SOLUBILITY ENHANCEMENT OF POORLY SOLUBLE DRUGS BY FORMULATION OF SOLID DISPERSION USING SOLUPLUS® AS A CARRIER

By

SHEIKH MOHAMMED FARHAN MOHAMMED MUSTAFA

Enrollment Number: 220521003

Research guide

Ms. REENA UGHREJA

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Dr. KEVINKUMAR C. GARALA

A Thesis Submitted to Atmiya University in Partial Fulfillment of the Requirements for the Master of Pharmacy in Pharmaceutics

JULY-2024

Department of Pharmaceutics

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CERTIFICATE

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THESIS APPROVAL

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DECLARATION

I hereby certify that I am the sole author of this thesis and that neither any part of this thesis nor the whole of the thesis has been submitted for a degree to any other University or Institution.

I certify that, to the best of my knowledge, my thesis does not infringe upon anyone's copyright nor violate any proprietary rights and that any ideas, techniques, quotations, or any other material from the work of other people included in my thesis, published or otherwise, are fully acknowledged per the standard referencing practices. Furthermore, to the extent that I have included copyrighted material that surpasses the bounds of fair dealing within the meaning of the Indian Copyright Act. I certify that I have obtained written permission from the copyright owner(s) to include such material(s) in my thesis and have included copies of such copyright clearances to my appendix.

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LIST OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Abbreviations

FT-IR: Fourier transform infrared spectroscopy

DSC: Differential Scanning Calorimetry

%: Percentage

µg/ml: Microgram per milliliter

nm: nanometer

°C: Degree Centigrade

SE: Solvent Evaporation

ME: Melt Evaporation

HME: Hot Melt Extrusion

SD: Solid dispersion

XRD: X-ray Diffraction

PD: Pure drug

PM: Physical Mixture

ABSTRACT

Treatment of tuberculosis makes great use of rifampicin. While Abiraterone Acetate is generally used for the treatment of prostate cancer, Duloxetine Hydrochloride is advised for the treatment of major depressive disorder. Still, the low water solubility of all these drugs affects their bioavailability. Thus, this work sought to generate solid dispersions thereby enhancing the solubility and hence the dissolution rate of Rifampicin, Duloxetine hydrochloride, and Abiraterone Acetate. Soluplus® was used as a carrier to enhance solubility; phase solubility investigations carried out in preliminary trials helped to ascertain the ratio. First investigations were carried out to select the suitable solvent and techniques; thereafter, solid dispersions were developed. The Physical characterization was done by DSC and FT-IR. DSC was performed to determine the thermal characteristics of the drug and FT-IR was performed to determine the compatibility between the drug and polymer. Melt and solvent evaporation techniques were used to produce the solid dispersion. The batches had ratios ranging from 1:1, 1:2, and 1:3. %Drug content, %yield, solubility studies, and in-vitro dissolution studies were among the evaluation parameters performed for the solid dispersion assessment. The batch showing good results was selected for further investigation with XRD, DSC, and FT-IR methods. The best batches of all the drugs (Rifampicin, Duloxetine HCL and Abiraterone Acetate) showed enhancement in the solubility and dissolution rate.

CHAPTER 1
INTRODUCTION

1. INTRODUCTION

Approximately 35-40% of medications are characterized by low solubility in water. The insolubility of certain substances might cause difficulties in their absorption from the gastrointestinal tract, leading to variations in absorption among individuals and even within the same individual [1]. Additionally, there is a reduction in the proportion of drug that can be absorbed via the mouth, therefore there is a necessity to increase the dosage of the drug to attain the required therapeutic effect, potentially leading to difficulties in formulating the medication.

To tackle these problems, a range of methods are utilized to create pharmaceutical formulations. The procedures encompass the formation of solid solutions or solid dispersions utilizing hydrophilic carriers, complexation, micronization, and solubilization. In addition, techniques such as employing dendrimers to enhance drug solubility and utilizing self-micro emulsifying drug delivery systems (SMEDDS) are used.[2]

There are a wide range of methods that have been employed to improve solubility, which also include the utilization of pro-drug strategies, spray drying, salt synthesis, and nanoparticle technologies. An especially encouraging option involves employing numerous hydrophilic carriers in a direct solid dispersion technique.[3]

In 1961, Sekiguchi and Obi enhanced the rate at which Sulfathiazole dissolves and becomes available for absorption in the body by utilizing a eutectic mixture of sulfathiazole with urea as an inactive carrier [4]. Subsequently, other researchers devised distinct methodologies for producing solid dispersions. Goldberg's research revealed that a specific portion of the medication can be evenly distributed at a molecular level inside the surrounding material, resulting in the formation of solid solutions [5]. According to some researchers, drug could potentially be integrated into the matrix in the form of amorphous substances.

Definition: Solid dispersion can be defined as the dispersion of one or more active pharmaceutical ingredients in an inert carrier at the solid state. It can also convert the API's crystalline state to an amorphous state for better solubilization.[3]

Solubility and bioavailability are interconnected. To understand bioavailability, it's important to grasp the Noyes-Whitney equation, as it helps comprehend dissolution [6]

Noyes-Whitney eq. is written as

$$\frac{dC}{dt} = \frac{AD(Cs - C)}{H}$$

Where,

dC/dt = It is the rate of dissolution.

A = Surface area appropriate for dissolution.

D = Diffusion coefficient.

Cs = Solubility of molecule in dissolution medium.

C = Concentration of a drug in the medium at time t.

H = Thickness of diffusion membrane

1.1 BCS Classification of Drugs

The Biopharmaceutical classification system classifies the drugs based on their aqueous solubility and intestinal permeability.[7]

This is an important classification system as it can reduce the need for in-vivo bioequivalence studies. With the Invitro characteristics of the drug, the BCS takes into account the 3 major factors which are intestinal permeability, aqueous solubility, and Dissolution rate.

The BCS classifies the drug into 4 different classes as shown in Table 1.1:

TABLE: 1.1 BCS CLASSIFICATION OF DRUGS

Class	Dissolution in aq. environment	Permeation over the intestinal membrane
1.	Fast	Fast
2.	Slow	Fast
3.	Fast	Slow
4.	Slow	Slow

1.2 Types of solid dispersion according to the generation of carriers used

The Solid dispersions are classified according to the generation of the polymer used in the formulation. Based on the generation of the polymers the classification is divided into 4 types.[8] They are as follows:

1. First Generation Solid Dispersion
2. Second Generation Solid Dispersion
3. Third-generation Solid Dispersion
4. Fourth Generation Solid Dispersion

1.2.1 First-generation solid dispersion: This formulation is made from crystalline carriers including urea and sugars. This method produces a thermodynamically stable crystalline solid dispersion (SD) with slow dispersal at last. The first step forward in the realm of Solid dispersions came from the creation of eutectic mixtures. The absence of any alteration in the melting points of both the drug and polymer shows the non-ideal nature of the monotectic mixture.

The Eutectic mixture shows lower melting points when compared to the melting points of the drug and carrier. Because the eutectic mixture crystallizes both the drug and the carrier instantly upon cooling, it is better than the monotectic combination. Reducing the particle size increases the specific surface area, therefore improving bioavailability and accelerating the dissolving rate.[9]

1.2.2 Second-generation solid dispersion: Part of the second generation of carriers, amorphous carriers such as Polyvinyl Pyrrolidone (PVP) and Polyethylene Glycol (PEG) are well-known for their exceptional thermodynamic stability when compared to the first generation. amorphous carriers can be synthetic and natural polymers.

Based on the physical state of the drug the amorphous Solid dispersions can either exist as solutions, suspensions, or a mixture of both. Due to the drug's limited solubility in the carrier, the amorphous Solid dispersions consist of two phases. In contrast, amorphous solid solutions evenly distribute components throughout the molecules. The medication may experience recrystallization during storage, leading to a reduction in dissolving crystals.[9], [10]

1.2.3 Third-generation solid dispersion: To address drug nucleation and agglomeration, the carrier in this iteration needs to exhibit surface activity or emulsifying activity. This quality

enhances the dissolution rate, physical stability, and chemical stability of the formulated drug while also hindering recrystallization.

Examples of third-generation carriers such as poloxamer (P188), are efficient in preventing recrystallization, and surfactants like Gelucire 44/14 and Solutol HS 15 are used to increase the dissolving rate of pharmaceuticals.[10]

1.2.4 Fourth-generation solid dispersion: The most recent development in dispersion technology, as opposed to amorphous Solid dispersions (ASD), is Controlled Release Solid dispersions (CRSD). Carriers such as HPC and ERS are suggested for the prolonged release of medications with short biological half-lives. The controlled-release drug delivery system's principal goals are controlled-release medication prolongation and improved solubility.[8]

1.3 Mechanism of solid dispersion

The mechanism of solid dispersion is divided into two parts they are Carrier-controlled and Drug-controlled.[11]

1.3.1 Carrier-controlled Release: A research study was conducted to monitor the dissolution rate of medication and the polymer (specifically PEG) it was integrated with. It was found that the dissolution rate of the drug was controlled by the dissolution rate of the polymer because of the correlation between the dissolution rate of the drug from the polymer and the dissolution rate of the polymer itself.

This observation was supported by another scholar, who noticed similar dissolution rates of various medications in a single carrier prepared under comparable conditions. In these instances, the particles dissolve rapidly into a polymer-rich diffusion layer. Such fast dissolution prevents the particles from being released in their original form into the surrounding liquid. The medicine is uniformly dispersed at a molecular level across this densely concentrated layer, leading to even distribution.[11], [12]

1.3.2 Drug-controlled Release: An investigation was conducted by a researcher in which, the particle size of griseofulvin particles released from dispersions was evaluated, revealing that the rate at which the particles dissolved was directly impacted by their size. Furthermore, Craig (2002) used a series of pharmaceuticals (para-aminobenzoates) to investigate the relationship between the

solid-state structure, drug solubility, and dissolution rate, aiming to reconcile these discrepancies.[13]

Their research showed that the solubility of the model pharmaceuticals was directly related to their intrinsic dissolution rate in the dispersions. The solubility rate was found to be directly related to drug characteristics, not polymer. There is a difference between carrier-controlled release and this method, it can be called the drug-controlled release.[14]

Slow solubility into the polymer diffusion layer is the key to drug-controlled dissolution, which allows for the controlled release of solid drug particles. Therefore, the drug's properties, including its size and physical shape, govern the dissolution process, rather than the polymer. Using larger surface area particles can still significantly improve solubility, leading to greater wetting and less agglomeration, even when using normal dose forms.[14], [15]

1.4 Mechanism of bioavailability enhancement

Making solid dispersions, which speeds up the medication's dissolving process, is the technique by which bioavailability is enhanced. This acceleration can be less than twice the dissolving rate or as high as 400 times that of pure medicine. The enhanced rate of dissolution might be ascribed to a multitude of causes, making it difficult to empirically demonstrate the relative significance of any individual element [16], [17]. Solid dispersions enhance the rate at which the drug dissolves through one of the following mechanisms:

- Decrease in particle size
- Enhancement in the ability of a substance to spread and mix with a liquid, as well as its ability to disperse evenly.
- Altering the drug's crystalline structure to an amorphous state.
- By reducing the clustering and clumping of medication particles.

1.5 Advantages and Disadvantages

1.5.1 Advantages: The improved solubility of poorly water-soluble drugs through SD technology can be linked to several factors [18], [19]. The advantages of Solid dispersions can be succinctly outlined as follows:

Particles with reduced particle size: Solid dispersions refer to the final stage of reducing particle size, where the medication is dissolved in an inert carrier or matrix and distributed at a molecular

level in the dissolution media. An elevated surface area is created, leading to an enhanced rate of dissolution, and further improving the bioavailability of the drug that is not easily soluble in water.

Particles with improved wettability: Improved wettability of drugs can lead to enhancement in solubility.

Particles with higher porosity: Higher porosity particles resulting from Solid dispersions depend on the characteristics of the carrier material with good characteristics can lead to the formation of Solid dispersions with higher porosity particles; the degree of enhancement determines this as well. Larger and more porous particles are generated from linear polymers than from Solid dispersions made using reticular polymers. The higher dissolving rate of the particles comes from their porous construction.

Drugs in the amorphous state: Generally speaking, low water solubility crystalline drugs show higher solubility in this form. The lack of energy required to disturb the crystal structure during the dissolving process causes a drug to show more drug release in an amorphous form.

1.5.2 Disadvantages: The primary drawbacks of Solid dispersions arise from their intrinsic instability. With time, the process of aging can cause alterations in the crystalline structure and a reduction in the pace at which a substance dissolves in different systems. Moisture absorption can initiate phase separation, formation of crystals, or a stable form from the unstable or less stable crystalline phase. This can impact the formulation and ultimately decrease the solubility of the drug. Solid dispersions are more vulnerable to the adverse impacts of moisture and temperature in comparison to physical mixes. At times, it can be difficult to handle because of its adhesive nature.[18], [19]

1.6 Formulation Methods

There are several methods involved in the formulation of solid dispersion. They are as follows:

1. Melting Fusion method
2. Melting Extrusion method
3. Solvent Evaporation method
4. Spray Drying method
5. Super Critical Fluid Technologies
6. Electro-spinning

7. Lyophilization. technique
8. Melt Evaporation method

1.6.1 Melting Fusion: In this process, the drug and polymer both are melted together to form a molten mass and then it's cooled rapidly by stirring continuously on an ice water bath.

Although it's easy and simple some drugs may get degraded due to high temperatures. One way is to handle is to physically heat it inside a jar hermetically or by using an inert gas such as nitrogen to shield the medication.[20]

1.6.2 Melting Extrusion: Like fusion, melt extrusion employs the same method but it does it by using an extruder through which the molten mass passes. Although the old melt fusion techniques have their disadvantages, mixing polymer and drug through an extruder is also quite difficult.

An appropriate matrix must be identified that can be suitable for this method. This method, however, is different from the traditional method as it is performed continuously.[21]

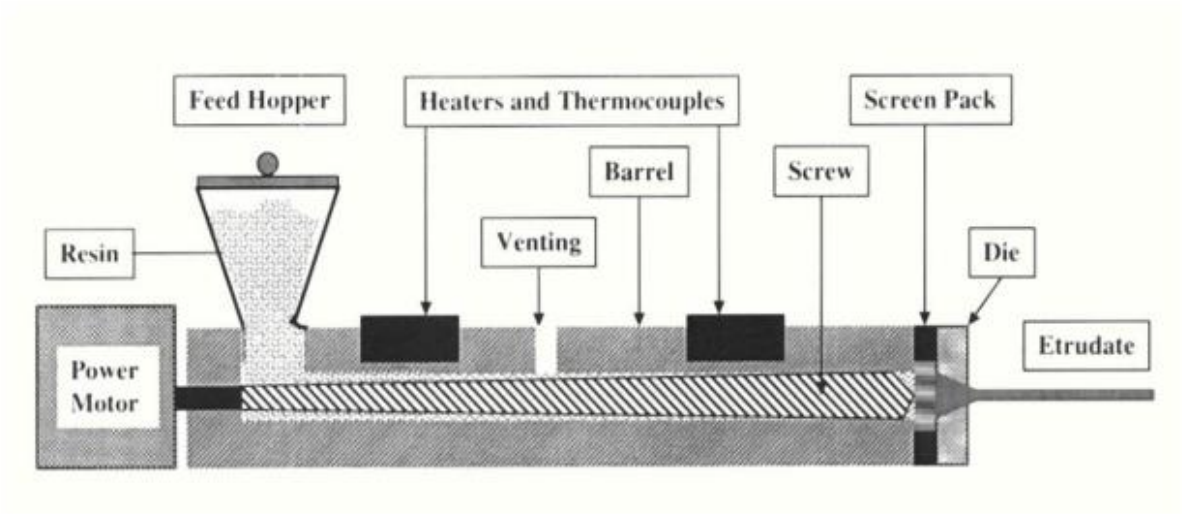

FIGURE: 1.1 SCHEMATIC DIAGRAM OF MELT EXTRUSION

1.6.3 Solvent Evaporation: In the initial stage of the solvent evaporation technique, a solution is created containing both the matrix material and the medication. The subsequent step involves removing the solvent(s), resulting in the formation of Solid dispersions. Achieving optimal dissolving qualities requires thorough mixing at the molecular level. However, pharmaceutical engineers face two challenges when employing the solvent technique. Due to substantial

differences in polarity, there is a huge obstacle to merging the drug and matrix in a single solution. By finely dispersing the drug and matrix in a solvent, the drug particle size in the Solid dispersions can be reduced. Ideally, both the drug and matrix material should be dissolved in a single solution.

Lipophilic medicine and hydrophilic matrix material have been combined in a single solution using various ways. However, because a lot of solvent has to be evaporated, this method is expensive and not practical. There has been an enhancement in the water-solubility of medication with the addition of cyclodextrins and surfactants like Tween80®.

The final product has a high amount of solubilizers or surfactants. These additives predominate in the Solid dispersions that eventually develop, which drastically changes the matrix's physical properties like its glass transition temperature (Tg). Furthermore, this method typically yields dose forms with minimal amounts of medication. These additive substances in high amounts can potentially be hazardous for the body. Chloroform or dichloromethane has been utilized to concurrently dissolve both the drug and PVP as a matrix.

Furthermore, these solvents are employed in alternative ways of preparation. However, as per the ICH guidelines, these solvents are classified as Class I, which includes the most dangerous solvents. Hence, the utilization of these solvents is deemed inappropriate and unfeasible because there may be a proportion of residual solvents left in the Solid dispersions which may be undetectable. The final approach for dissolving both the medication and matrix involves the utilization of solvent combinations. For this aim, water and ethanol, or dichloromethane and ethanol have been employed.

Nevertheless, achieving the desired concentration or ratio of drug and matrix dissolution in these mixtures is not always feasible. The second obstacle in the solvent approach is to avoid phase separation, such as the crystallization of either the medication or the matrix, while removing the solvent(s). Subjecting the material to elevated temperatures accelerates the drying process and diminishes the duration during which phase separation can occur. Conversely, when exposed to high temperatures, the drug and matrix molecules maintain a high level of mobility, which promotes the separation of phases, such as crystallization.

Vacuum drying is frequently employed to remove moisture from solutions. Under controlled heating and the use of a vacuum, the moisture present in the solution is removed. Sometimes a rotating evaporator is utilized for the removal of moisture or solvent. Vacuum desiccators can also

be utilized to store Solid dispersions for the removal of moisture content. Vacuum drying at high temperatures poses the risk of phase separation due to the gradual decrease in the mobility of the medication and matrix.

