a concentration range of 2 - 12 µg/ml. The regression coefficient, with a value of 0.99, indicated a strong linear relationship between the concentration and absorbance, as demonstrated in the accompanying Figure-5.1.

Table-5.1: Standard Graph of Imatinib Mesylate by UV-Spectrophotmetry

CONCENTRATION (µg/ml)	**ABSORBANCE**
2	0.147
4	0.226
6	0.324
8	0.436
10	0.572
12	0.652

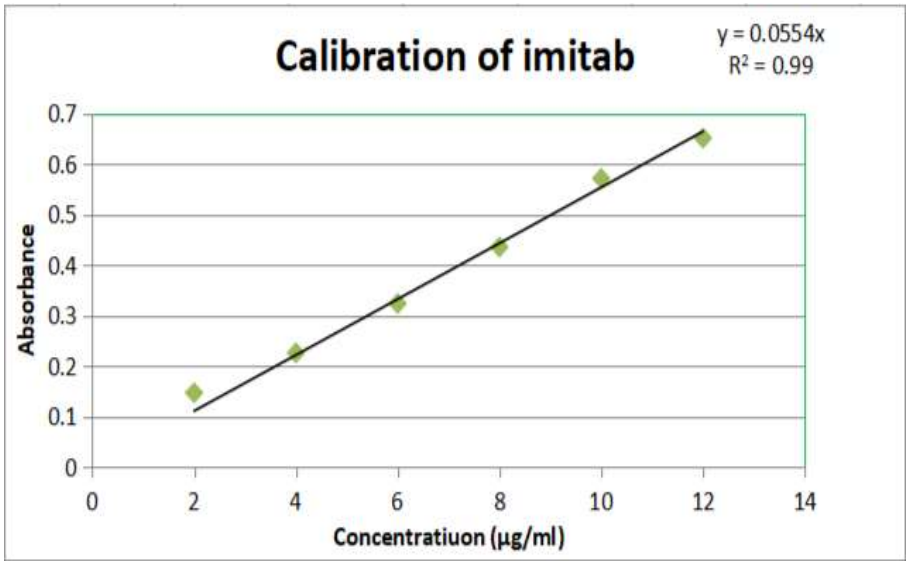

Fig-5.1:Standard graph of Imatinib mesylate

5.2. Drug excipient compatibility test

Drug-excipient compatibility test was performed by FTIR spectroscopy by using KBr pellet press. The major peaks present in the pure drug Imatinib mesylate spectra were also present in the optimized formulation blend spectra. The drug and excipients in the formulation are compatible with each other shown in the figures-5.2 & 5.3.