In addition, the Solid dispersions produced through spray drying are composed of particles that can be tailored in size by adjusting the droplet size to fulfill specific needs for subsequent processing or application, such as the production of easily flowing particles or particles suitable for inhalation. The process of spray-drying normally leads to the development of the medication or drug in its non-crystalline state, although there are times when the drug may become partially crystalline during the process [22], [23]

1.6.4 Spray Drying: Spray drying lets many pharmaceutical businesses manage the size and shape of the particles while rapidly drying items. Furthermore, cheap and simple since it costs "50 times less than freeze-drying. The technique atomizes suspensions or solutions into small droplets and then dries them to produce solid particles. This method is dependable. The technique produces finely ground powder free from dust and agglomerated powder satisfying set parameters. Great volatility and strong power to dissolve poorly water-soluble drugs define commonly utilized organic solvents in the spray-drying process. Solid dispersions form, degree of dissolution, and stability are affected by the process parameters and equipment geometry. Changing the solute concentration in the liquid used for spray-drying and the droplet size during the spray-drying process will affect the particle size in spray-dried Solid dispersions. Rankell et al. devised this method to create loperamide Solid dispersions using PEG 600. They spray dry using loperamide at a fixed concentration and solutions varied in PEG 6000 concentration. Chouhan et al. investigated if this method would be appropriate for generating Solid dispersions (SD) of glibenclamidepolyglycerides.[23]

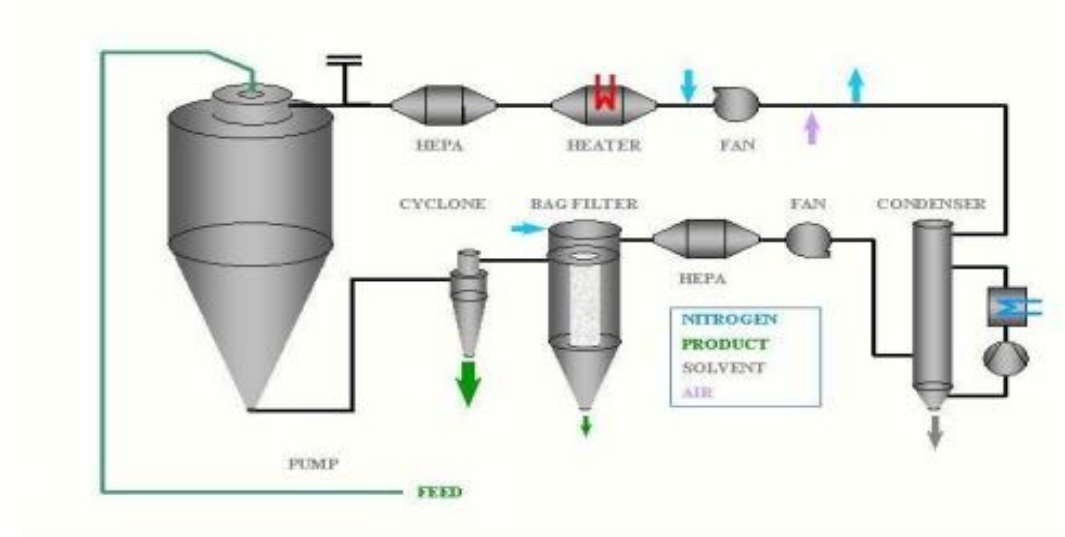

FIGURE: 1.2 SCHEMATIC DIAGRAM OF SPRAY DRYING

1.6.5 Supercritical fluid Technologies: Mostly used as either an anti-solvent or a solvent for pharmaceuticals and matrices, supercritical fluid techniques rely on both the matrix and the medicine is dissolved using supercritical CO_2 as a solvent. Then, when sprayed from a nozzle into an expansion vessel with low pressure, the resulting solution produces particles. The combination of experiencing adiabatic expansion produces a rapid temperature drop. Since carbon dioxide is good for the environment, this process—which does not call for organic solvents—is frequently called "solvent-free".

Still, the usefulness of this method is very restricted since most pharmaceutical compounds have quite poor solubility in CO_2, usually less than (<0.01wt-%), and this solubility further lowers as the polarity increases. This method is not applicable for preparation meant on a kilogram scale.

All other processes in a supercritical condition are precipitation techniques. All of these supercritical fluid techniques use organic solvents to dissolve both the drug and matrix, occasionally referred to as solvent-free due to the limited solubility of drugs in CO_2. A technique called the Gas Anti-solvent strategy is used.

The answer comes across under compressed CO_2. The settings are chosen to guarantee that, under supercritical levels, CO_2 is soluble in the solution; the drug and matrix will separate when the solution is extended. The solvent strength—that is, the power to dissolve the medication—falls as

the volume of the solution rises. This results in the firm deposit of the matrix and the medicine developing. PEG is widely employed as the matrix in this technique, so it results in Solid dispersions with a crystalline matrix usually of type II or III.

Using atomizing a drug-and-matrix solution through a nozzle, one can transport it to a container of liquid or supercritical anti-solvent second way of precipitation. The drug and matrix solidify and generate particles when the supercritical anti-solvent droplets supersaturation occurs.

Still, mixing the drug and matrix into a single solution is the most important part of these dissolution methods, just like it was in earlier solvent-based methods. Due to the lesser solubility of compressed CO_2 in water, the amount of water that can be used is limited because of this reason sometimes methanol or dichloromethane are used to mix drug and matrix.[22], [24]

1.6.6 Electro-spinning: In electro-spinning, solid threads are created by applying pressure to a polymeric liquid that is released from the nozzle. Using a powerful electric field, a conductive capillary, and a conductive collection screen, a polymer solution can be separated from its storage. Due to the increase in the strength of the electrostatic field, there is a conversion in the shape of the hanging droplet into a cone called Taylor's cone caused by the accumulation of charged particles on the surface of the droplet.

A cone-shaped device emits a polymer jet, either positively or negatively charged, when the charge reaches a specific amount. This means that the charge is free. Electricity will be used to move the charged jet toward the screen to catch it. Because of the way Coulomb resistance works, the screen gets smaller. The charged jet, on the other hand, runs out because it gets harder for its thickness to go down as its viscosity rises.[25]

1.6.7 Lyophilization Technique: Lyophilization is somewhat similar to solvent evaporation as both drug and carrier are dissolved in the same solvent but instead of evaporation here the solvent along with the drug is frozen and then sublimed to produce Solid dispersions

Combine the medication with a solvent at a consistent concentration. Combine the carrier with water until it completely disperses. Combine the solution in a volumetric ratio of 40 parts solution A to 60 parts solution B. Afterwards, the mixture is submerged in liquid nitrogen until it becomes completely frozen. Different concentrations of the medicine in the Solid dispersions are achieved by altering the concentrations of the carrier while keeping the drug concentration constant.

Subsequently, freeze-dry the solution using a lyophilizer. Lyophilization is conducted using a two-step process. 1) The pressure is set to 0.22 mbar and the shelf temperature is set to -35°C for one day. 2) Then, gradually decrease the pressure to 0.05 mbar, while simultaneously increasing the shelf temperature to 200 degrees. Continue to uphold these circumstances for an additional day. The samples are kept in a vacuum desiccator for a day at room temperature after they are removed from the freeze-dried.

Combine the medicine with a solvent at a consistent concentration and mix it with water as a carrier. Dilute the solution at a volumetric ratio of 40 parts solution to 60 parts solvent. Inject the solutions into liquid nitrogen using a nozzle. Adjust the rate at which the liquid is fed, and the flow of air used for atomization.[26], [27]

1.6.8 Melting Evaporation: The process entails creating Solid dispersions by dissolving the medicine in a compatible liquid solvent and thereafter adding the solution straight into the molten carrier. The mixture is then evaporated until a transparent film, devoid of any solvent, remains. Dry the film. The solid characteristic of the carrier remains largely unaffected when incorporating liquid chemicals at a concentration of 5-10% (w/w). There is always a chance that the melted carrier may not be compatible with the chosen solvent or the dissolved drug. The precipitation of the drug as a Solid Dispersion can be highly affected by the solvent, as it can influence the polymorphic structure of the drug. This technique combines the distinct advantages of both the fusion and solvent evaporation procedures.[28]

1.7 Type of Carriers

There are several types of carriers utilized in the formulation of solid dispersions and some of those carriers are mentioned below [29], [30]:

Sugars: Sucrose, Mannitol, Lactose

Acids: SA and CA

Polymeric Materials: Povidone, Polyvinyl pyrrolidone, Polyethylene Glycol, Hydroxy polymethyl Cellulose, Methyl Cellulose, HEC, Cyclo-dextrin, HPROSTATE CANCER, Pectin, Soluplus®

Insoluble and Enteric Polymers: HPMC phthalate, Eudragit L-100, Eudragit S-100, Eudragit RL, and RS.

Surfactants: Renex poloxamer 188, Deoxycholic acid, Polyoxyethylene Stearate, Texafor AIP, Tweens, Spans

Miscellaneous: Penta erythritol, Penta erithryl tetra acetate, Urea, Urethane, Hydroxy alkyl Xanthin.

1.8 Current Trends in Solid Dispersion:

The formulation of viable dosage forms has become difficult for the scientists because of the low water solubility of many novel medication candidates. The reason behind this is the usage of combinational chemistry and high-throughput screening.

A chemical with low water solubility is traditionally defined as one that dissolves in less than 0.01% (1 part per 10000) of water. It has been stated that a medicine that does not dissolve properly in water has been described as taking longer time to dissolve in the fluid of the digestive system than it does in the digestive tract. A complete understanding of the mechanism of drug absorption and drug dissolution in the body must be known to completely transform the poorly soluble drugs into formulations that can be easily absorbed by the body.[31]

Historically, techniques like salt creation and reduction in the size of particle have been used to increase the rate at which pharmaceuticals dissolve. But these methods also have their own sets of limitations which could affect the bioavailability of final products. As a result of this, many investigators are seeking techniques or methods that can enhance drug absorption for medications that are poorly soluble in water. Medications can be made more bioavailable by forming them into Solid dispersions.[32]

Solid dispersion is the process of dispersing one or more active constituents in a solid state within an inert carrier or matrix. This is achieved using methods such as melting (fusion), solvent, or the melting solvent method. According to Sekiguchi and Obi, the API existed in a microcrystalline form in the eutectic mixture. This was then supported by Goldberg et al. after a few years. According to a report, not all drugs or APIs are present in the micro-crystalline state as some part of the medication may exist as a molecular dispersion inside the matrix, which leads to the formulation of solid solutions.

Surface-active agents are compounds that, when present in small amounts, attach to the surfaces or interfaces of a system and modify the free energy and tension of the surface or interface. Surface-active drugs exhibit a distinctive molecular structure, containing both hydrophilic (polar) and hydrophobic (non-polar) regions. The surface-active carriers are characterized as amphipathic.[32]

1.8.1 Newer Techniques: Both the utilization of surface-active carriers and self-emulsifying carriers and the development of methods for filling of Solid dispersions in gelatin capsules can be considered a breakthrough in the field of Solid dispersions formulation. The original description of the process of filling hard gelatin capsules with Solid dispersions in a molten condition was given by Francol and Jones in 1978. The dispersion then solidifies at room temperature. Nevertheless, the potential use of such technology was immediately apparent to Chatham. The carriers should be able to be filled with liquid and subsequently formed into hard gelatin capsules to make the production process easier. To make sure the solutions don't go over the maximum temperature that may be tolerated for hard gelatin capsule shells, the carriers' melting points should be lower than approximately 70°C.[33]

The dissolution of the drug is slower compared to the water-soluble carrier. Due to the formation of a dense layer containing a large amount of drug on the surface of the dissolving plug hinders the release of the drug from Solid dispersions continuously. Consequently, the act of directly filling a hard gelatin capsule is not a viable approach for creating Solid dispersions, unless precautions are implemented to hinder the development of a concentrated layer of medication on the exterior of the dissolving plug.

The self-emulsifying agent functions as a dispersing or self-emulsifying agent for the drug. It prevents the creation of any water-insoluble surface layer, hence increasing the dissolution of the drug. However, the freed drug remains undissolved in the dissolving medium. When the concentration reaches the maximum amount, because of the surface activity of the dissolved ingredients it will either break down or emulsify into smaller particles. This will increase the surface area, making it easier for it to dissolve in the gastrointestinal fluid.

Serajuddin et al. conducted a study on enhancing the dissolution of dispersions of REV-5901. The user prepared Solid dispersions of the poorly water-soluble compound REV-5901 (alpha-pentyl-3-(2-quinolinylmethoxy) benzene methanol) in different polyethylene glycols (PEGs) and

Gelucire® 44/14. Subsequently, the blend was introduced into a rigid gelatin capsule. The Gelucire® 44/14 formulation demonstrated efficient and rapid dispersion of the medication in both water and simulated stomach fluid. However, the PEG formulations were only successful in achieving limited dispersion of the medicine. Removing the Gelucire® 44/14 formulation from a soft gelatin capsule does not affect REV-5901's solubilization capabilities.[34], [35]

The most often employed surface-active carrier is Gelucire® 44/14, along with different variations of Gelucire®. These carriers are formulated to possess a high melting point, not exceeding 70°C, to be compatible for filling into hard gelatin capsules. The grades of Gelucire® are distinguished by different numbers, such as Gelucire® 44/14 and Gelucire® 50/13. The melting point and HLB values of the carrier are represented by the first and second digits, respectively. Based on these qualities, these classes are classified and used for diverse reasons. Glyceryl and the long-chain fatty acid-derived PEG-1500 ester make up Gelucire® 44/14. In the European pharmacopeia, it is listed as lauryl macrogol glycerides.

To find out how Gelucire® 44/14 affected the solubility of Temazepam, Dordunoo et al. compared it to different PEGs. The results demonstrated a notable increase in the water solubility of Gelucire® 44/14. A firm gelatin capsule containing 12.5% Triamterene dispersion in various PEGs or Gelucire® 44/14 was compared to a capsule containing the drug alone in a study by Dordunoo et al. about the dissolving of the two. Without excipients, the dissolving studies showed that Triamterene dissolved to a mere 30%. The active ingredient, on the other hand, broke down totally in less than an hour after PEG-1000 or Gelucire® 44/14 was added.[34], [35]

Gelucire® 44/14 and Labrasol were used as carriers in an in vivo test by Aungst B.J. and coworkers to improve the oral bioavailability of an HIV protease inhibitor.

The HIV protease inhibitor DMP-323 has a solubility in water of less than 10 µg/ml. Aungst et al. tested several concentrations of excipients in a water-based combination to find the apparent solubility of DMP-323 in Gelucire® 44/14 and PEG-400. Gelucire® significantly enhanced the apparent solubility of the medicine, but PEG-400 did not have any solubilization effect on the drug.

Chen et al enhanced the solubility and absorption of ABT-963, a chemical with low water solubility, by creating Solid dispersions utilizing Pluronic F-68 as a carrier through the processes

of evaporation and hot melt. The findings indicate that Solid dispersions are a highly promising method for enhancing oral bioavailability.[36]

Passerini et al created granules incorporating Ibuprofen, a model medication with low solubility, by the process of melt granulation. The objective was to enhance the process of dissolving and making a substance available by including lactose as a diluting agent and Poloxamer 188 (Lutrol F68) as a novel hydrophilic binder with a metastable property. The conclusion proposes that the melt granulation technique is a simple and rapid approach to enhance the dissolving rate of ibuprofen. This is achieved by utilizing Poloxamer 188 as a novel hydrophilic binder with metastable properties.

The Solid dispersions system of nifedipine in a polymer matrix consisting of Pluronic F 68 and Gelucire 50/13 in a 1:1:1 ratio was studied by Vippagunta et al. to determine its nature and solid-state properties. The findings show that the Solid dispersions of nifedipine are physically stable. Nifedipine's Solid dispersions helped it to be released more quickly than pure crystalline form.

1.8.2 Future Prospects: The simplicity of manufacturing and scale-up techniques causes the physicochemical properties to vary as expected during the scale-up. For this reason, the popularity of Solid dispersion systems to oversee challenging bioavailability problems concerning poorly water-soluble pharmaceuticals will develop quickly.[37]

One problem with making Solid dispersion systems might be that drugs do not dissolve well in carriers. Having more options will help make dose form development more successful.

Further research should focus on identifying carriers or excipients that can impede or inhibit the crystallization of medicines from supersaturated solutions. It is important to carefully consider the physiological and pharmacological impacts of the carriers that are being employed. Several surface-active and self-emulsifying carriers are lipid-based. Therefore, it is important to carefully assess the possible impact of these carriers on drug absorption, particularly their influence on p-glycoprotein-mediated drug efflux. Furthermore, current studies on SD systems have focused on the advancement of extended-release dosage forms, in addition to improving bioavailability. The availability of surface-active and self-emulsifying carriers, along with the development of innovative capsule-filling techniques, has revitalized research in this field. Given that the development of Solid dispersions for improving the absorption and prolonging the release of drugs involves mostly the same procedures, except for employing carriers that dissolve at a slower rate

for the latter purpose, it is anticipated that research in these two fields will advance concurrently and mutually benefit each other.[37]

1.9 Introduction to Diseases

1.9.1 Introduction to Tuberculosis

Tuberculosis (TB), sometimes called the "white death" or "consumption" in the past, is an infectious disease that is mainly caused by the Mycobacterium tuberculosis (MTB) bacteria. People with tuberculosis usually get it in their lungs, although it has the potential to disseminate to other organs and tissues.[38]

To decrease the spread of TB and prevent it, is possible by screening people who are at high risk for TB, finding and treating cases, and getting vaccinated with BCG vaccine. People who interact on a day-to-day basis with someone who has current TB are at higher risk compared to others. The medications are supposed to be taken over a long period for the treatment to work. Multiple drug-resistant tuberculosis (MDR-TB) rates are going up, which is a sign that antibiotic resistance is getting worse.[38], [39]

According to an estimation in 2018 it was recorded that almost 25% of people around the world carried a latent TB infection. Roughly 1% of the population develops a fresh disease annually. In 2022, 1.3 million individuals died and almost 10.6 million persons developed active TB. This is the second most often occurring cause of death from a viral disease after COVID-19. By 2021, the number of new cases was going down by about 2% each year. About 80% of people in Asian and African countries show TB positive by Tuberculin test. In the US, only 5–10% of people who take the test are positive. Tuberculosis has been around in people for a very long time.[40]

1.9.1.1 Signs and Symptoms

Based on signs and symptoms, TB can be divided into two types Latent TB and Active TB. Latent TB is asymptomatic; however, it can be determined using either a skin test or a blood test.[38]

Active tuberculosis symptoms in the lungs include:[41]

- Coughing for more than 3 weeks
- Chest pain
- Blood found in cough

- Persistent fatigue feeling
- Night sweats
- Chills
- Fever
- Anorexia
- Weight loss

Patients may experience the same symptoms along with localized pain in the affected area if the lungs are affected by tuberculosis.

Adolescents, youngsters, and infants may exhibit diverse tuberculosis symptoms. The symptoms experienced by teenagers are like those experienced by adults. Children aged one to twelve may have weight loss and a persistent fever.[41]

Babies may:

- Exhibit immobility or sluggishness
- Present a swelling in the fontanelle
- Display excessive irritability
- Experience vomiting or encounter difficulties while eating

1.9.1.2 Etiology

Mycobacterium tuberculosis is a particular kind of bacterium causing an infection that results in tuberculosis (TB). TB bacteria inhaled can settle in the lungs and start development. These bacteria then can spread via the bloodstream to the kidney, spine, and brain among other anatomical areas. The tuberculosis (TB) germs can live in the body in a dormant or latent state, not inflicting any symptoms at all. Latent tuberculosis (TB) infection is characterized by the presence of TB germs in the body without the outward manifestation of active TB disease symptoms. They do not show any symptoms of TB, do not have any signs of sickness caused by TB, and cannot transmit TB bacteria to other people. Those close by could breathe these bacteria and then start to feel sick. Treating latent tuberculosis (TB) is vital to stop the disease from turning active.[41], [42]

1.9.1.3 Pathophysiology

The way tuberculosis (TB) affects the body involves a complex relationship between the bacteria and the immune system of the person infected.[43], [44]

The disease advances through several stages: aerosolization, phagocytosis, phagolysosome obstruction, and replication. When someone who has active tuberculosis coughs, sneezes, or sings, they release tiny droplets into the air that contain the bacteria. When another person breathes in the air, the bacteria present in the air enter the respiratory system.

Aerosolization and Phagocytosis: The disease advances through several stages: aerosolization, phagocytosis, phagolysosome obstruction, and replication. People affected with active TB release tiny droplets containing bacteria when they cough or sneeze which mix with the air. Later when another person breathes the air, he/she also breathes in the bacteria that enter their respiratory system.

Phagocytosis and Phagolysosome Blockage: When the bacteria enter the lungs, they are engulfed by macrophages, which are a specific type of immune cell. The bacteria multiply within phagolysosomes, which are special organelles responsible for breaking down foreign particles and are found in macrophages. However, Mycobacterium tuberculosis (Mtb) can evade the immune response of the host by blocking the phagolysosomes, allowing it to survive and reproduce.

T-Helper Response and Granuloma Formation: The infection triggers the host's immune system to activate T-lymphocytes, a specific type of immune cell. T-lymphocytes identify the Mtb antigens and initiate an immunological reaction, resulting in the development of granulomas, which are collections of immune cells that enclose and try to control the infection.

Clinical Manifestations and Active Disease: The Location of infection and the immunological response of the individual can cause variance in the symptoms of TB. Tuberculosis commonly manifests in the lungs as a persistent cough, elevated body temperature, loss of body mass, and a general feeling of discomfort. Without treatment, the condition might advance to active tuberculosis (TB), which can result in respiratory failure, widespread infection, and mortality.

Extrapulmonary TB: Tuberculosis (TB) can disseminate to several regions of the body, including the lymph nodes, bones, joints, and kidneys, resulting in extrapulmonary TB. The manifestations of extrapulmonary tuberculosis differ according to the specific site of infection but can encompass

symptoms such as elevated body temperature, loss of body mass, and discomfort in the affected region.

Pathophysiological Stages

The pathophysiology of TB can be divided into several stages:

1. **Primary TB**: The primary infection, which frequently lacks symptoms and resolves on its own.
2. **Latent TB:** The germs remain in a state of dormancy within the host, and the individual does not possess the ability to transmit the infection.
3. **Active TB**: The bacteria undergo replication and induce symptoms, rendering the individual contagious.
4. **Extrapulmonary TB**: The germs disseminate to other regions of the body, resulting in extrapulmonary tuberculosis.

1.9.1.4 Treatment

Tuberculosis (TB) is a serious contagious disease that needs proper medical treatment to prevent it from spreading and to ensure complete recovery. Typically, doctors use four drugs, namely Isoniazid (INH), Rifampin, Pyrazinamide, and Ethambutol, to treat active tuberculosis (TB). These drugs work in tandem to eliminate the bacteria that cause TB and help prevent the bacteria from becoming resistant to treatment.

Treatment Regimen: Typically, TB is treated with a medication regimen lasting from six to twelve months. Factors such as the specific type of tuberculosis, the patient's age, and any pre-existing medical conditions can influence the duration of tuberculosis treatment[45], [46]. While there may be different approaches, the most used ones are:

- The standard treatment for drug-susceptible tuberculosis is a 6-month course. The treatment regimen requires the administration of four drugs over six months.
- The 4-month regimen is recommended for patients with smear-negative, culture-negative, non-cavitary pulmonary tuberculosis (TB) illness. The treatment entails the administration of four drugs over four months.

- The 4-month rifapentine-moxifloxacin regimen is employed to treat drug-susceptible pulmonary tuberculosis. The treatment entails the administration of two drugs over four months.

Treatment for Latent TB Infection: Commonly known as TB infection, it can also be called asymptomatic TB where there are no symptoms, and the bacteria present in the body have non-active replication. The common treatment of latent TB involves a single therapy approach such as isoniazid for 9-12 months. [45], [46].

Treatment for Drug-Resistant TB: Usually referred to as multidrug-resistant tuberculosis (MDR-TB), drug-resistant tuberculosis occurs when the bacteria develop resistance to the initial tuberculosis therapies. mainly consisting of second-line drugs including Bedaquiline, Pretomanid, and linezolid, given for a period of 18 to 24 months, the standard treatment for multidrug-resistant tuberculosis (MDR-TB) mainly consists of. [45], [46], [47].

1.9.2 Introduction to Major Depressive Disorder

Major depressive disorder (MDD), also known as recurrent depressive disorder, clinical depression, major depression, unipolar depression, or unipolar disorder, is a mental illness characterized by episodes of passive sadness, followed by low self-esteem and lack of interest in day-to-day activities.[48]

A person with a serious depressive disorder must consistently lack enjoyment or enthusiasm in daily activities or persistently have a low mod for two weeks or more, these shifts in mood can be due to either social, educational or occupational, and other aspects of functioning.[48]

1.9.2.1 Types of Depression

Primarily two categories of depressive illnesses are there [49]. They are as follows:

A) Unipolar Depression: About 75% of cases of unipolar depression—which usually does not run in families—are closely associated with demanding life events. Sometimes referred to as reactive depression, it is typified by restlessness and anxiety. About 25% of cases—known as endogenous depression—show a hereditary pattern and are not affected by outside events. Furthermore, present among these people are different symptoms. Although this difference is demonstrated in a clinical environment, there is little data to justify the belief that antidepressant drugs show appreciable specificity in differentiating between these disorders.

B) Bipolar Depression: Usually showing up in early adulthood, bipolar depression is somewhat rare and consists of alternating spells of mania and sadness spanning several weeks. Genetic linkage studies of afflicted families or using comparison between affected and non-affected individuals have not identified any specific genes that increase an individual's vulnerability to the disorder, despite a clear hereditary tendency. It is alternatively referred to as manic depression.

1.9.2.2 Signs and Symptoms

There are various signs and symptoms, intensity varying from patient to patient[49], [50]. Some of them are mentioned below

- Depressed mood
- Diminished interest or pleasure in all activities
- Decrease or increase in appetite
- Insomnia or hypersomnia nearly every day
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feelings of worthlessness or excessive or inappropriate guilt
- Diminished ability to think or concentrate
- Recurrent thoughts of death
- Recurrent suicidal ideation without a specific plan, or a suicide attempt

1.9.2.3 Etiology

Like other mental illnesses, the genesis of affective ones is still obscure. Combining genetic, hormonal, physiological, environmental, and social elements influence depression; each one of them adds to a person's sensitivity to acquiring the disorder. Furthermore, significant events in life can also have an influence. Although pharmaceutical therapies are helpful, emotional problems and metabolic abnormalities have no clear relationship.[50]

1.9.2.4 Pathophysiology

Like other mental illnesses, the genesis of affective ones is still obscure. Combining genetic, hormonal, physiological, environmental, and social elements influence depression; each one of them adds to a person's sensitivity to acquiring the disorder. Furthermore, significant events in life

can also have an influence. Although pharmaceutical therapies are helpful, emotional problems and metabolic abnormalities have no clear relationship.[51]

1.9.2.5 Treatment of Depression

The medications used in the treatment of Major depressive disorder are mainly Antidepressants.[49], [52]

A) Antidepressant drug treatment:

Antidepressant drugs fall into the following categories

1. Monoamine uptake inhibitors:
    - Non-selective uptake inhibitors, such as tricyclic antidepressants (TCAs) like imipramine and amitriptyline, as well as more contemporary antidepressants like venlafaxine (which is slightly selective for serotonin, albeit less so than selective serotonin uptake inhibitors), work by inhibiting the uptake of both noradrenaline and serotonin.
    - Including paroxetine, sertraline, fluvoxamine, fluoxetine, and duloxetine, selective serotonin reuptake inhibitors (SSRIs)
    - Maprotiline and reboxetine are selective, noradrenaline reuptake inhibitors
2. Monoamine Oxidase (MAO) Inhibitors:
    - Irreversible, non-competitive inhibitors not specific for the MAO-A and -B subtypes are tranylcypromine and phenelzine.
    - One such reversible inhibitor aiming especially at MAO-A is moclobemide.
3. Miscellaneous receptor-blocking drugs with poorly understood antidepressant effects include mianserin and trazodone.

B) Other treatments

- Electroconvulsive theory
- Nondrug treatment

1.9.3 Introduction to Prostate Cancer

The hallmark of prostate cancer is the too-rapid proliferation of cells in the prostate, a gland in the male reproductive system below the bladder. Screening procedures—typically using blood tests

measuring levels of prostate-specific antigen (PSA)—often reveal aberrant growth of prostate tissue. [53]

Tumors can metastasize, enabling them to migrate to different regions of the body, with a particular tendency to affect bones and lymph nodes.

1.9.3.1 Signs and Symptoms:

In most cases prostate cancer cases are asymptomatic, certain individuals may develop symptoms as the cancer progresses and metastasizes [54], [55], [56]. The following are typical indications and manifestations of prostate cancer:

Symptoms related to the urinary system:

- Excessive urination, particularly during nighttime\
- Urinary hesitancy or retention
- Diminished or disrupted urinary flow
- Hematuria
- Dysuria, characterized by pain or a burning sensation during urination
- Additional manifestations:
- Discomfort or rigidity in the dorsal region, pelvis, or upper legs
- Legs experiencing diminished strength or loss of sensation
- Anorexia
- Reducing body mass
- Tiredness
- Occasionally, individuals may experience erectile dysfunction.

1.9.3.2 Etiology

The development of prostate cancer is a complicated process with many factors that affect it[54], [56]. While the exact cause of prostate cancer is still not fully understood, several factors have been identified as possible culprits.

Risk Factors:

- **Age**: The chances of getting prostate cancer increase with age. People with age 60 or more are more susceptible to prostate cancer

- **Family History:** Men who have a history of prostate cancer in their family, especially close relatives like fathers, brothers, or sons, are more likely to get the disease themselves.
- **Ethnicity:** African American men are at a greater risk of getting prostate cancer compared to other men.
- **Genetics:** Genetic defects can lead to prostate cancer. Some of these genes including BRCA1 and BRCA2 carry these mutations.
- **Diet:** Prostate cancer risk is higher in those who overconsume red meat, dairy, and animal fat.
- **Hormones:** Hormones, particularly androgens like testosterone, are the primary agents that influence and drive the progression of this disease.
- **Infections:** people who contract infections caused by bacteria such as bacterium chlamydia are more susceptible to this sort of cancer.
- **Obesity:** People who are overweight or obese have a great risk of getting this cancer.
- Other Factors:
- **Environmental Factors:** Heavy metals and pesticides increase the risk of getting prostate cancer
- **Lack of Physical Activity:** men with little to no activity are also at high risk
- **Smoking:** Smoking enhances the chances of getting prostate cancer

Unknown Factors:

- **Genetic Predisposition:** According to some investigations done by researchers, PROSTATE CANCER may be caused by genetic elements, the exact genetic processes are yet unknown.
- **Epigenetic Factors:** Two epigenetic changes that might help prostate cancer progress are changes to histones and DNA methylation.
- **Microbiome:** The gut microbiome might help prostate cancer spread even if the exact processes are yet unknown.

1.9.3.3 Pathophysiology

Most prostate tumors start in the prostate's periphery. An abnormal cluster of cells known as prostatic intraepithelial neoplasia (PIN) forms when cell growth becomes uncontrolled. While

some PINs proliferate and develop into new layers of tissue, the genes expressed by these new layers shift from those of the original tissue location (p63, cytokeratin 5, and cytokeratin 14) to those of the cells lining the pancreatic duct (cytokeratin 8 and cytokeratin 18). An additional characteristic of these multilayered PINs is the overexpression of the AMACR gene, which is linked to the advancement of prostate cancer.[57]

PINs have the potential to develop into tumors in the long run. There are typically significant alterations to the genome that accompany this, such as the repeated duplication of chromosome sequences or the rearrangement of chromosome sequences.[54]

RB1 is responsible for one percent of tumors in localized areas and more than five percent of tumors in metastatic areas; protein kinase K (p53) is responsible for eight percent of tumors in localized areas and more than twenty-seven percent of tumors in metastatic areas; and many more mutations are found in genes that keep DNA from being damaged. The gene ATM is implicated in DNA repair. Mutations in ATM are identified in approximately seven percent of cases with localized disease and five percent of cases with metastasized malignancy.[55]

Alterations are displayed in more than 70% of cases in the androgen receptor signaling pathways. Alterations like these cause an increase in receptor activity or enhanced expression of the receptor gene, its activators (such as FOXA1), or its negative regulators (such as ZBTB16 and NCOR1). Androgen receptor disruptions are found in only 6% of castrate-sensitive metastatic cancer biopsies. Approximately 12-17% of tumors that exhibit sensitivity to castration treatment display deletions in the tumor suppressor PTEN gene. In contrast, a significantly higher percentage, exceeding 40% of tumors that are resistant to castration treatment also possess these deletions. PI3KCA/PI3KCB mutations are responsible for 6% of tumors, while AKT1 mutations account for 2% of tumors. Aberrant activation of the Wnt signaling pathway is found in 9% and 4% of tumors, respectively, making them less common.[57]

1.9.3.4 Treatment

The treatment of prostate cancer is divided according to the different stages of prostate cancer [58]. They are as follows:

Treatment of Stage I Prostate Cancer:

- Overseeing the patient

- Active observing. Hormone treatment can be prescribed should the cancer start to spread.
- Following a pelvic lymphadenectomy and radical prostatectomy, patients may undergo adjuvant radiation therapy
- Patient can undergo hormone treatment after undergoing External radiation therapy
- Patients can undergo brachytherapy also known as Internal radioactive seed radiation treatment.
- Clinical trial therapy consists of high-intensity focused ultrasound.
- Photodynamic therapy which uses photosensitizer or photosensitizing agent to kill cancer cells.
- Cryoablation and cryotherapy

Treatment of Stage II Prostate Cancer:

- Overseeing the patient
- Patient monitoring. Hormone treatment could be prescribed should the cancer start to spread.
- Following a pelvic lymphadenectomy and radical prostatectomy, patients may undergo adjuvant radiation therapy
- Patient can undergo hormone treatment after undergoing External radiation therapy
- Patients can undergo brachytherapy also known as Internal radioactive seed radiation treatment.
- Cryoablation and cryotherapy
- Clinical trial therapy consists of high-intensity focused ultrasound.
- Proton beam therapy
- Photodynamic therapy which uses photosensitizer or photosensitizing agent to kill cancer cells.
- Hormone treatment after radical prostatectomy as guided by clinical studies

Treatment of Stage III Prostate Cancer:

Patients can undergo hormone treatment after undergoing external radiation therapy

- After hormone therapy is given, the patient undergoes radiation therapy.
- Following a radical prostatectomy, patients may undergo adjuvant radiation therapy

- Waiting and watching.
- Monitoring the patient and if the cancer grows hormone therapy may be given

Treatment that can control cancer's growth and reduce the urinary symptoms may include the following:

- Patient can undergo brachytherapy also known as Internal radioactive seed radiation treatment
- Endocrine therapy
- Radiation therapy of new types from clinical trials.
- Cryoablation and cryotherapy

Treatment of Stage IV Prostate Cancer: Treatment for stage IV prostate cancer typically encompasses the following:

- Administration of hormones to regulate physiological processes.
- Combining hormone therapy with chemotherapy.
- Treatment with bisphosphonates.
- Post-radiation hormone therapy may be administered.
- Treatment using alpha emitter radiation.
- Observation without immediate intervention.
- A study that looks at the effectiveness of a radical prostatectomy with orchiectomy.
- To address an enlarged prostate, surgeons perform transurethral resection of the prostate, also known as TURP.
- The use of high-energy radiation in medical treatment with the specific goal of destroying cancer cells.

CHAPTER 2
LITERATURE REVIEW

2. LITERATURE REVIEW

2.1 Review of work done on Solid dispersion

Patel et al., (2014) [59] prepared and characterized ternary solid dispersion of domperidone fast-dissolving tablets. Ternary solid dispersion of domperidone was created to formulate stable sand fast-dissolving tablets. Both ternary and binary solid dispersion were obtained through the fusion method. Both were evaluated by drug content, dissolution efficiency, in-vitro dissolution studies, and solubility studies. While their solid-state characteristics were evaluated by DSC, FTIR, and XRD. The solid dispersion was then converted into tablets with a direct compression process. Stability studies were performed along with pre- and post-compression studies. The drug-to-polymer ratio of 1:2:1.5 of the drug: Gelucire 50/13: Poloxamer 188 containing solid dispersion showed the best results in dissolution studies. The FTIR, DSC, and XRD were found to be accurate. The ternary solid dispersion showed better results compared to binary solid dispersion in stability studies. As a disintegrant crospovidone (4%) showed good results with a disintegrating time of 19s and almost 100% dissolution in 30mins in 0.1N HCL. The results revealed that ternary agents stabilize and enhance the dissolution of solid dispersion compared to binary agents.

Aya M et al., (2022) [60] prepared and characterized fast-dissolving haloperidol solid dispersion tablets. This study was performed to formulate fast-dissolving tablets of haloperidol in solid dispersion form to enhance its dissolution properties and its anti-psychiatric effect. Preliminary trials were performed for solubility with various polymers. Formulation of solid dispersion were carried out using two techniques solvent evaporation and melting methods with peg 4000 as a carrier. Other excipients were used to formulate the solid dispersion into tablet forms. Pre and post-compression studies were performed. Solid excipients and drugs showed good compatibility when performed pre-compression studies. The SD2 batch showed good disintegration and water absorption ratio. Thermodynamic studies and in-vitro dissolution studies showed good results for batch SD2 and also the batch produced with the melting method. When the haloperidol SD tablets were compared with normal haloperidol tablets in rats the SD one showed better results.

Verma et al., (2017) [61] prepared and characterized Ivermectin's solid dispersion. This study work was done to create a formulation with enhanced solubility. Ivermectin comes in BCS class 2 because of its high permeability and low solubility. Because of its low solubility, there is variance in the absorption of drug from oral dosage forms. This low solubility of ivermectin can be

enhanced by formulating solid dispersion with Gelucire (44/14). The formulated solid dispersions were then evaluated further with drug content, yield, solubility studies, in-vitro dissolution studies, and solid-state characteristics were evaluated with FT-IR, DSC, and XRD.

Ramu A et al., (2024) [62] developed, tested, and analyzed how super disintegrants affected Olmesartan Medoxomilfast-dissolving tablets. This study was performed to enhance the dissolution rate and solubility of poorly soluble drugs by formulating them into solid dispersion. The formulation was done by 3 methods including physical mixing, SE, and KM using soluplus® as a carrier. The formulated solid dispersions were then evaluated for drug content, solubility studies, flow characteristics, and in-vitro dissolution studies. The solid-state characteristics were evaluated with FT-IR, DSC and XRD. The optimized solid dispersion was then converted into fast-dissolving tablets with the help of disintegrants like crocarmellose, crospovidone etc. The formulated fast-dissolving tablets were then evaluated for further parameters like weight variation, friability, disintegration test, dissolution studies, and content uniformity. The fast-dissolving tablets were prepared by combining solid dispersion with disintegrants.

Thota V, (2024) [63] prepared and characterized amorphous solid dispersion of atorvastatin calcium trihydrate using hot melt extrusion. This work aimed to enhance the solubility of calcium trihydrate by formulating solid dispersion by HME. Because of its scalable, single-step, continuous manufacturing technique, the HME technique shows success. HPMC K100 LV and PEG 3350, plasticizer was used to produce Atorvastatin solid dispersion with the help of a Hot-melt extruder. Milled extrudes were converted into tablets and their saturation solubility studies were performed in water for 48 hrs. The extruder milled extrudes with varying drug loading to investigate how drug loading affects drug release. The lead formulation F4 showed the best results when evaluated. The DSC performed showed the amorphous conversion of Atorvastatin calcium trihydrate which showed better results when compared with physical mixture lead formulation. so, indicating that this is the case even in terms of drug release. After one month of accelerated stability testing, the lead formulation showed no obvious changes.

Alotaibi BS et al., (2024) [64] designed and described glipizide solid dosage form with improved solubility. A poor water-soluble medicine in the BCS class II group is glipizide. For Formulating solid dispersion PVP and PEG both are utilized. The Drug to polymer ratio of 1:1, 1:2, 1:3, 1:4 was produced. The SE technique was utilized for formulation and PVP k-30,90 and PEG-600 were

utilized because of their higher effect on solubility of Glipizide. The In-vitro dissolution test was performed for all batches which showed that there is an increase in the dissolution rate of the drug when there is an increase in the concentration of polymer. The batch with polymer PVP showed better results than the batch with PEG. The Best batches were then converted into fast-dissolving tablets which passed Pharmacopeial and non-pharmacopeial tests. Drug: polymer interactions in the solid state were indicated by Fourier transform Infrared (FTIR) spectroscopy X-ray diffraction (XRD) and Differential scanning calorimetry (DSC). Characteristics of the solid dispersion samples revealed their compatibility with the polymer and drug.