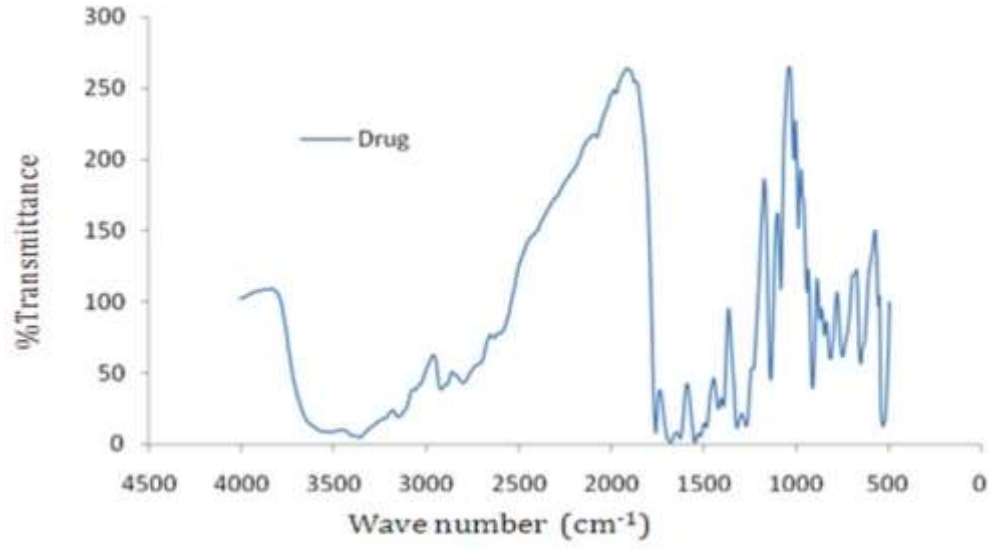

Fig-5.2: FTIR Spectra of Pure drug Imatinib mesylate

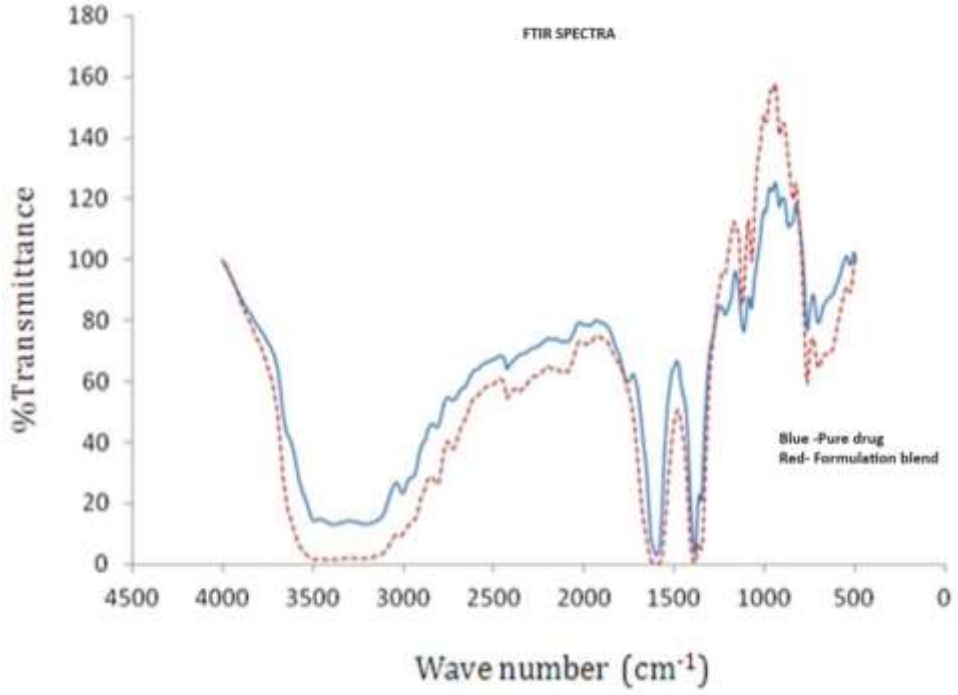

Fig-5.3: FTIR Spectra of Optimized formulation blend

5.3. Preformulation studies of Lubricated blend

Preformulation studies of a lubricated blend involve characterizing and evaluating the physical and chemical properties of the blend, as well as studying its stability, compatibility, and performance. The drug, polymers, binders, glidants, lubricants and colours are blended and below evaluations were performed. All the were showing good flowability shown in table-5.2.

Table-5.2: Preformulation studies of Lubricated blend

Formulation	Angle of Repose	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index	Hausner's Ratio
F1	28.60±0.05	0.450±0.07	0.525±0.09	14.5±0.06	1.20±0.03
F2	28.67±0.08	0.446±0.02	0.514±0.04	13.2±0.09	1.15±0.05
F3	28.08±0.13	0.482±0.04	0.544±0.02	11.3±0.10	1.12±0.06
F4	29.90±0.15	0.476±0.07	0.551±0.06	14.6±0.07	1.15±0.05
F5	29.87±0.18	0.470±0.06	0.547±0.07	13.8±0.05	1.13±0.03
F6	28.27±0.06	0.456±0.05	0.522±0.04	12.2±0.09	1.16±0.06
F7	28.85±0.13	0.448±0.07	0.517±0.09	13.8±0.06	1.17±0.03
F8	29.45±0.07	0.462±0.02	0.535±0.07	14.8±0.09	1.15±0.07
F9	28.73±0.17	0.446±0.04	0.527±0.06	12.6±0.10	1.19±0.05
F10	28.87±0.15	0.474±0.07	0.534±0.04	11.9±0.07	1.12±0.06

5.4. Post -compression studies of Imatinib Mesylate controlled release tablets

The post-compression studies of Imatinib Mesylate controlled release tablets were studied for weight variation, thickness, hardness and friability were shown in table-5.3.