Mir KB et al., (2024) [65] prepared and characterized a pharmacokinetic assessment of glibenclamide dispersion for bioavailability enhancement in Wistar rats. ASDs of GLB were prepared with poloxamer-188 to enhance their bioavailability. The solubility of the drug was enhanced with poloxamer-188 which in turn increased the dissolution rate. The formulation of ASD was done by the SE method. The physical state was defined by DSC, XRD, and FT-IR. GLB: PLX-188 ratio of 1:6 (SDE4) showed the best results in-vitro dissolution by releasing 90% of the drug in 3 hrs. The pharmacokinetic analysis was performed in rats with SDE4 batch which showed increased bioavailability. During the six-month study, solid dispersion formulation (SDE4) formulation was found to be stable.

Adeli E, (2016) [66] prepared and characterized azithromycin binary solid dispersions with multiple grades of PEG. Thus, the main goal of this work was to formulate solid dispersions of azithromycin using several grades of PEG to enhance solubility and dissolution. The formulation was done by SE method and PEG grades of 4000, and 6000. 8000, 12000, and 20000 were used in different ratios. From the Infrared (IR) spectra, the drug and polymer had no chemical incompatibility. Using DSC, XRD, and SEM the formulations were evaluated for solid-state characteristics. The batch with PEG 6000 showed increased solubility and dissolution rate compared to others.

Simonazzi A et al., (2018) [67] prepared and characterized solid dispersion as a means of enhancing Albendazole Biopharmaceutical Behavior. Albendazole (ABZ) solubility and dissolution profiles were improved by formulating solid dispersion using poloxamer 407. After the formulations of solid dispersions mathematical models and comparison with physical mixtures, pharmaceutical ABZ, and a commercial formulation were computed. There was an exponential increase in the dissolution rate of ABZ. When the solid dispersion ABZ was compared with the commercial

formulation, the commercial formulation showed dissolution in 40minutes all the solid dispersion needed only 2.2minutes to reach 90% ABZ dissolution

Sood S et al., (2020) [68] improved nitazoxanide solubility using solid dispersions technique: formulation, testing cytotoxicity. Nitazoxanide (NTZ) finds extensive use as an anti-microbial agent. The NTZ is poorly soluble which affects its bioavailability. Usually considered as a fundamental requirement for improved absorption and bioavailability is low aqueous solubility. This study aimsto formulate solid dispersions of NTZ by the HME technique. Later on, evaluations were performed such as drug content, solubility, in vitro dissolution, FTIR, DSC, SEM, XRD, in vitro MTT safety on HEK-293 and A-549, and stability study. XRD results revealed following the formation of solid dispersion. The solid dispersion showed the disappearance of crystalline peaks which is attributed to its Amorphous nature. NTZ released from solid dispersion into a simulated gastric releasing medium (pH 1.2) was found in vitro to be rather efficient. Moreover, cytotoxicity research revealed a safe for human use. Stability analyses showed no clear variation in the physical characteristics of solid dispersion.

Yang HB et al., (2017) [69] characterized and prepared solid dispersion of quercetin using phospholipids. In This study, the lipid solubility of the drug Quercetin was enhanced by formulation of solid dispersion with phospholipid. Physical characterizations of the drug as well as its PM were performed by FTIR, DSC, SEM, and XRD, to determine any changes that can occur in the formulations. Solubility of free quercetin and Solid dispersion were performed in n-octanol and water with different ph. It was demonstrated that after solid dispersion, the apparent oil/water partition coefficient changed dramatically; this could help to improve bioavailability and lower the dosage of the drug.

Alhamhoom Y et al., (2024) [70] prepared and characterized pH-modified amorphous solid dispersion-based ODTs tablets of cefdinir. pH-modulated solid dispersions were formulated by solvent evaporation techniques using hydrophilic polymer and alkalizers. Enhancement of solubility was found in pH 1.2 by ASD produced using PEG 6000 with meglumine as alkalizers among several carriers. Physical characterization (DSC, FTIR) showed no signs of polymer-drug incompatibility. ASD8 showed an amorphous state in physical characterization. In in-vitro dissolution, ASD8 showed greater results than any other batch which is why it was chosen. The ODTS were prepared for ASD8. Under demanding physiological pH conditions common in the

stomach, the tablets or ODTs produced from ASD8 showed a reduction in pH-dependent solubility and dissolution characteristics associated with CEF. ODTs of ASD8 thus probably help to efficiently control different infections and prevent the emergence of drug-resistant strains, thus improving the curing rates.

Pardhi VP et al., (2024) [71] designed, developed, and tested bedaquiline fumarate – Soluplus® – solid dispersion. This drug comes under BCS class 2 because of its poor solubility which affects the bioavailability of the drug. This work aims to use Soluplus® to enhance the solubility and dissolution of drugs by formulating solid dispersion. Two solid dispersion systems were generated: binary solid dispersion (BD) and ternary solid dispersion (TSD), where ternary solid dispersion showed greater solubility compared to binary solid dispersion in BQF. Because of the higher solubility of Soluplus® than Poloxamer 188, Soluplus® was used. The amorphous Soluplus® polymer was chosen in the present work to formulate BSD and TSD with BQF.BQF was found to be amorphous in solid dispersion when several characterization tests were performed. FTIR showed no incompatibility between the drug and polymer. TSDs have shown improved solubility and bioavailability in pharmacokinetic studies. Therefore, the present work reveals a feasible formulation approach to improve the solubility of BQF so raising its biopharmaceutical performance.

Nijhawan M et al., (2024) [72] prepared and characterized Felodipine Solid Dispersion using Hot Melt Extrusion for Solubility Enhancement. After oral administration, the drug undergoes significant first-pass metabolism which leads to only 15% of bioavailability. This causes difficulty in therapeutic efficiency. The solubility and dissolution rate of the drug were enhanced by immediate release formulation prepared by solid dispersion technique. The carrier Eudragit EPO, NE30Dwas used according to the drug-polymer ratio. The best batch turned into tablets. Evaluation parameters were performed for the formulated batches. Based on the cumulative percentage release it was found that among the several combinations of drug and Eudragit EPO, only drug and Eudragit EPO by themselves were released in high percentage. It was found that by increasing the concentration of Eudragit NE30D the dissolution rate decreases. Drug release dropped dramatically even with a smaller ratio increase in stabilizers. According to the dissolution profile, the solid dispersion tablets and the solid dispersion alone have rather similar release profiles. HME raises the felodipine dissolution rate by solid dispersion formulation.

Thawani LM, (2023) [73] prepared and characterized in-vitro mefenamic acid oral disintegrating tablets using solvent evaporation and HME. This study was conducted to enhance the solubility of mefenamic acid. Thus, to increase the solubility, the solid dispersion was formulated for Mefenamic acid and Eudragit RL PO by SE method; then, Hot Melt Extrusion was used to produce the extrudes.; prepared extrude were assessed for their physical and chemical characteristics. The melting temperature of the Mefenamic Acid (MA) dropped with increasing drug loading, according to the Differential Scanning Calorimetry (DSC) thermograms. The FT-IR spectra showed no new formation of bonds between drug and polymer. This implies that during the extrusion process, the drug and polymer stayed physically mixed and underwent no chemical transformation. In-vitro-dissolution studies were performed which showed that extrudes had a higher dissolution rate compared to pure MA. The increase in drug loading also increased the dissolution rate.

Alghadi RY et al., (2023) [74] improved solubility of Atorvastatin Tablets utilizing Fenugreek Seed Mucilage and Solid Dispersions. Since atorvastatin is very slightly soluble in distilled water and pH 7.4 phosphate buffer, there is restricted absorption of the drug orally leading to a reduction in the bioavailability (about 14%). The aim of this work was to enhance the solubility which leads to an increase in the bioavailability by formulating solid dispersion of fenugreek seed mucilage. Extracted from the seed, mucilage was assessed for percentage practical yield, flow characteristics, pH value, FTIR spectroscopy, and flow dynamics. Saturation solubility was determined for Fenugreek seed mucilage SDs, HPMC SDs and pure drug from solid dispersion with varying polymer concentrations. Tablets were tested and assessed first from solid dispersion with the highest saturation solubility. The tablets displayed acceptable physicochemical properties when evaluated for different parameters. FSM can be considered a potential ingredient to enhance solubility by forming solid dosage form.

Adsare MV et al., (2024) [75] designed, developed, characterized, and optimized a Fast-Dissolving Tablet for Celecoxib. This study was performed todevelop fast-dissolving tablets of Celecoxib by formulating solid dispersions with PVP k30 and then making tablets out of those solid dispersions. The researchers prepared different batches according to drug-to-polymer ratio and found that the batch containing a ratio of 1:4 showed good solubility compared to pure drug and other batches The FDTs were tested in a 2% SLS solution, and the in vitro release was ranked by the amount of drug that was released after 50 minutes. The findings showed that FDTs including 1:4 ratio

celecoxib solid dispersions showed better solubility than the pure drug. This formulation approach sought to reach a supersaturated drug release, enabling quick absorption upon oral intake.

Tabassum G et al., (2023) [76] prepared and characterized Resveratrol's solid dispersion is rather poor. This study work was conducted to formulate the solid dispersion of resveratrol with HP β-Cyclodextrin to enhance the dissolution rate of this drug. Using HP β-Cyclodextrin different drug-to-polymer ratios of 1:2, 1:5, and 1:8 formulations were created with 4 different techniques (Physical mixture, Co-precipitation method, Co-evaporation method, kneading method). Different pre-formulation studies were performed like FT-IR, determination of Lambda Max, solubility studies, melting point, ionization study, and drug-polymer compatibility study. Weight variation tests, drug content, lock length, moisture permeation tests, in-vitro dissolution studies, stability studies, and post-formulation studies were conducted. Every preformulation study produced results within the specification references. All the investigations performed showed better results and passed the IP criteria. Using HP β-Cyclodextrin as a carrier, formulation "K1," with a 1:2 ratio, prepaid by the Kneading method shows better release i.e., 84.06% based on the in-vitro drug dissolution profiles than other techniques.

Nakka VN et al., (2024) [77] prepared and characterized Efavirenz Solid Dispersion using Fusion Techniques and SE. In the present work, Efavirenz (EFV) was formulated into solid dispersion by fusion method and SE method where Sugar carriers like xylitol, sorbitol, lactulose, and one non-sugar carrier like surplus are used. The solubility of the drug was first evaluated in solvent and then through the use ofthe fusion method and SE method with several different carrier ratios (1:0.5, 1:1, 1:1.5, 1:2, and 1:3) Solid dispersion (S.D.s) was produced. Drug content uniformity, saturation solubility analyses, and in vitro dissolution investigations were applied to the produced SDs. The formation of intramolecular hydrogen bonds was discovered by FTIR and pre-formulation studies. In the 7.4 pH phosphate buffer, EFV proved to be more soluble than among the other solvents. Carrier concentration and %yield changed EFV's saturation solubility; in vitro drug dissolution studies were conducted on the S.D.s. The studies showed that the SDs produced through the SE method released more amount of drug than SDs produced by the Fusion method however the Release of formulations was greater than pure drug.

Gill et al., (2014) [78] formulated and evaluated Glimepiride solid dispersion tablets. Glimepiride is a poorly soluble drug that has limited bioavailability. The solid dispersion was created with

Poloxamer-188 to create a model medicine by formulating tablets from the optimal batch of solid dispersions. Different concentrations of disintegrant croscarmellose are used during the direct compression process to make tablet formulations. The formulated tablets from solid dispersion were further evaluated with different parameters including weight variation, %friability, % drug content, hardness, disintegration test, dissolution efficiency, XRD, and in-vitro dissolution studies. Among all the batches, the batch with drug to polymer ratio of 1:4 provides the best results in dissolution efficiency and dissolution profiles and in tablet formulation the batch with 5% croscarmellose shows the best disintegration and dissolution profile. Results showed that Poloxamer-188 presents a potential polymer for improving GMP solubility.

2.2 Review of work done on Rifampicin

Theja D et al., (2012) [79] formulated and evaluated solid dispersion of rifampicin. Solubility is a crucial factor in achieving the desired concentration of a drug in the systemic circulation to elicit a pharmacological reaction. Water-insoluble medicines may necessitate high dosages to achieve therapeutic plasma concentrations following oral delivery. For a medicine to be absorbed, it must be in the form of a watery solution at the location where absorption occurs. Most medications exhibit weak acidity and weak basicity, resulting in limited solubility in water. Therefore, several methods are employed to enhance the solubility of medications that have low water solubility. These methods include micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, and hydrotropy. The objective of this study was to elucidate the improved solubility of rifampicin through the utilization of solid dispersion technology and physical mixing with PEG6000. The drug and carrier ratio are 1:1, 1:2, 1:3, and 1:10, respectively. The generated samples underwent evaluation using scanning electron microscopy (SEM), drug content analysis, in-vitro tests, wettability and solubility testing, infrared spectroscopy (IR) research, and angle of repose measurement. The in-vitro drug release of the solid dispersion (SD 10) was seen to be rapid and complete within 2 hours under pH 7.4 conditions. This release profile was then compared to that of the pure drug and physical mixture. The IR Spectra analysis indicated that there was no interaction between the medication and polymers in the produced solid dispersions.

Rajesh et al., (2013) [80] performed liquisolid technique to enhance the solubility of rifampicin**.** Various techniques are used for the enhancement of the solubility of poorly soluble drugs which include liquisolid technique, micronization, nanonization, sonocrystallization, supercritical fluid method, spray freezing into liquid and lyophilization, evaporative precipitation into aqueous

solution, use of surfactant, use of co-solvent, hydrotropy method, use of salt forms, solvent deposition, solubilizing agents, modification of the crystal habit, co-crystallisation, complexation and drug dispersion in carriers. The "Liquisolid" technique is a novel and capable addition towards such an aim for solubility enhancement and dissolution improvement, thereby increasing bioavailability. Rifampicin is an orally administered broad-spectrum anti-tubercular drug. It is freely soluble in chloroform and DMSO; soluble in ethyl acetate, methanol, tetrahydrofuran; and slightly soluble in acetone, water, and carbon tetrachloride. Liquisolid formulations were prepared by Avicel PH 102 as carrier material and Aerosil 200 as coating material. PEG 400, PG, and Polysorbate 80 were used as liquid vehicles. The absence of significant drug-carrier interaction was confirmed by IR studies. High drug content and high dissolution rate were observed in F2.

Arca et al., (2018) [81] formulated Amorphous Solid Dispersion of rifampin in Cellulose ω-Carboxyalkanoate Matrices**.** Tuberculosis (TB) is a deadly infectious disease; approximately 2 billion people are currently latently infected with the causative agent *Mycobacterium tuberculosis*. Approximately 8 million new active cases and 2 million deaths due to TB are recorded annually.[1] Rifampin (Rif) is a vital first-line TB treatment drug. Its effectiveness is hampered by the high dose required (600 mg 1×/day) and by its moderate, variable bioavailability. These issues can be explained by Rif instability at gastric pH, limited solubility at neutral pH, polymorphism, and stimulation of its metabolism. To overcome these obstacles, we developed new cellulose-based oral drug delivery systems aiming to increase and make more consistent Rif solubility and bioavailability. Amorphous solid dispersions (ASDs) of Rif with cellulose ω-carboxyalkanoates (cellulose acetate suberate, cellulose acetate propionate adipate, and cellulose acetate butyrate sebacate) were prepared and compared with crystalline Rif (negative) and carboxymethyl cellulose acetate butyrate ASD (positive) controls. Cellulose ω-carboxyalkanoate ASDs prevented acid-catalyzed degradation in conditions mimicking the acidic stomach and provided the complete release of intact Rif at intestinal ph. Rif incorporation into ASD in these novel cellulose derivative matrices creates the potential for convenient, robust, consistent, and high Rif oral bioavailability for the treatment of TB.

2.3 Review of work done on Duloxetine Hydrochloride

Pandya et al. (2015) [82] formulated and characterized ternary complex of poorly soluble Duloxetine Hydrochloride. Duloxetine hydrochloride (DXH) suffers from poor solubility and

thereby poor absorption, which ultimately leads to poor bioavailability. In present study, an attempt has been made to formulate and characterize duloxetine hydrochloride (DXH) complex, using β-cyclodextrin (β-CD) and different hydrophilic polymers in order to enhance its solubility and dissolution rate. Phase solubility study was used to investigate the interaction of the drug in binary systems (DXH-β-CD) as well as ternary systems (DXH-β-CD-hydrophilic polymer). It was observed that solubilization of DXH by β-CD was further enhanced by using HPMC K4M at 0.1% w/v concentration. Several methods were used to prepare ternary complex of DXH-β-CD-HPMC K4M. Ternary complex prepared by co-evaporation method containing DXH-β-CD-HPMC K4M in the ratio of 1:1.10:0.01 has shown the fastest dissolution rate (53.65 ± 2.83% in 5 min) as compared to pure DXH (3.03 ± 1.88% in 5 min) as well as other methods used to prepare these complexes. The prepared ternary complex system was characterized by the help of X-ray powder diffraction studies, differential scanning calorimetry and scanning electron microscopy. It was observed that enhancement in solubility as well as dissolution rate of DXH was due to formation of ternary complex system.

Aaron A et al., (2023) [83] formulated a solid dispersion of Duloxetine Hydrochloride to enhance its solubility. The core objective of the present study is to enhance the solubility of poorly-water soluble drug Duloxetine HCl, a selective serotonin and norepinephrine reuptake inhibitor antidepressant (SSNRI) by using different hydrophilic carriers and formulating them into solid dispersions with solvent evaporation technique and establishing shelf life of the same by conducting stability studies. The solubility of Duloxetine HCl in various hydrophilic carriers (polymers) such as PVP K30, HPMC, HPMC AS, and Killiphor P188 was studied. A total 0f 15 SD formulations were prepared by solvent evaporation technique with different polymers and evaluated for preformulation studies, particle size analysis, drug content, in-vitro dissolution studies, and accelerated stability studies. The dissolution profile of pure SD formulation F14 prepared with HPMC AS in 1:3:(0.5+0.5) ratio of drug: polymer: surfactants [Table.3] showed a maximum drug release of 99.94 in 15 mins. Solubility of Duloxetine HCl was also increased by 15 folds in SD formulation F14 when compared to pure drug. Maximum dissolution rate is attributed to the use of a combination of surfactants which showed a synergistic effect in decreasing the interfacial tension and enhancing the wettability. This synergistic effect acted as the key factor in further enhancing the dissolution rate to the maximum.

2.4 Review of work done on Abiraterone Acetate

Katekar et al. (2022) [84] augmented experimental design for bioavailability enhancement a robust formulation of abiraterone acetate. Abiraterone acetate (ABRTA) is clinically beneficial in management of metastatic castration-resistant prostate cancer (PC-3). With highlighted low solubility and permeability, orally hampered treatment of ABRTA necessitate high dose to achieve therapeutic efficacy. To triumph these challenges, we aimed to develop intestinal lymphatic transport facilitating lipid-based delivery to enhance bioavailability. ABRTA-containing self-nano emulsified drug delivery (ABRTA-SNEDDS) was statistically optimized by D-optimal design using design expert. Optimized formulation was characterized for particle size, thermodynamic stability, *in vitro* release, *in vivo* bioavailability, intestinal lymphatic transport, *in vitro* cytotoxic effect, anti-metastatic activity, and apoptosis study. Moreover, hemolysis and histopathology studies have been performed to assess pre-clinical safety. Nano-sized particles and successful saturated drug loading were obtained for optimized formulation. *In vitro* release upto $98.61 \pm 3.20\%$ reveal effective release of formulation at intestinal pH 6.8. ABRTA-SNEDDS formulation shows enhanced *in vivo* exposure of Abiraterone (2.5-fold) than ABRTA suspension in Sprague–Dawley rats. *In vitro* efficacy in PC-3 cell line indicates 3.69-fold higher therapeutic potential of nano drug delivery system. Hemolysis and histopathology study indicates no significant toxicities to red blood cells and tissues, respectively. Apparently, an opportunistic strategy to increasing bioavailability of ABRTA *via* intestinal lymphatic transport will create a viable platform in rapidly evolving chemotherapy. Enhanced translational utility of delivery was also supported through *in vitro* therapeutic efficacy and safety assessments.

Yang et al. (2022) [85] prepared multicomponent crystal forms of Abiraterone Acetate to enhance its dissolution and bioavailability. Abiraterone acetate (ABA), the first-line drug for the treatment of metastatic castration-resistant prostate cancer (mCRPC), is administered at a high daily dosage of 1000 mg due to its poor solubility, and its fasted absolute oral bioavailability is estimated to be less than 10%. In this work we have focused on developing multicomponent forms with improved dissolution behaviors and bioavailability. Two salts of ABA with malonic acid (ABA-MA) and saccharin (ABA-SAC), and five cocrystals with *trans*-aconitic acid (ABA-TAA), 1-hydroxy-2-naphthoic acid (ABA-1HNA), pyrocatechol (ABA-PCA), resorcinol (ABA-RES) and hydroquinone (ABA-HDE) were successfully obtained. Their crystal structures were elucidated by single crystal X-ray diffraction, and these multicomponent forms were fully characterized by powder X-ray diffraction, thermal analysis and Fourier Transform Infrared spectra. Among them,

ABA-TAA cocrystal shows substantial enhancements both in the solubility and intrinsic dissolution rates in different buffer solutions. In the meantime, we unexpectedly found the gelation of ABA-MA salt and ABA-SAC salt in pH 2.0 buffer solution. The gel-like materials generated on the surface of the drug will suppress the release of ABA. Moreover, *in vivo* pharmacokinetic study on beagle dogs was conducted for ABA-TAA cocrystal preparation and ABA commercial product, and ABA-TAA cocrystal preparation shows enhanced absorption. These advantages in dissolution behaviors and bioavailability demonstrate the potential of ABA-TAA cocrystal to be a better candidate for the treatment of mCRPC compared with ABA.

Liu et al. (2022) [86] developed abiraterone acetate nanocrystal tablets to enhance its oral bioavailability. Abiraterone acetate is a prodrug of abiraterone used in combination with prednisone as a standard therapeutic strategy for hormone-resistant prostate cancer (mCRPC). Due to the poor solubility and permeability, the release and absorption of abiraterone acetate are low and reduce its bioavailability. In this project, abiraterone acetate tablets prepared using nanocrystal technology were developed to overcome the drawbacks of normal tablets by enhancing in vitro dissolution rate and oral bioavailability. The abiraterone acetate nanocrystal suspensions were prepared by top-down wet milling method using a planetary ball mill with the mixture of Poloxamer 407 and Poloxamer 188 as the optimized stabilizer at a ratio of 7:1. The optimized nanocrystals were freeze-dried and characterized using DLS, TEM, DSC, and XRD. The abiraterone acetate nanocrystal tablets significantly improve the in vitro dissolution rate of abiraterone acetate compared to raw materials. Although exhibiting a similar dissolution rate compared to the Zytiga® tablets, the nanocrystal tablets significantly improve the oral bioavailability with C_{max} and AUC_{0-t} being 3.51-fold and 2.80-fold higher, respectively, in the pharmacokinetic study. The present data indicate that nanocrystal is a promising strategy for improving the dissolution and bioavailability of abiraterone acetate.

CHAPTER 3
AIM AND OBJECTIVES

3. AIM AND OBJECTIVES

3.1 Aim

The main aim of this research work was to augment the solubility of poorly water-soluble drugs, such as rifampicin, Duloxetine Hydrochloride, and Abiraterone Acetate, by formulating them into solid dispersions. This formulation process was intended to enhance the dissolution rate of the drugs.

Insufficiently soluble medicines require greater doses to achieve therapeutic levels in the bloodstream following oral ingestion. Enhancing the degree and speed of dissolution is extremely advantageous for compounds like this, as it can result in higher and more consistent absorption through the oral route, leading to a reduction in the required dose for effective treatment.

Currently, pharmaceutical procedures offer numerous methods to improve the rate at which poorly water-soluble medicines dissolve. The solid dispersion technique is employed to improve the solubility, dissolution rate, and absorption of many medications that are not soluble in water.

The Secondary aim is to investigate the potential of Soluplus® as carrier for the enhancement of those poorly soluble drugs and to evaluate its impact on the solid dispersion formulation.

3.2 Objectives

The Specific Objectives of the present research were:

1. Review existing Literature on solid dispersion technology, including its origins, characterization, and preparation Methods.
2. To study the possible interaction between Drug and polymer by FTIR
3. To select a suitable method for the preparation of solid dispersion and compare them
4. To formulate Solid Dispersion.
5. To Characterize the physical properties of solid Dispersion Including Drug Content, percentage yield, DSC, XRD, etc.
6. To conduct dissolution studies to evaluate the release behavior of solid dispersion.
7. To compare the release behavior of the solid dispersion with the pure drug.

Rifampicin is a prominent medicine used in the treatment of Tuberculosis. It was chosen for its low solubility and specific solubility in acidic environments, which makes it suitable for improving solubility. This study aims to improve the solubility of the substance and decrease its solubility that is reliant on pH.

Similarly, Duloxetine hydrochloride is employed for treating major depressive illness. Despite its low dosage, it can still lead to toxicity. Therefore, by increasing the drug's solubility, we can minimize the required dosage.

Among these three medications, Abiraterone Acetate has the greatest dosage. Due of its limited solubility, the current dosage is 1 gram per day, and our goal is to decrease the dosage by improving its solubility.

CHAPTER 4
PROFILES

4. PROFILES

4.1 Drug Profiles:

4.1.1 Rifampicin (Rifampin)

Rifampin, sometimes referred to as rifampicin, falls into the antibacterial class of medications. Many different mycobacterial infections as well as gram-positive bacterial infections are managed and treated with this drug. Against a broad spectrum of gram-positive cocci, including Mycobacteria and Clostridium difficile, as well as particular gram-negative species including Neisseria meningitidis, N gonorrhoeae, and Hemophilus influenza, rifampin has antibacterial action.[87], [88], [89]

Drug: Rifampicin

IUPAC-Name: 5,6,9,17,19,21-Hexahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-8-[N-(4-methyl-1-piperazinyl)formimidoyl]-2,7(epoxypentadeca[1,11,13]trienimino)naphtho[2,1-b]furan-1,11(2H)-dione 21-acetate

Structure:

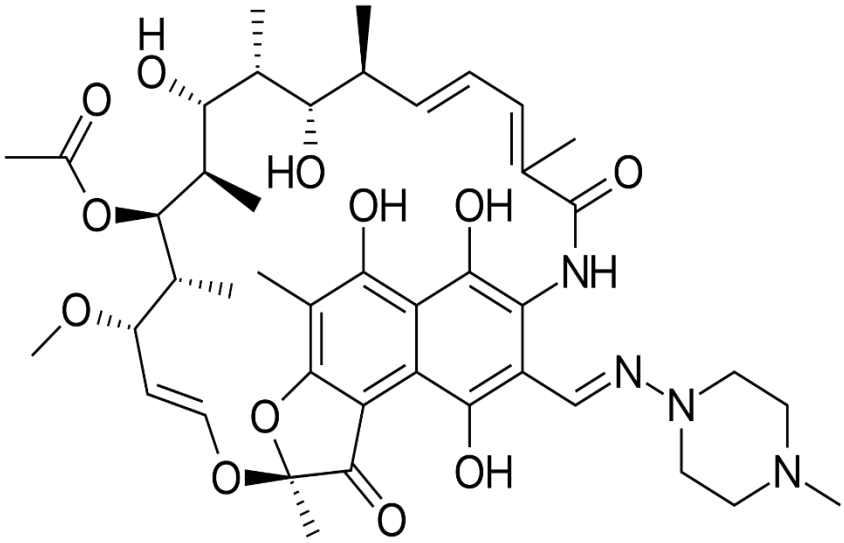

FIGURE: 4.1 CHEMICAL STRUCTURE OF RIFAMPICIN

Molecular Formula: $C_{43}H_{58}N_4O_{12}$

Molecular weight: 822.953 g/mol

Melting point: 192°C

Description: Red powder and crystalline in nature

Solubility: Soluble in DMSO, Methanol, Chloroform, and Acetone.

Stability/Storage: Protect it from light exposure. Rifampicin remains stable as a solid at temperatures up to 70°C. Acidic or alkaline conditions at 25°C can lead to degradation.

Dosage form: Capsule, Injection

Dose: Capsule-150, 300, and 600mg, Injection-600mg/10ml

Mechanism of action: Rifampicin hinders bacterial DNA-dependent RNA synthesis by blocking bacterial DNA-dependent RNA polymerase.

Crystallographic and biochemical evidence indicates that Rifampicin interacts with the RNA polymerase β subunit's pocket located within the DNA/RNA channel, but not at the active site. The inhibitor hinders RNA synthesis by physically obstructing elongation, hence inhibiting the production of host bacterial proteins. Rifampicin inhibits RNA synthesis by utilizing the "steric occlusion" mechanism. It hinders the formation of the second or third phosphodiester link between nucleotides in the RNA backbone, hence limiting the extension of the RNA transcript beyond 2 or 3 nucleotides from the 5' end.

A recent study demonstrated that Rifampicin binds to cytochrome P450 reductase, causing changes in its shape and activity. This alteration affects the enzyme's ability to assist the metabolism of progesterone through CYP21A2.

Bioavailability: >70%

Protein binding: 80%

Metabolism: Liver and intestinal wall

Plasma half-life: 3–4 hours

Time to peak: The time to peak concentration for Rifampicin (also known as Rifampin) varies. When taken orally, it typically reaches peak serum levels within 2 to 4 hours after administration.

Peak plasma concentration: Within two hours of taking a single 600 mg dose, the serum concentration usually reaches its peak, which is around 10 μg/ml. Furthermore, an independent

indicator of sterilizing action is a peak concentration (Cmax) of Rifampicin that exceeds 8.2 µg/ml. Monitoring the levels of the therapeutic drug at 2, 4, and 6 hours after taking the dose can help in adjusting the dosage to reach the desired concentration of Rifampicin, which is advised to be 8 µg/mL or higher.

Excretion: 30% in urine, 60-65% in feces

Adverse effects: Rifampicin, sometimes referred to as Rifampin, can induce a range of adverse effects. Below are many often encountered examples: Gastrointestinal discomfort, acid reflux, queasiness, or headache may manifest. Rifampicin can induce a change in the color of body fluids, such as urine, perspiration, saliva, or tears, resulting in an orange-red hue. This side effect is benign and will resolve upon discontinuation of the medication.

Apart from above mentioned side effect, more detrimental outcomes such as: Agitation, Gums that are actively releasing blood, the presence of blood in urine or stools, Contusion, Tightness in the chest, confusion, Pyrexia with or without rigors, Vertigo, Elevated blood pressure Itching, rashes, or redness of the skin, Abnormal bleeding or bruising, Jaundice may occur.

Applications: Rifampicin, sometimes referred to as Rifampin, has multiple significant applications

Treatment of Tuberculosis (TB):

- Rifampicin is an essential element in the therapy of tuberculosis.
- It is utilized in conjunction with other antibiotics, including Pyrazinamide, Isoniazid, and Ethambutol.
- The conventional treatment protocol entails the daily administration of medication for a minimum duration of six months in order to effectively combat tuberculosis.

Prophylaxis for Meningococcal Meningitis and Haemophilus influenzae Type B Meningitis:

- As standalone treatment for prophylaxis for people who were in close proximity to person who were suffering from certain forms of meningitis Rifampin is used.
- Helps in the prevention of infection in individuals.

Combination Therapy to Prevent Resistance:

- To prevent the emergence of drug resistance, Rifampicin is provided in tandem with other medications.
- Additionally, it reduces the total length of the treatment.

4.1.2 Duloxetine Hydrochloride

Drug: Duloxetine Hydrochloride

Duloxetine hydrochloride is a medicine used to treat depression. It works by selectively inhibiting the reuptake of serotonin and norepinephrine, which are neurotransmitters in the brain. Its main application is in the treatment of depression, anxiety, fibromyalgia, and chronic pain diseases including diabetic peripheral neuropathy, chronic musculoskeletal pain, and arthritis. Duloxetine functions by augmenting the concentrations of serotonin and norepinephrine in the brain, thereby facilitating the regulation of mood and pain.[90], [91], [92]

IUPAC-Name: (3*S*)-*N*-methyl-3-naphthalen-1-yloxy-3-thiophen-2-ylpropan-1-amine; hydrochloride

Structure:

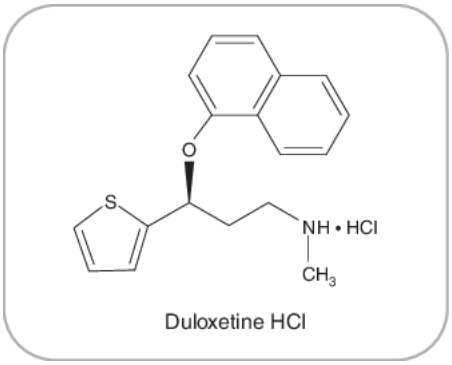

FIGURE: 4.2 CHEMICAL STRUCTURE OF DULOXETINE HYDROCHLORIDE

Molecular Formula: $C_{18}H_{19}NOS$ HCL

Molecular weight: 297.4145 g/mol

Melting point: 169°C

Description: white Powder

Solubility: soluble in organic solvents such as Ethanol, DMSO, and dimethyl formamide (DMF).

Stability/Storage: Keep duloxetine hydrochloride containers tightly sealed in a cool, shaded spot with good air circulation and ignition sources. The recommended storage temperature is 4°C (sealed storage, away from moisture). In solvent: -80°C (for 6 months) or -20°C (for 1-month, sealed storage, away from moisture)

Dosage form: capsules

Dose: 20-60mg

Mechanism of action: Duloxetine HCl works by inhibiting the uptake of serotonin and norepinephrine in neurons. Enhancement of the effect of serotonin and norepinephrine in CNS can be attained by Duloxetine HCl. Duloxetine exhibits a notable affinity for multiple receptors.

Bioavailability: 50%

Protein binding: 95%

Metabolism: Hepatic

Plasma half-life: 12h

Time to peak: Six hours or so taken without food. If taken with food, though, it might take up to ten hours to reach optimal concentration.

Peak plasma concentration: The maximum concentration of duloxetine hydrochloride (DUL) in the bloodstream is reached around 6 hours after taking the dose. The PPC ranges between roughly 47 μg /ml (40 mg twice daily) and 110 μg /ml (80 mg twice daily).

Excretion: 70% in urine, 20% in feces

Adverse effects: Duloxetine hydrochloride (DUL) might have several adverse effects. Below are many often-encountered examples: The side effects of the medication include nausea, xerostomia, constipation, drowsiness, dizziness, insomnia, anorexia, and heightened perspiration. Furthermore, there are certain uncommon yet highly detrimental effects: Symptoms include confusion, easy bruising or bleeding, decreased interest in sexual activity, Alterations in sexual potency, symptoms of muscle cramps/weakness, shaking, difficulty urinating and Indications of liver issues

Applications: Duloxetine hydrochloride (DUL) has several applications:

MDD:

- DUL is prescribed as a treatment for depressive disorders
- It aids in regulating the levels of serotonin and norepinephrine in the brain.

General Anxiety Disorder (GAD):

- Duloxetine Hydrochloride can treat GAD in Patients from 7 to adults

Nerve Pain:

- DUL is utilized to alleviate neuropathic pain resulting from diabetes (diabetic neuropathy).
- Persistent muscle pain and bone pain can be aided with the help of Duloxetine HCl

Fibromyalgia:

- Certain brands of DUL (such as Cymbalta) have a stated purpose of treating fibromyalgia in both adults and children aged 13 and above.

4.1.3 Abiraterone Acetate

Drug: Abiraterone Acetate

A medication used in treating prostate cancer is abiraterone acetate. Its mode of action is lowering body testosterone levels, preventing the spread and growth of prostate cancer cells. Often used in conjunction with prednisone, abiraterone acetate treats castration-resistant prostate cancer—a disorder in which prostate cancer has spread and responded poorly to treatments lowering testosterone levels.[93], [94, [95]

IUPAC-Name: [(3S,8R,9S,10R,13S,14S)-10,13-dimethyl-17-pyridin-3-yl-2,3,4,7,8,9,11,12,14,15-decahydro-1H-cyclopenta[a]phenanthren-3-yl] acetate

Synonyms: CB-7630, JNJ-212082, 17-(3-Pyridinyl)androsta-5,16-dien-3β-ol acetate, Abiraterone (BAN UK), Abiraterone acetate (JAN JP), Abiraterone acetate (USAN US), Zytiga, Yonsa, Others

Structure:

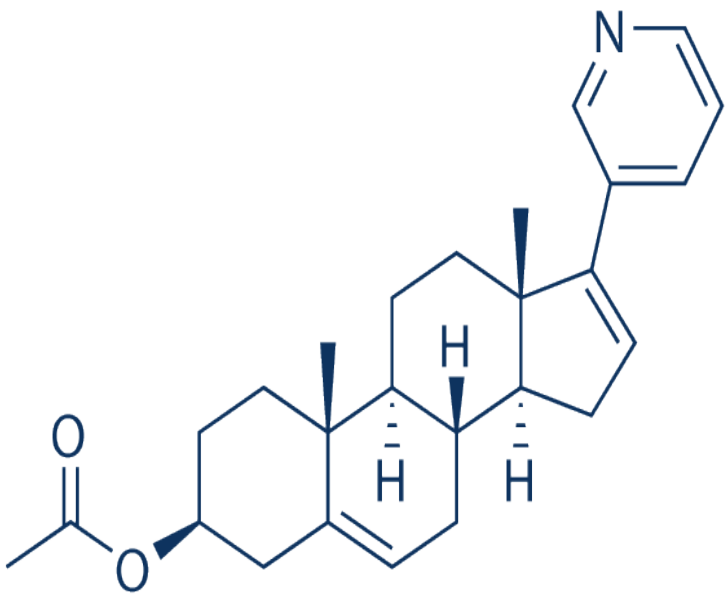

FIGURE: 4.3 CHEMICAL STRUCTURE OF ABIRATERONE ACETATE

Molecular Formula: $C_{26}H_{33}NO_2$

Molecular weight: 391.555 g/mol

Melting point: 144.98°C

Description: White Powder

Solubility: In Methanol, Ethanol, DMF, and DMSO

Stability/Storage: Abiraterone acetate should be stored at 20°C to 25°C (68°F to 77°F), with excursions permitted between 15°C and 30°C (59°F and 86°F)

Dosage form: Tablet

Dose: 125mg, 250mg, 500mg and 1000mg

Mechanism of action: Abiraterone acetate works by suppressing the production of androgens – specifically, it inhibits the enzyme CYP17A1. By doing so, it decreases the production of testosterone, which is crucial in prostate cancer

Bioavailability:<10%

Protein binding: 99.8%

Metabolism: Esterases, CYP3A4, SULT2A1

Plasma half-life: 12-24hr

Time to peak approximately 2 hours after ingestion

Peak plasma concentration: The maximum plasma concentration (C_{max}) of Abiraterone acetate is approximately 54.67 ± 68.30 µg/ml, and the median time to maximum concentration (t_{max}) is 5.53 hours (range: 2.67–35.00 hours)

Excretion: 80% in feces, 5% in Urine

Adverse effects: Detrimental effects that you should report

Allergic reactions: Itchiness, rashes, swelling of the face, tongue, or throat.

- Heart rhythm changes: Fast or irregular heartbeat, dizziness, feeling faint or lightheaded, chest pain, trouble breathing, Increase in blood pressure.
- Common shown effects are Arm, back, or jaw pain, chest tightness or heaviness.
- Clay-colored stools.
- Cool, sweaty skin.
- Dark urine.

Applications: It's one of the core treatment plan for treating metastatic castration-resistant prostate cancer and metastatic high-risk castration-sensitive prostate cancer.