Table-5.3: Post -compression studies of Imatinib Mesylate controlled release tablets

Formulations	Weight variation(mg) (n=10)	Thickness(mm) (n=10)	Hardness(kp) (n=10)	Friability (%) (n=10)
F1	445±1.6	3.52±0.03	6.5±0.5	0.64±0.06
F2	446±1.5	3.57±0.03	6.5±0.2	0.95±0.06
F3	444±1.6	3.52±0.06	6.3±0.6	0.71±0.06
F4	475±1.6	3.57±0.05	6.2±0.4	0.66±0.02
F5	465±1.5	3.52±0.03	6.4±0.2	0.78±0.04
F6	463±1.6	3.54±0.06	6.5±0.4	0.91±0.02
F7	456±1.5	3.52±0.04	6.3±0.6	0.73±0.04
F8	466±1.5	3.55±0.06	6.2±0.2	0.67±0.06
F9	443±1.5	3.57±0.06	6.3±0.5	0.75±0.02
F10	446±1.6	3.52±0.03	6.5±0.6	0.72±0.04

5.5. Dissolution Studies of Imatinib Mesylate CR tablets

The dissolution studies were conducted for F1-F9 formulations, the results were shown in the table-5.4 & 5.5 and Figure-5.4 & 5.5. The drug release kinetics models were shown in figures-5.6 to 5.10.

Table-5.4: Dissolution Studies of Imatinib Mesylate CR tablets in 0.1N HCl followed by 6.8 pH buffer (F1 -F6)

	% Cumulative Drug release				
Time (hrs)	**F-1**	**F-2**	**F-3**	**F-4**	**F-5**
1	2.5±0.1	3.1±1.2	2.8±1.2	3.4±1.2	2.9±1.4

2	6.8±2.4	5.9±3.4	9.1±2.3	6.3±2.5	5.2±3.1
3	19.8 ±11.6	18.5 ±14.6	25.5 ±16	11.5 ±18.1	14.9 ±12.9
4	87.4 ± 2.0	88.5 ±2.8	38.9 ±9.8	25.9 ±9.5	45.8 ±6.5
6	95.5 ± 1.2	99.2 ±2.5	55.8 ±7.0	62.8 ±5.5	69.9 ± 5.2
8	-	-	88.5 ± 3.5	75.6 ±2.5	98.2 ± 4.8
10	-	-	99.5 ±2.4	89.6 ±3.4	-
12	-	-	-	100.5 ±1.5	.-
24	-	-	-	-	-

Table-5.5: Dissolution Studies of Imatinib Mesylate tablets in 0.1N HCl followed by 6.8 pH buffer (F6 -F10)

	% Cumulative Drug release				
Time (hrs)	**F- 6**	**F-7**	**F-8**	**F-9**	**F-10**
1	1.5±0.1	3.8±1.3	4.8±2.1	5.2±3.4	1.5±2.1
2	6.2±2.4	16.4±4.5	9.5±2.8	6.8±3.6	3.4±1.2
3	12.9 ± 16.4	38.9 ±15.5	38.5 ±14.5	15.5 ±6.8	5.8 ±5.6
4	30.8 ±8.5	48.5 ±10	45.9 ±9.8	22.9 ±6.5	1.5 ±5.8
6	65.5 ±7.2	58.5 ±5.5	70.9 ±5.5	29.8 ±4.5	23.8 ±3.5
8	85.9 ±4.2	80.9 ±4.5	85.5 ±4.2	41.9 ±5.3	35.9 ±2.1
10	98.6 ±2.1	95.2 ±2.5	89.6 ±3.5	52.8 ±3.5	43.8 ±1.8
12		101.2 ±1.1	90.2 ±2.0	59.5 ±2.8	56.2 ±1.5
24				100.9 ±0.8	68.8±0.5