4.2 Polymer Profile

Introduction: Soluplus® is a polymeric solubilizer with an amphiphilic chemical structure, that was specifically designed for the formulation of solid solution.[96], [97]

Description: Soluplus® is a polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft co-polymer.

Composition: Being a Graft co-polymer it has multiple uses

- **Polyvinyl Caprolactam:** provides solubility enhancement and stability
- **Polyvinyl Acetate:** forms part of the unique structure
- **Polyethylene glycol:** contributes hydrophilic properties

Appearance: White to yellowish free-flowing granules

Molecular weight: 118,000g/mol

Critical Micelle concentration: 7.6mg/L

HLB: Approximately 14

Melting Point: 76°C

Structure:

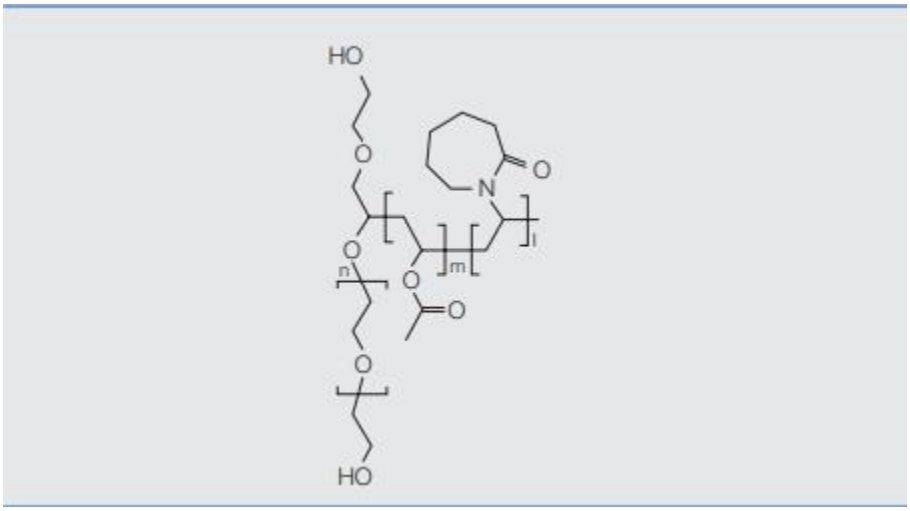

FIGURE: 4.4 CHEMICAL STRUCTURE OF SOLUPLUS®

Solubility: Soluble in Water, Methanol, Ethanol, Acetone and dimethylformamide

Applications: Soluplus® was designed for solubilizing high concentrations of poorly water-soluble APIs in amorphous solid dispersions (ASDs) – these can be produced using a multitude of technologies

CHAPTER 5
MATERIALS AND METHODS

5. MATERIALS AND METHOD

5.1 Materials

5.1.1 Chemicals

TABLE: 5.1 LIST OF CHEMICALS

Sr. No.	Chemicals Name	Obtained From
1	Rifampicin	Lupin Pharmaceuticals
2	Duloxetine Hydrochloride	Atom Pharma
3	Abiraterone Acetate	Bulat Pharmaceuticals
4	Soluplus®	BASF
5	Potassium Dihydrogen phosphate	National Chem Labs
6	Disodium Hydrogen Phosphate	National Chem Labs
7	Sodium Chloride	National Chem Labs
8	Methanol	Lab pro inc.

5.1.2 Equipments

TABLE: 5.2 LIST OF EQUIPMENTS

Sr. No.	Equipment Used	Manufacturer
1	Pipette, Beakers, Volumetric Flasks, Funnel etc.	Borosil
2	Hot-air Oven	Labindia Instruments
3	UV-spectrophotometer	Shimadzu 1700
4	Dissolution Apparatus	Electro lab
5	pH Meter	Eutech
6	FT-IR	Perkin Elmer Spectrum GX

7	DSC	Perkin Elmer DSC-8000
8	Xray Diffractometer	Bruker D8 Advance
9	Digital Weighing Machine	Citizon
10	Magnetic Stirrer	Remi
11	Hot Plate	Remi
12	Evaporating Dish	Randhawa Global

5.2 Methods:

5.3.1 Preparation of Solid Dispersion

Solvent evaporation: The solid dispersion was formed by precisely measuring the required quantities of the medication and polymer. Afterward, the determined amounts of the medicine and polymer were separately dissolved in methanol to achieve a homogeneous solution. A molecular dispersion of medication and polymer was achieved by introducing the drug solution into the polymer solution while stirring constantly. The solvent was then evaporated to create a solid dispersion, which was later dried and triturated.

Melt Evaporation: During this procedure, the solid dispersion is created by initially heating the polymer until it reaches a molten state. Simultaneously, a drug solution is made using methanol, following the formulation requirements. The drug solution is gradually introduced into the molten carrier as the mixture is being cooled in an ice bath. Subsequently, the solvent is evaporated, and the mixture is dried, pulverized, and sieved.

Rifampicin formulations

(TABLE: 5.3) COMPOSITION BATCHES OF RIFAMPICIN FORMULATIONS

Sr. No.	Code	Ratio	Method
1	R1	1:1	SE (RIF + SOLUPLUS)
2	R2	1:2	SE (RIF + SOLUPLUS)
3	R3	1:3	SE (RIF + SOLUPLUS)

4	R4	1:1	ME (RIF + SOLUPLUS)
5	R5	1:2	ME (RIF + SOLUPLUS)
6	R6	1:3	ME (RIF + SOLUPLUS)

Duloxetine HCl formulations

(TABLE: 5.4) COMPOSITION BATCHES OF DULOXETINE HCl FORMULATIONS

Sr. No.	Code	Ratio	Method
1	D1	1:1	SE (D.HCL + SOLUPLUS)
2	D2	1:2	SE (D.HCL + SOLUPLUS)
3	D3	1:3	SE (D.HCL + SOLUPLUS)
4	D4	1:1	ME (D.HCL +SOLUPLUS)
5	D5	1:2	ME (D.HCL +SOLUPLUS)
6	D6	1:3	ME (D.HCL +SOLUPLUS)

Abiraterone Acetate formulations

TABLE: 5.5 COMPOSITION BATCHES OF ABIRATERONE ACETATE FORMULATIONS

Sr. No.	Code	Ratio	Method
1	A1	1:1	SE (A.A. + SOLUPLUS)
2	A2	1:2	SE (A.A. + SOLUPLUS)
3	A3	1:3	SE (A.A. + SOLUPLUS)
4	A4	1:1	ME (A.A. + SOLUPLUS)
5	A5	1:2	ME (A.A. + SOLUPLUS)
6	A6	1:3	ME (A.A. + SOLUPLUS))

5.3.2 Evaluation Parameters

5.3.2.1 Solubility Studies: The solubility data for Rifampin, Duloxetine Hydrochloride, and Abiraterone Acetate, physical mixture, and solid dispersions prepared using the Solvent Evaporation method and Melt Evaporation method in distilled water, were determined. Quantities of the solid dispersion equivalent to 10 mg of the drug were added to 25 mL of distilled water in a beaker. The beaker contents were stirred for 2 hours at room temperature using a magnetic stirrer. The resulting solution was kept aside for 24 hours and then it was filtered, and diluted according to the requirement, and the filtrate was analyzed spectrophotometrically based on their respective lambda Max. [98]

5.3.2.2 Drug Content: 50 mg of solid dispersions were taken in a beaker and dissolved with 50 ml of methanol. The resulting solution was filtered, suitably diluted, and analyzed for drug content using a UV spectrophotometer at their respective Lambda max. Each sample was analyzed in triplicate.[98] Actual drug content was calculated for all batches using the equation as follows:

$$\textbf{DC \%} = \frac{\textbf{Actual API content in weighed quantity of solid dispersion}}{\textbf{Theoretical amount of API in Solid dispersion}} \textbf{ X 100}$$

5.3.2.3 %Yield: Solid Dispersion recovered at the end of the formulation was weighed and their %Yield was calculated.[99]

$$\textbf{\%Yield} = \frac{\textit{Total Weight of solid dispersion}}{\textit{Total weight of Drug and Polymer}} \textbf{ X 100}$$

5.3.2.4 In-vitro drug release studies: The in-vitro dissolution studies for all drugs (Rifampicin, Duloxetine Hydrochloride, and Abiraterone Acetate) were carried out in a USP paddle-type dissolution test apparatus.

1. Rifampin

Preparation of dissolution medium: To create a phosphate buffer with a pH of 7.4, dissolve 2.38 grams of disodium hydrogen phosphate, 0.190 grams of potassium dihydrogen phosphate, and 8 grams of sodium chloride in enough distilled water to make 1000 milliliters of the buffer solution.[100]

Dissolution rate determination: Following the estimation of drug content in solid dispersions, we proceeded with dissolution testing to evaluate the release rate from the dispersions. The dissolution was conducted at 37.5°C and 75 rpm for two hours using pH 7.4 phosphate buffer as the dissolution medium [79]. The pure drug, PM, and SD in respective weights, based on content evaluation studies, were placed into corresponding baskets.

At intervals of 10 minutes, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, and 120 minutes, 5ml samples were withdrawn from each basket, and the same volume of fresh dissolution medium was added after each withdrawal. Each 5ml sample was then diluted to 10ml with 7.4 pH phosphate buffer solution.

2. Duloxetine Hydrochloride

Preparation of dissolution medium: To prepare a 6.8 pH phosphate buffer, dissolve 28.80 grams of disodium hydrogen phosphate and 11.45 grams of potassium dihydrogen phosphate in sufficient distilled water to produce 1000 milliliters of the buffer solution.[101]

Dissolution rate determination: Following the estimation of drug content in SDs, we proceeded with dissolution testing to determine the release rate from the dispersions. The dissolution was conducted at 37.5°C and 100 rpm for two hours using pH 6.8 phosphate buffer as the dissolution medium[83]. The Pure Drug, PM, and SD in respective weights, based on content evaluation studies, were placed into corresponding baskets.

At intervals of 10 minutes, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, and 120 minutes, 5ml samples were withdrawn from each basket, and the same volume of fresh dissolution medium was added after each withdrawal. Each 5ml sample was then diluted to 10ml with 6.8 pH phosphate buffer solution.

3. Abiraterone Acetate

Preparation of dissolution medium: To prepare a 4.5 pH phosphate buffer, dissolve 6.80 grams of potassium dihydrogen phosphate in sufficient distilled water to produce 1000 milliliters of the buffer solution.[100]

Following the estimation of drug content in SDs, we proceeded with dissolution testing to determine the release rate from the dispersions. The dissolution was conducted at 37.5°C and 75 rpm for two hours using pH 4.5 phosphate buffer as the dissolution medium[86]. The pure drug, PM, and SD in respective weights, based on content evaluation studies, were placed into corresponding baskets.

At intervals of 10 minutes, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, and 120 minutes, 5ml samples were withdrawn from each basket, and the same volume of fresh dissolution medium was added after each withdrawal. Each 5ml sample was then diluted to 10ml with a 4.5 pH phosphate buffer solution.

FT-IR: The FT-IR spectrum was performed for all the 3 drugs, polymer, and their physical mixtures to determine the compatibility between drug and polymer.

DSC: Differential Scanning calorimetry was performed for the drug, polymer, physical mixture, and SDs formulation to determine their thermal characteristics, thermal transitions etc.

XRD: X-ray diffraction of the drug and the final formulation was performed to determine the crystallinity and quantification of percent crystallinity of drug and the final formulation.

CHAPTER 6
RESULTS AND DISCUSSION

6. RESULTS AND DISCUSSION

6.1 Preliminary Trials

Multiple trial batches were produced to assess certain criteria that might or might not affect the formulation of additional batches of SDs before beginning the development for them.

6.1.1 Method-selection: Among other techniques including melt fusion, melt agglomeration, or kneading method, solvent evaporation and melt evaporation techniques were selected. Comparative studies between melt evaporation and solvent evaporation were performed because in both techniques solvent system is removed to formulate the SDs and are somewhat similar.

Some of the main causes are versatility concerning choices of polymers, preventing thermal decomposition of drugs or carriers, and because evaporation occurs at low temperatures also ensuring solubility. Furthermore, a simple technique improving dissolution capacity helps drug absorption by solvent evaporation

Soluplus® has a melting point of 76°C while the Melt evaporation method requires a polymer or a carrier that can melt at lower temperatures. This is why Soluplus® can be used in both techniques SE and ME.

Now the reason for not choosing techniques like melt fusion or kneading method is because the melt fusion technique causes a decrease in yield percentage, changes in crystallinity over time, and also the development of dark lumps (Rifampicin) in the SDs which may affect the general condition of formulation.

Because of water evaporation and also compared to Solvent evaporation and melt evaporation the practical yield is less when passing the drug-carrier mass (dough-like) through a sieve. Formulation of SDs by the kneading method is much time-consuming. Also, there is a possibility of moisture entering the formulation causing formulation degradation.

6.1.2 Solvent-selection: Solubility of the API or medicine in the particular solvent helped to guide the choice of solvent for both techniques. Methanol, ethanol, DMSO, DMF, and Chloroform are organic solvents in which the drugs are soluble.

Because of its fast evaporation and great solubility of medication and polymer, methanol was selected as the solvent for SDs.

Either heating the solvent to evaporate it or letting it evaporate at room temperature produced batches. The batch made by evaporating at room temperature came out preferred since it had somewhat more solubility and the yield Acquired was more. The color shade of rifampicin also changed in the SD batch; the room temperature batch had light red while the batch with heat had dark red color.

Formulations using ethanol were also conducted; however, it was not chosen later due to its high evaporation temperature at 70°C. Methanol allowed all three of the three medications selected for formulation (Rifampin, Duloxetine HCl, AbirateroneAcetate) to be soluble.

6.1.3 Carrier-selection: Soluplus® was selected as the polymer since of its low melting point and solubility power. Beacause of its bifunctional nature it can be matrix polymer on one hand and solubilizer on other.

Because of their amorphous form Rifampin, Duloxetine HCl and Abirateronewere dissolved in distilled water containing Soluplus® to ascertain whether it increased the solubility and it did enhance the solubility of drugs in water.

A research study was conducted to compare PEG 6000 and Soluplus® in terms of their ability to enhance the dissolution of a drug. Soluplus® demonstrated greater enhancement in the drug's dissolution compared to PEG 6000.

Soluplus® is chosen as a carrier in part because of its solubility in wide range of organic solvents

6.1.4 Solubility of medication: Solubility of drugs was enhanced when they were formulated into SDs. When the solubility of the SDs was compared with that of the pure drug, the SDs showed higher solubility. The increase in solubility of SDs was directly proportional to the concentration of the polymer.

6.1.5 % Yield: Although both Duloxetine HCL and Rifampin became highly soluble after being formulated into SDS, in some cases concentration batches had less yield because of stickiness caused by the increased concentration of polymer, which was the problem. Both Solvent evaporation and melt evaporation were appropriate for the drugs involved; some were good for a particular drug which can be considered to be used for manufacturing of that drug in the industrial level.

6.2 Results:

6.2.1 Rifampicin

1. %Drug content, %Yield and Solubility studies:

TABLE: 6.1 CHARACTERIZATION OF RIFAMPICIN, ITS PHYSICAL MIXTURE, AND ITS SDs

Name	%Drug content	%Yield	Solubility (µg/ml)
Pure Drug	-	-	11.03 ± 0.08
Physical Mixture	80.23 ± 0.3	-	17.84 ± 0.065
(SE-SD 1:1) R1	82.23 ± 0.45	88.24	14.77 ± 0.053
(SE-SD 1:2) R2	81.40 ± 0.63	87.13	18.55 ± 0.046
(SE-SD 1:3) R3	88.87 ± 0.25	85.05	22.24 ± 0.060
(ME-SD 1:1) R4	79.65 ± 0.5	85.42	15.38 ± 0.074
(ME-SD 1:2) R5	86.57 ± 0.35	84.23	19.67 ± 0.059
(ME-SD 1:3) R6	89.25 ± 0.4	86.56	24.63 ± 0.036

*All values are in mean ± SD (n=3)

The drug content and %yield was found to be above 80%, which can be considered good. Amongst all the batches, batches R3 and R6 showed better results. This may be probable because of the increase in concentration of carrier. Two-fold increase can be seen in solubility when pure drug compared to Best formulations R3 and R6 Thus, the increase in the concentration of the carrier can lead to an increase in the solubility of the drug. Similar results were shown in a study performed by Theja D et al., (2012)[79]

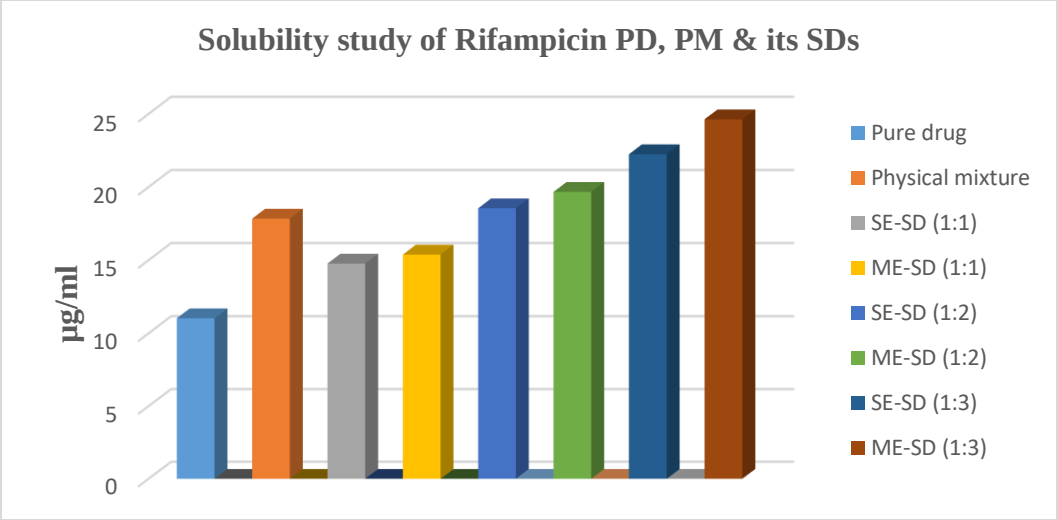

FIGURE: 6.1: SOLUBILITY STUDY OF RIFAMPICIN PD, PM & ITS SDs

2. In vitro-release Studies:

From the dissolution data, it was observed that the prepared SDs showed an enhanced dissolution rate when compared to pure drug. The probable reason is the crystalline drug was converted to the amorphous form. The amorphous solid has high free energy, due to which in the process of stabilization, they form hydrogen bonds with the water molecules and get converted into the solution form.

Among all the batches A3 and A6 showed greater dissolution rate releases up to 62.8% and 63.59% of the drug.

Other batches also show Increased dissolution compared to pure drug which proved that formulation of SDs with Soluplus® enhances the dissolution rate of this drug. Similar results were obtained in a study performed by Shamsuddin et al. (2016)[102]

TABLE: 6.2 DISSOLUTION PROFILE OF RIFAMPICIN, ITS PHYSICAL MIXTURE, AND ITS SDs

Time (Min)	Percentage Drug Release (%)							
	Pure Drug	**Physical Mixture**	**SE-SD (1:1) (R1)**	**SE-SD (1:2) (R2)**	**SE-SD (1:3) (R3)**	**ME-SD (1:1) (R4)**	**ME-SD (1:2) (R5)**	**ME-SD (1:3) (R6)**
10	2.34	10.138	9.39	11.421	13.287	7.4768	10.542	16.778
20	5.67	13.77	16.34	18.215	20.28	13.746	15.198	24.811
30	10.12	19.158	23.45	24.968	30.885	20.606	20.15	32.519
40	15.78	32.231	31.969	34.56	41.473	26.769	29.039	44.49
50	20.45	38.681	40.621	45.67	49.662	35.038	38.067	53.975
60	23.89	44.908	44.68	56.78	60.502	46.818	47.516	62.242
70	27.01	55.393	57.121	67.89	70.026	55.823	56.326	74.598
80	30.23	62.01	63.639	75.9	78.162	63.749	65.002	84.449
90	31.44	69.268	65.212	83.29	86.113	69.793	73.192	88.099
100	32.56	73.583	72.734	85.13	90.717	74.813	79.35	91.687
110	34.67	77.412	73.071	86.65	93.716	75.118	83.328	94.538
120	35.6	80.13	73.882	87.22	**96.59**	76.01	85.23	**97.8**

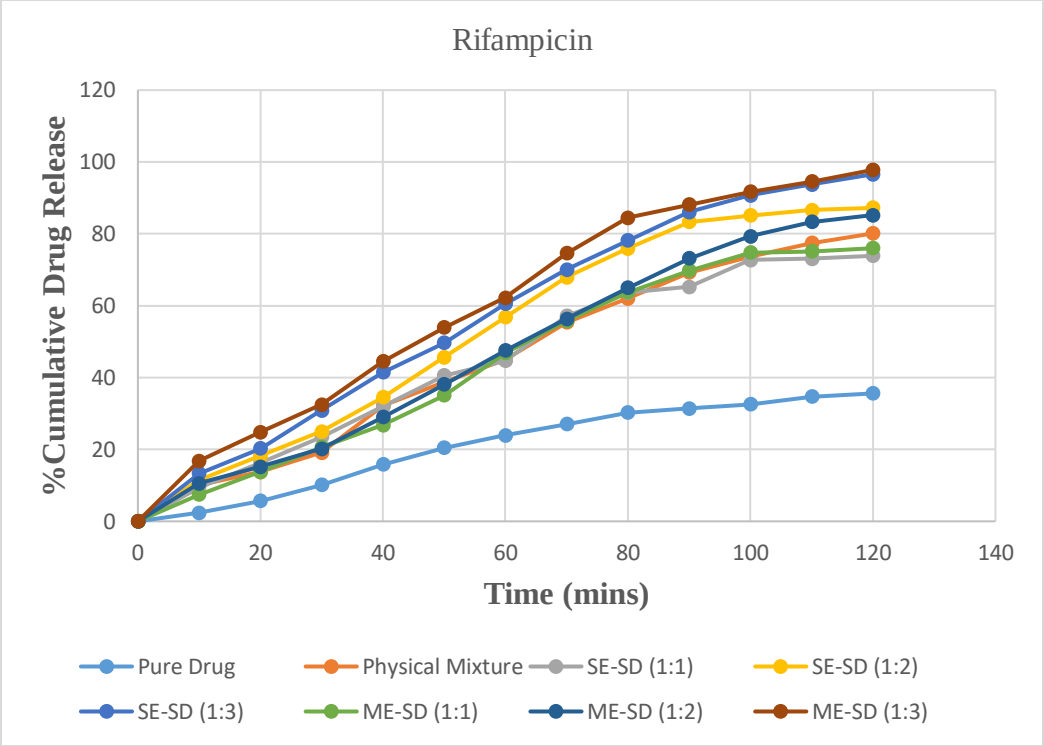

FIGURE: 6.2 CUMULATIVE % RELEASE STUDIES OF RIFAMPICIN, ITS PHYSICAL MIXTURE, AND ITS SDs

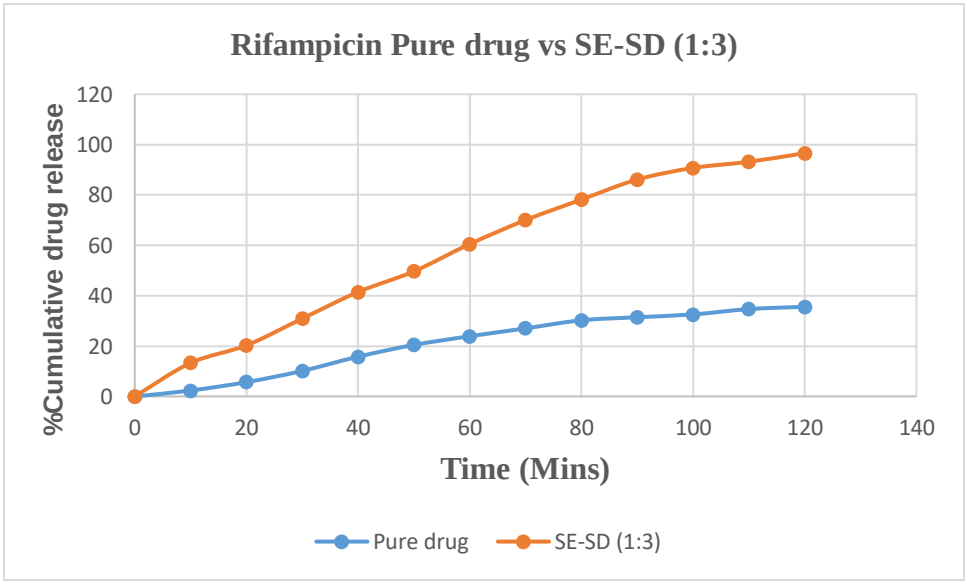

FIGURE: 6.3 RELEASE STUDIES OF RIFAMPICIN PURE DRUG VS FORMULATION (SE-SD 1:3)

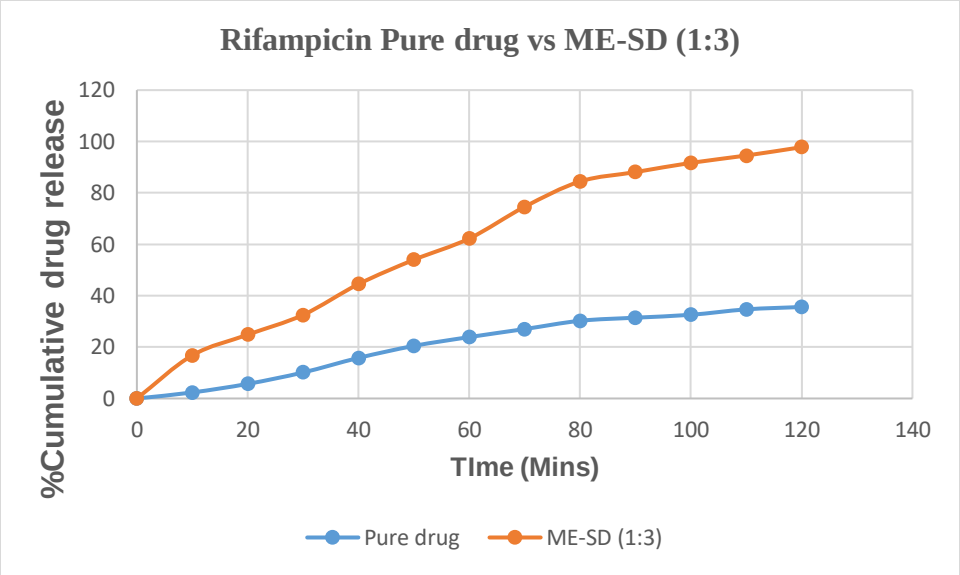

FIGURE: 6.4 RELEASE STUDIES OF RIFAMPICIN PURE DRUG VS FORMLATION (ME-SD 1:3)

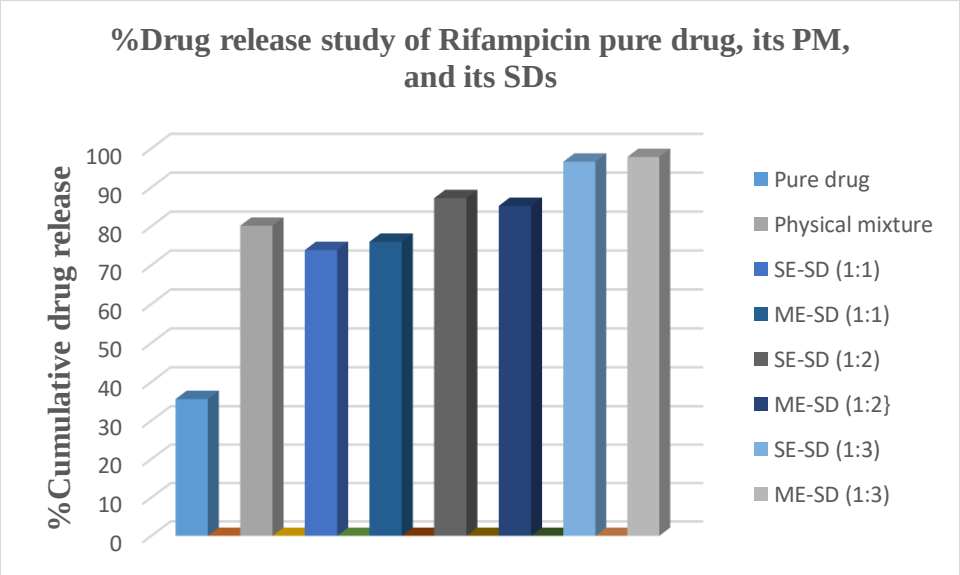

FIGURE: 6.5 %DRUG RELEASE OF RIFAMPICIN PURE DRUG, PM, AND ITS SDs

3. **FT-IR:** FT-IR studies were performed for the compatibility studies. The peaks of the drug from spectra (Figure 6.6) were compared with peaks of the physical mixture (Figure 6.8) as shown in Table 6.3 and no interaction or shifts were observed. The formulations (Figure 6.4 and 6.5) also showed all the peaks shown in Table 6.3. Similar results were shown in a study performed by Theja D et al., (2012) [79]

   Rifampin shows all the respective peaks

TABLE: 6.3 COMPARISON OF FTIR WAVELENGTHS OF RIFAMPICIN, ITS PHYSICAL MIXTURE, AND ITS SDs

Functional groups	Pure drug (cm^{-1})	Physical mixture (cm^{-1})	R3 (cm^{-1})	R6 (cm^{-1})
-C=N	1562.06	1562.06	1558.2	1558.2
C=O	1712.48	1731.76	1735.62	1730.62
C-H	2977.5	2977.55	2977.55	2938.98

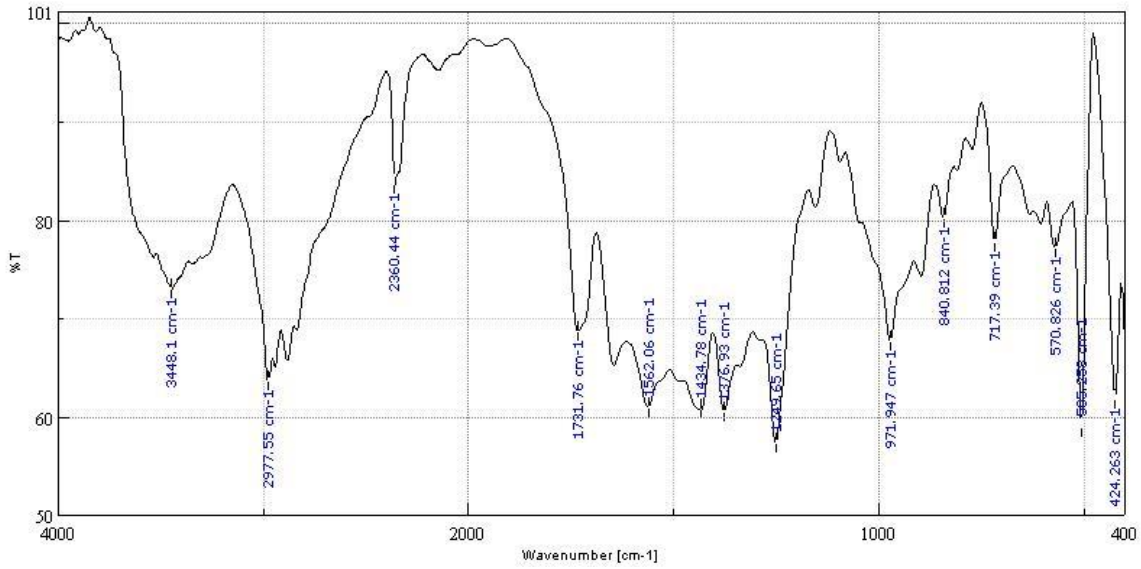

FIGURE: 6.6 FTIR SPECTRA OF RIFAMPICIN

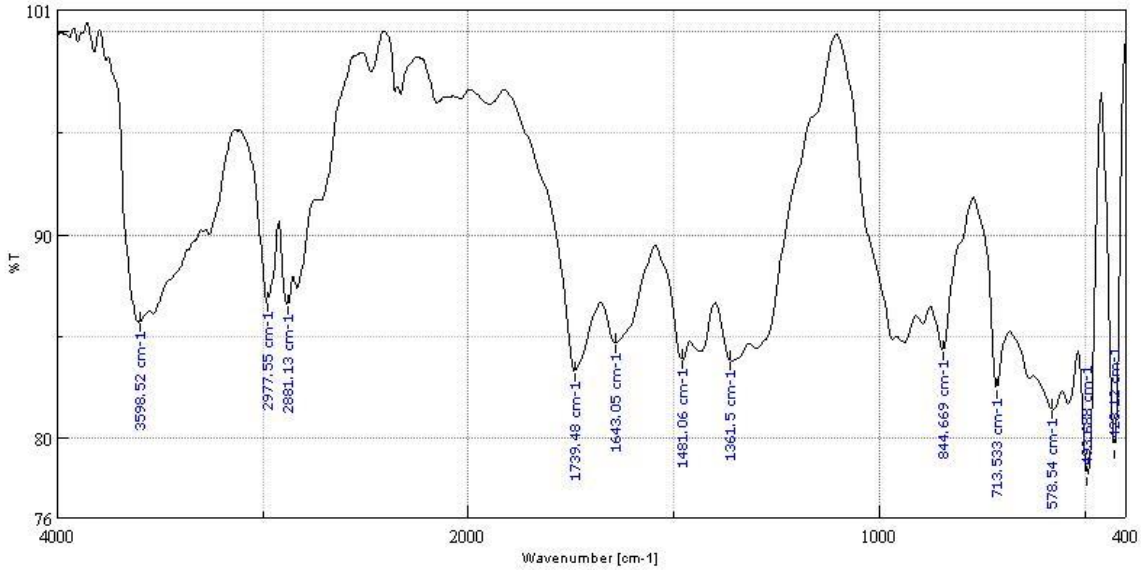

FIGURE: 6.7 FTIR SPECTRA OF SOLUPLUS®

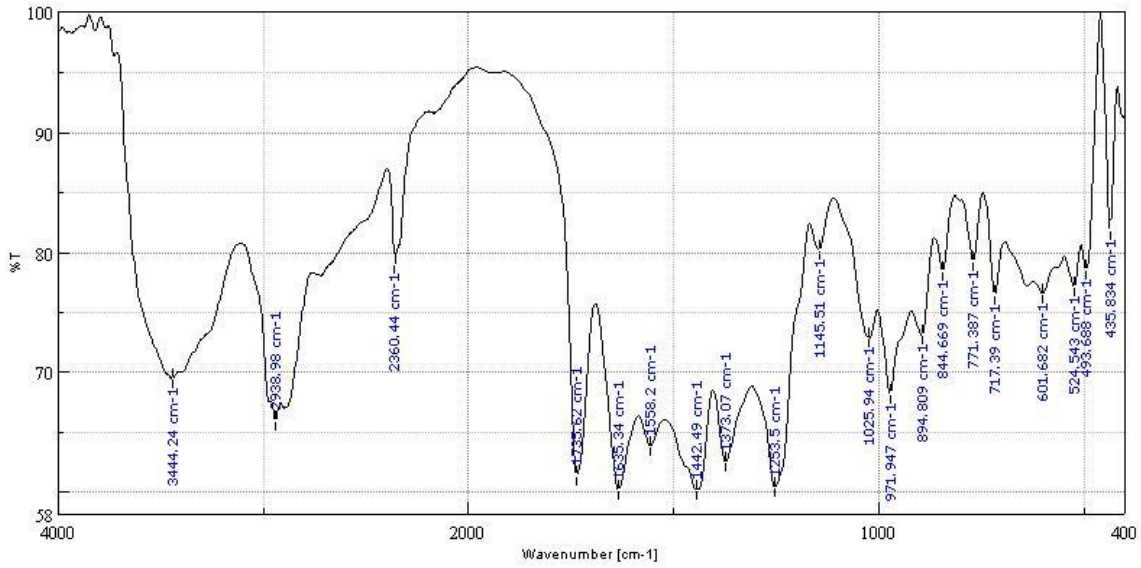

FIGURE: 6.8 FTIR SPECTRA OF RIFAMPICIN PHYSICAL MIXTURE

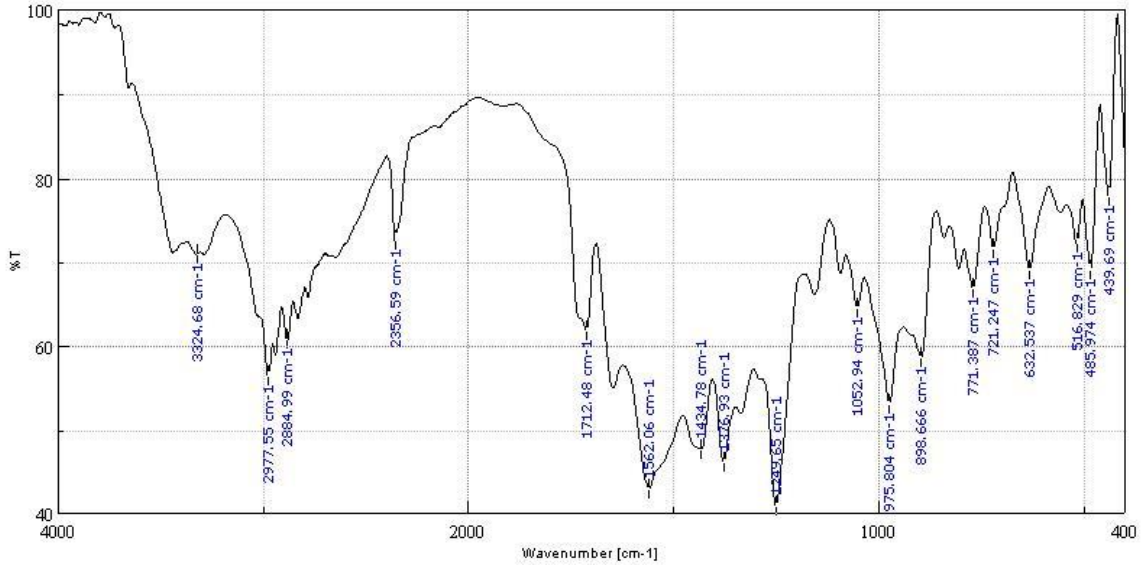

FIGURE: 6.9 FTIR SPECTRA OF RIFAMPICIN FORMULATION R3 (SE-SD 1:3)

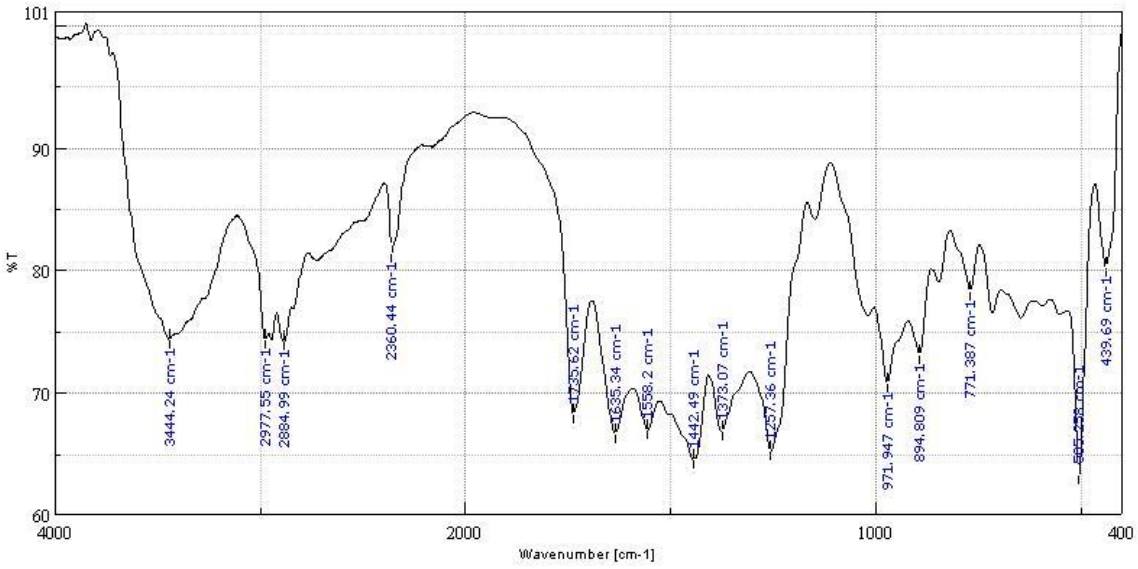

FIGURE: 6.10 FTIR SPECTRA OF RIFAMPICIN FORMULATION R3 (ME-SD 1:3)