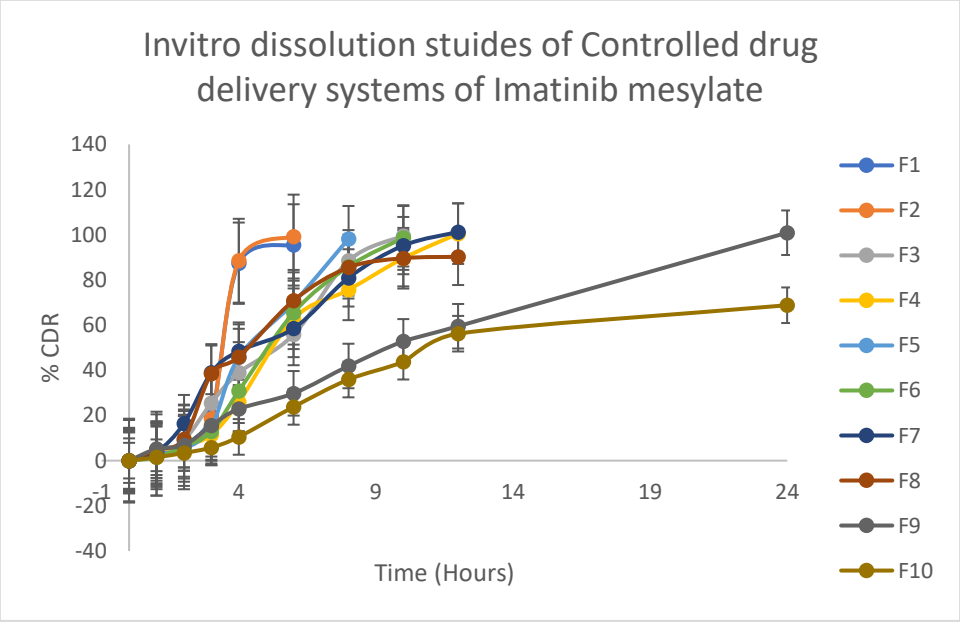

Fig-5.4: Dissolution Studies of Imatinib Mesylate tablets in 0.1N HCl followed by 6.8 pH buffer

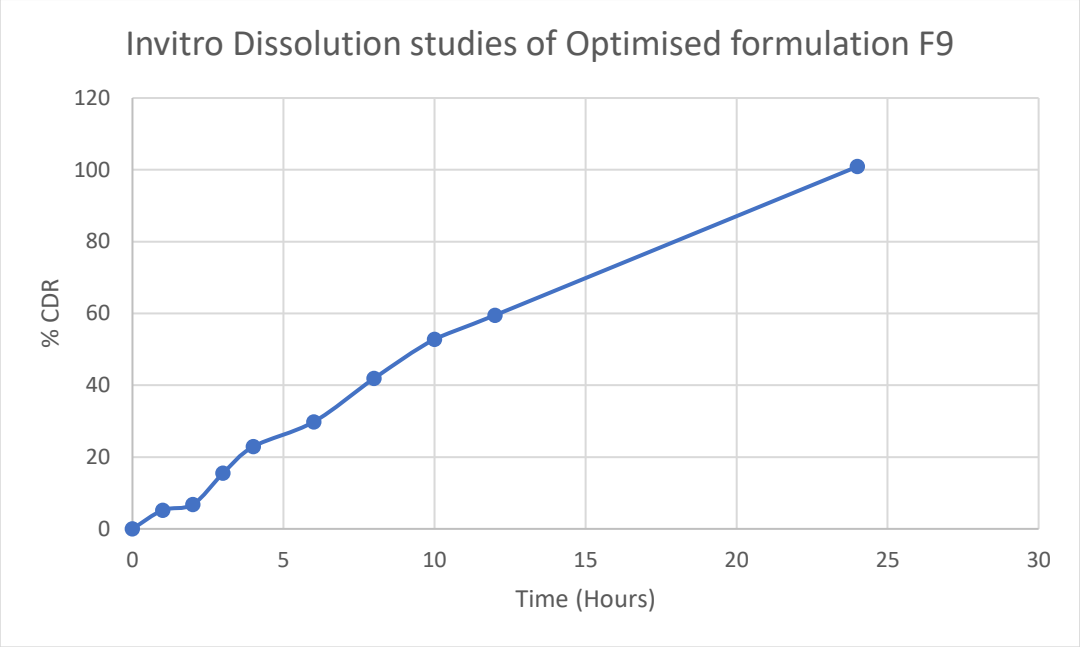

Fig-5.5: Dissolution Studies of Optimized Imatinib Mesylate (F9) controlled release tablets

Time (Hours)	%CDR	Log % CDR	SQRT	Log T	$Wo^{1/3}$-$Wt^{1/3}$	% DR	Log % DR
0	0	0	0	0	0	100	2
1	5.2	0.0000	1.0000	0.0000	1.7325	94.8	1.97681
2	6.8	0.8325	1.4142	0.3010	1.8945	93.2	1.96942
3	15.5	1.1903	1.7321	0.4771	2.4933	84.5	1.92686
4	22.9	1.3598	2.0000	0.6021	2.8397	77.1	1.88705
6	29.8	1.4742	2.4495	0.7782	3.1003	70.2	1.84634
8	41.9	1.6222	2.8284	0.9031	3.4733	58.1	1.76418
10	52.8	1.7226	3.1623	1.0000	3.7516	47.2	1.67394
12	59.5	1.7745	3.4641	1.0792	3.9040	40.5	1.60746
24	100.9	2.0039	4.8990	1.3802	4.6555	-0.9	#NUM!

Table-5.6: Dissolution Studies of Optimized Imatinib Mesylate (F9) controlled release tablets

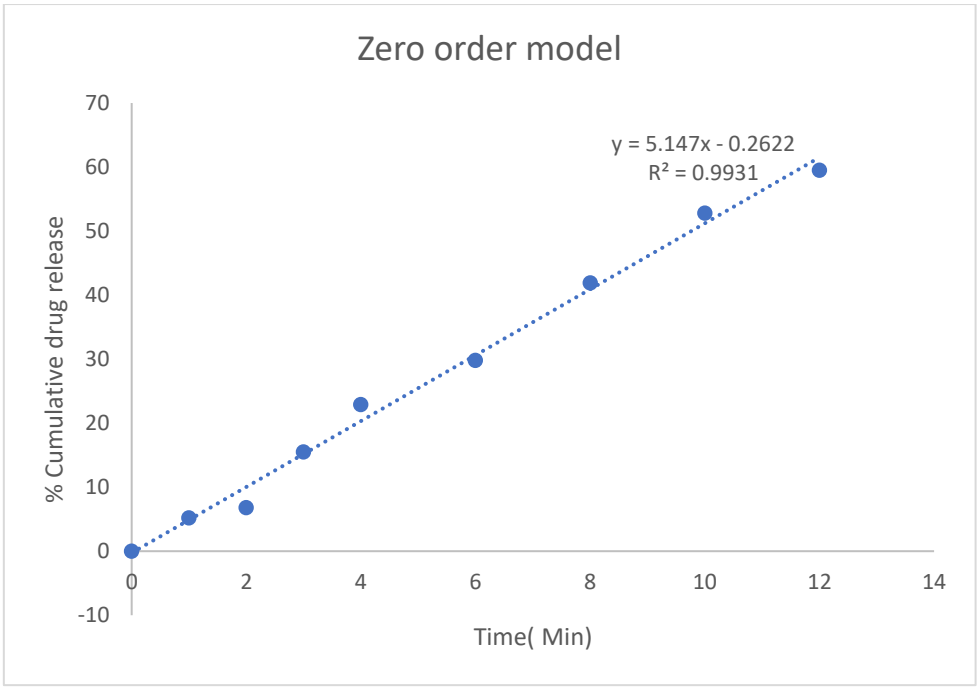

Fig-5.6: Zero order model kinetics for Imatinib controlled release tablets

Fig-5.7: First order model kinetics for Imatinib controlled release tablets

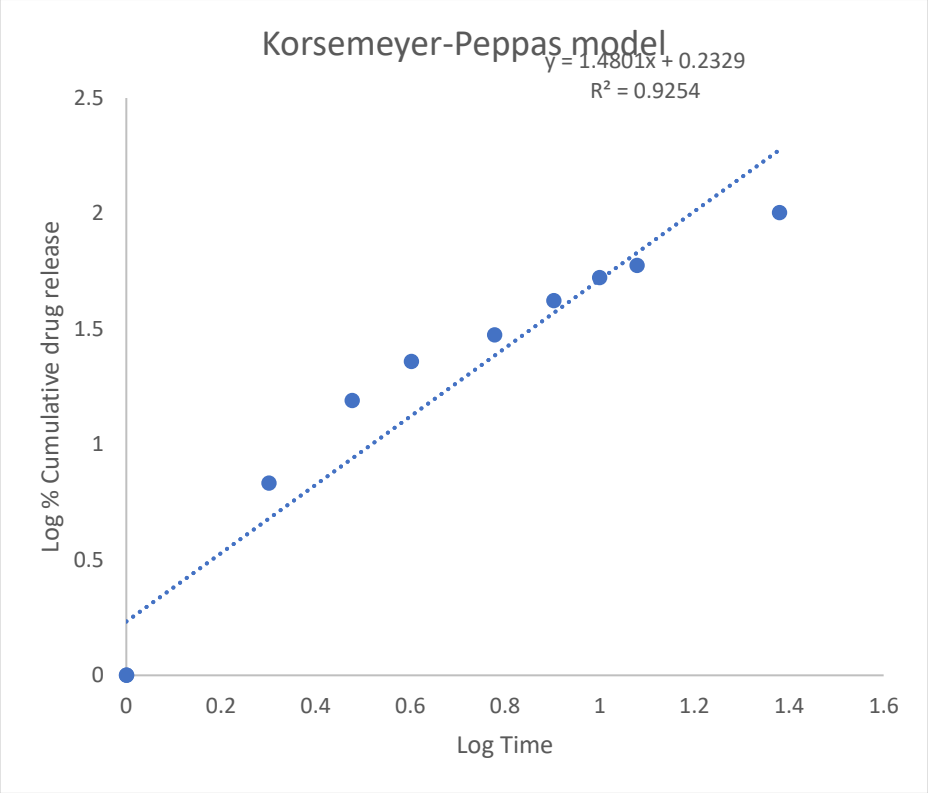

Fig-5.8:Korsemeyer-peppas model kinetics for Imatinib controlled release tablets

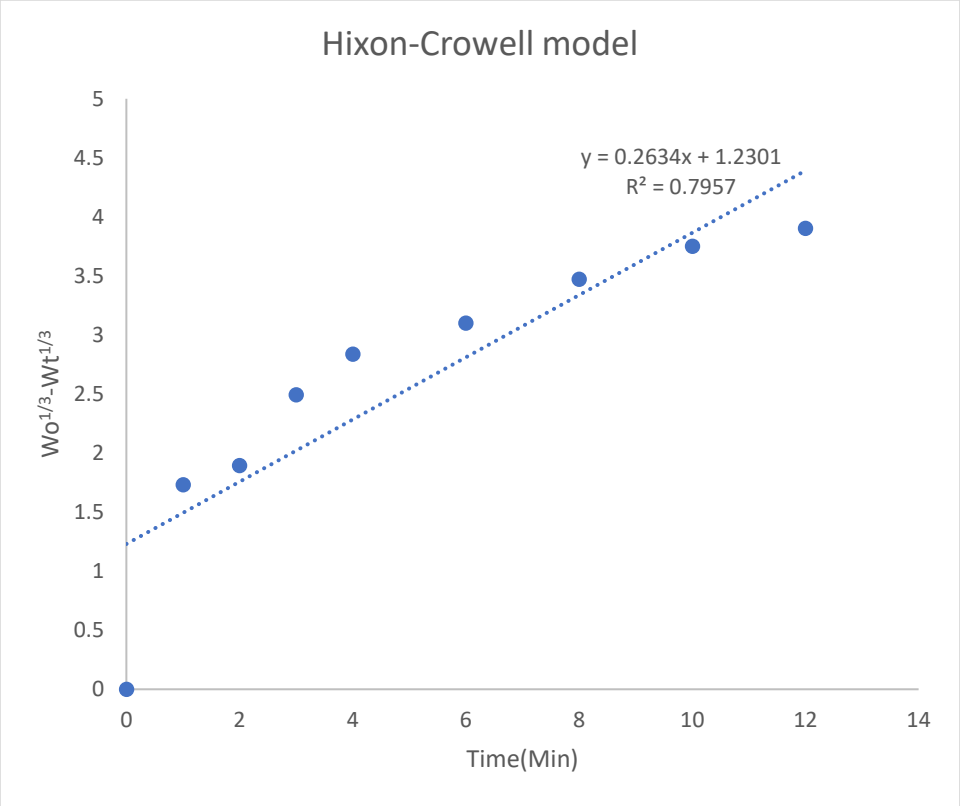

Fig-5.9: Hixson-crowell kinetics for Imatinib controlled release tablets

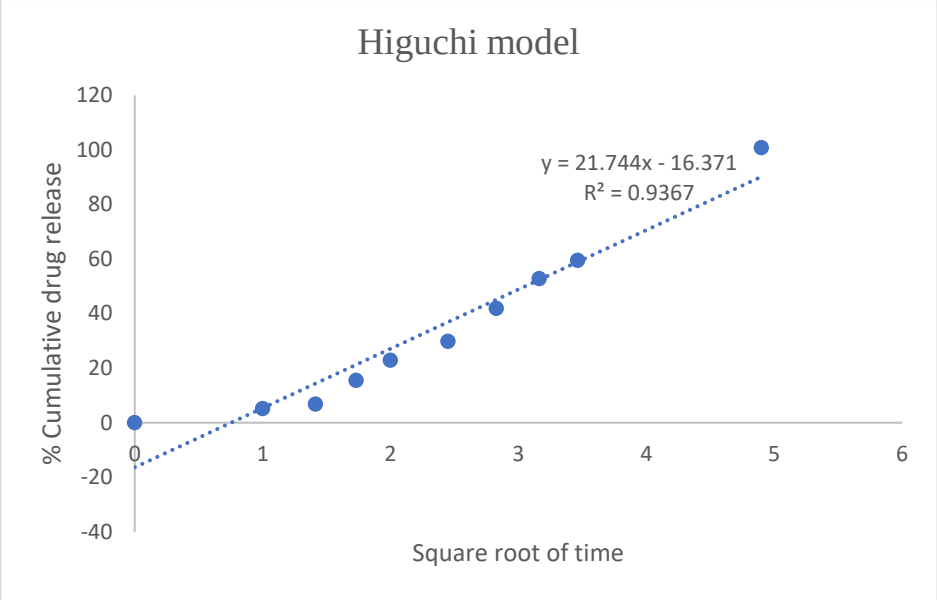

Fig-5.10: Higuchi model kinetics for Imatinib controlled release tablets

Table-5.7: % Assay of Imatinib Mesylate Tablets

Formulations	**% Assay (n=10)**
F1	99.40±2.5
F2	98.81±4.8
F3	99.40±3.4
F4	98.22±5.7
F5	99.40±6.3
F6	98.60±7.4
F7	99.40±3.5
F8	98.34±4.8
F9	99.30±5.9
F10	98.28±6.7

Table-5.8: Accelerated Stability Studies for Optimized formulation

Parameters	**Condition: 40ºC±2 ºC & 75%R± 5%RH**			
	Initial	**1st month**	**2nd month**	**3rd month**
% Average weight-mg (n=10)	445±0.36	445±0.28	443±0.42	443±0.37
Thickness – mm (n=10)	3.52±0.04	3.57±0.01	3.52±0.03	3.52±0.03
Hardness- kp (n=10)	6.5±0.06	6.5±0.04	6.3±0.04	6.2±0.02
Assay- % (n=5)	99.40±0.81	98.81±0.54	99.41±0.71	98.32±0.29

4.Summary and Conclusion

Imatinib mesylate (IM) is a widely used drug for the treatment of certain types of cancer, such as chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GIST). The objective of the present study was to design a matrix-embedded oral controlled-release (CR) formulation by using polymers, to overcome the limitations associated with the conventional multi-dose dosage form of IM for long-term therapy and improved patient compliance.

The study aimed to develop a controlled-release formulation of IM that would provide sustained therapeutic drug levels in the body over an extended period. This is crucial for the effective management of cancer, as maintaining consistent drug concentrations is essential for achieving optimum therapeutic outcomes. The use of matrix-embedded technology allowed for the incorporation of these polymers to act as barriers, controlling the release of IM from the formulation.

The formulation is designed by combination of Hydroxy propyl methyl cellulose (E-15) and Hydroxy propyl methyl cellulose (K100) gradesfor achieving controlled release of the drug from the dosage form for 24 hours. The formulation F9 was with 1:1 ratio of polymer has shown drug release for a period of 24 hours. The optimized formulation F9 was following zero order diffusion release which was predicted by drug release kinetic models.

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