DSC: Thermal characteristics of Rifampin along with the physical mixture and SDs were determined using DSC analysis. The endothermic peak shown in Figure 6.11 corresponds to the melting temperature of the drug. The Polymer showed an endothermic peak at 76°C as shown in Figure 6.12 which corresponds to its melting point. The formulation SE-SD 1:3 showed perfect encapsulation as shown in Figure 6.13 and formulation ME-SD 1:3 showed a reduction in exothermic peak as shown in Figure 6.14 which indicates a reduction in crystallinity. Similar results were shown in a study performed by Ramu A et al., (2024) **[62]**

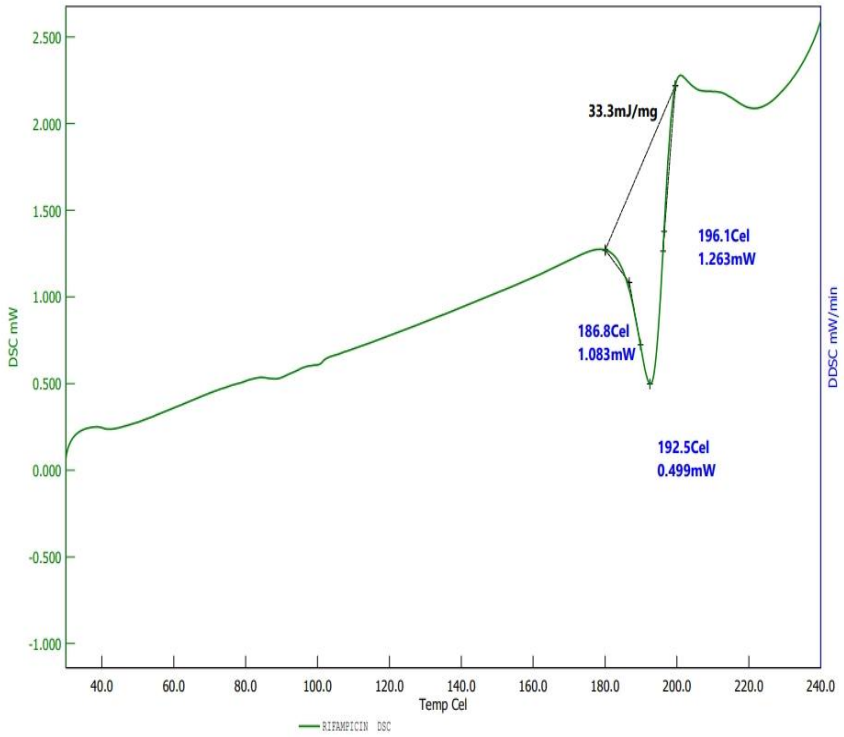

FIGURE: 6.11 DSC THERMOGRAM OF RIFAMPICIN

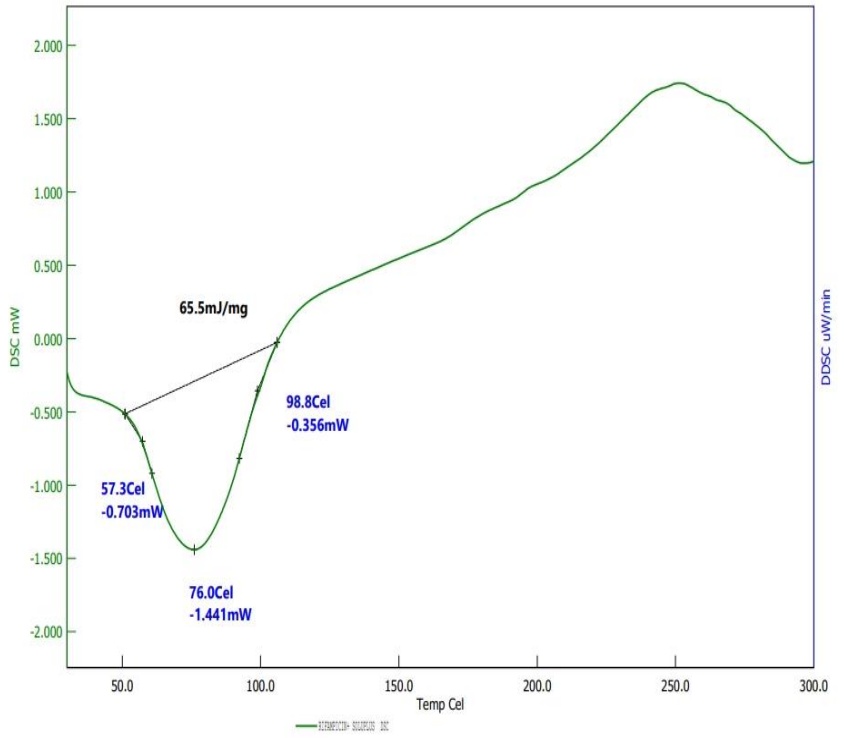

FIGURE: 6.12 DSC THERMOGRAM OF SOLUPLUS®

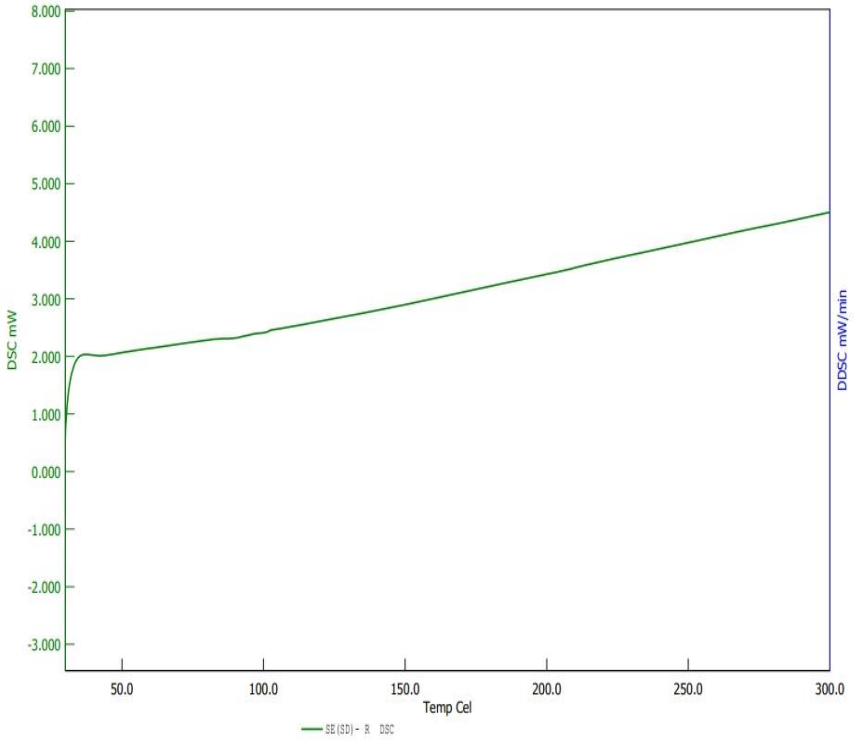

FIGURE: 6.13 DSC THERMOGRAM OF RIFAMPICIN FORMULATION R3 (SE-SD 1:3)

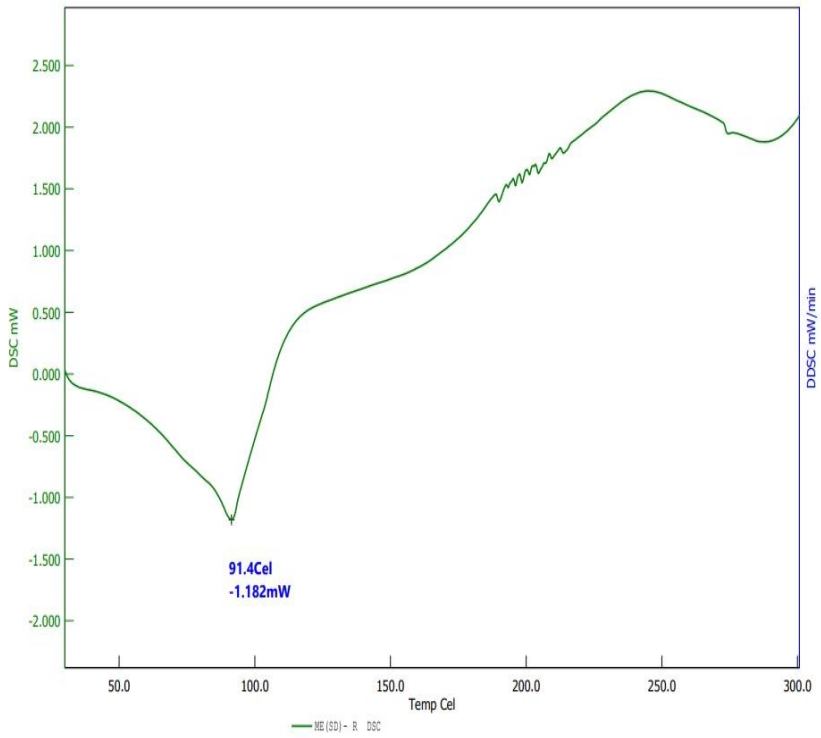

FIGURE: 6.14 DSC THERMOGRAM OF RIFAMPICIN FORMULATION R3 (ME-SD 1:3)

XRD: XRD of Rifampicin was performed to assess the crystallinity of the formulations. The XRD of Rifampicin showed sharp peaks as seen in Figure 6.15 which can be attributed to its crystalline nature. The XRD of Soluplus® showed broad peaks which correspond to its amorphous nature as show in Figure 6.16. Compared to the XRD of pure drug, the formulations showed reduction and broadness in peaks as shown in Figures 6.17 and 6.18. Similar results were shown in a study performed by Ramu A et al., (2024) [62]

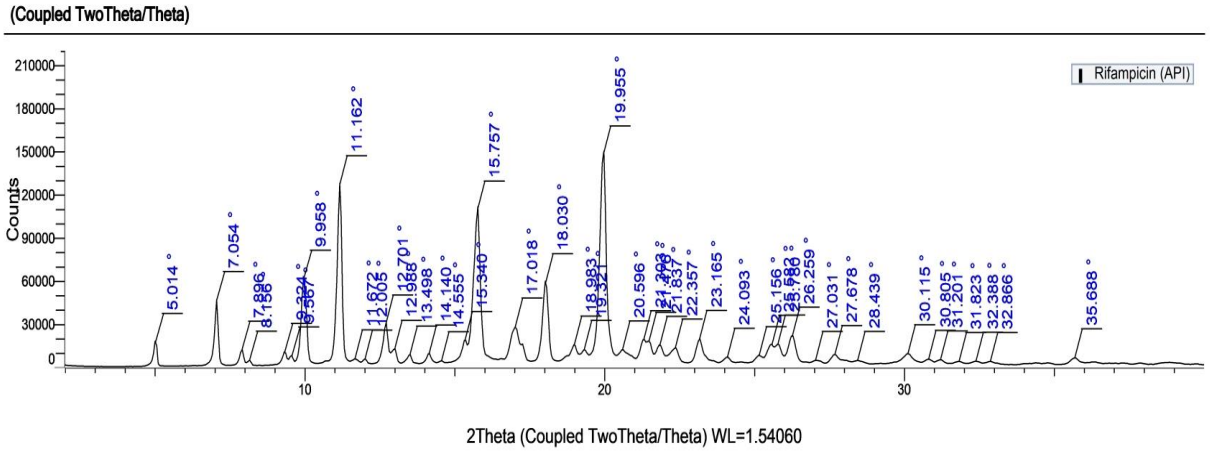

FIGURE: 6.15 XRD SPECTRA OF RIFAMPICIN

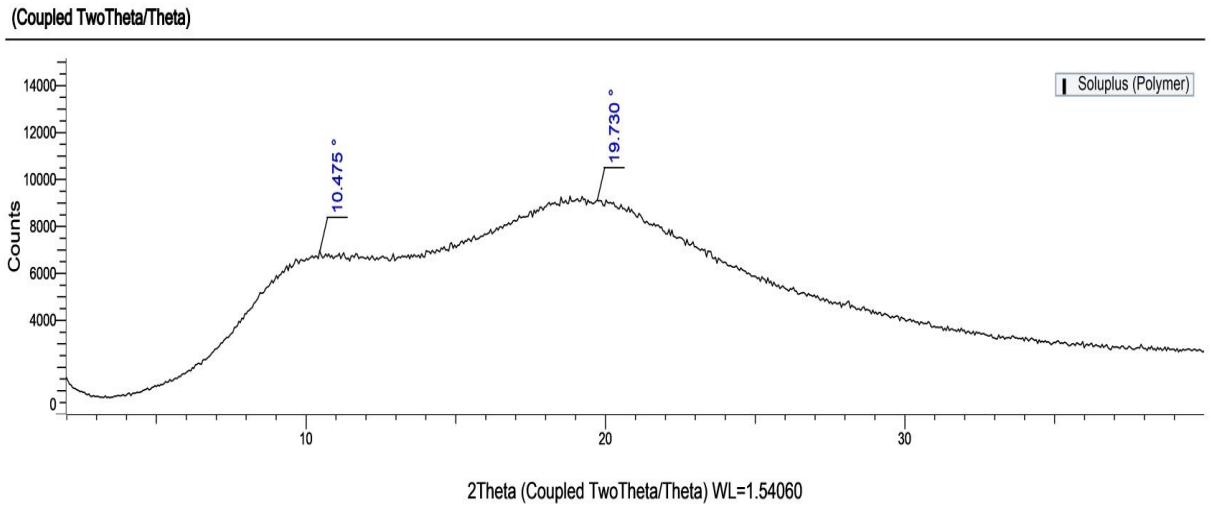

FIGURE: 6.16 XRD SPECTRA OF SOLUPLUS®

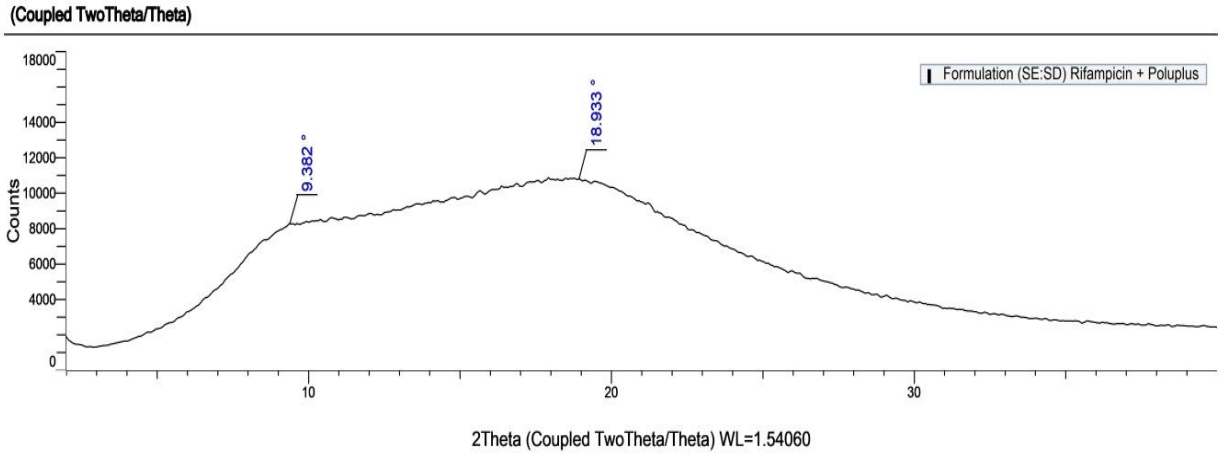

FIGURE: 6.17 XRD SPECTRA OF RIFAMPICIN FORMULATION R3 (SE-SD 1:3)

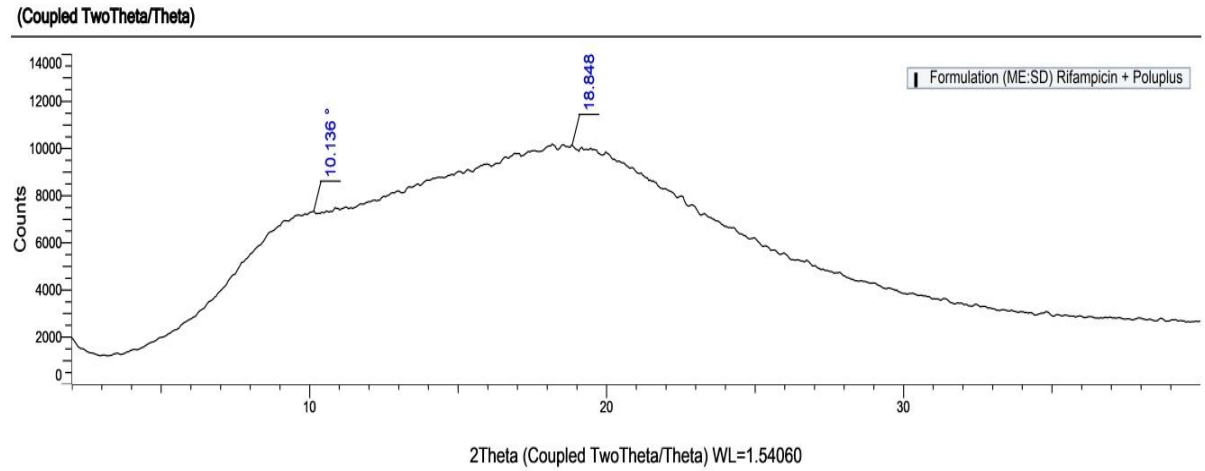

FIGURE: 6.18 XRD SPECTRA OF RIFAMPICIN FORMULATION R6 (ME-SD 1:3)

6.1.2 Duloxetine HCL

1. %Drug Content, %yield and solubility:

(TABLE: 6.4) CHARACTERIZATION OF DULOXETINE HCL, ITS PHYSICAL MIXTURE, AND ITS SDs

Name	%drug content	%yield	Solubility (µg/ml)
Pure drug	-	-	10.36 ± 0.067
Physical mixture	83.85 ± 0.62	-	17.02 ± 0.091
(SE-SD 1:1) D1	80 ± 0.9	60.31	14.16 ± 0.059
(SE-SD 1:2) D2	78.4 ± 0.76	58.4	18.24 ± 0.13
(SE-SD 1:3) D3	88.98 ± 0.56	57.20	23.61 ± 0.088
(ME-SD 1:1) D4	82.14 ± 0.40	62.54	13.45 ± 0.074
(ME-SD 1:2) D5	84.63 ± 0.68	59.12	16.23 ± 0.085
(ME-SD 1:3) D6	91.25 ± 0.45	61.48	22.75 ± 0.096

*All values are in mean ± SD (n=3)

The percentage drug content obtained from the six batches was in the range of 78.4-91.2 among which D6 showed good content as well as solubility. The solubility shows two-fold enhancement when best formulations D3 and D6 compared to pure drug. The solubility can be seen increasing with the concentration of polymer which shows the enhancing ability of Soluplus®. Similar results were shown in a study performed by Elmubarak et al. (2021)[103]

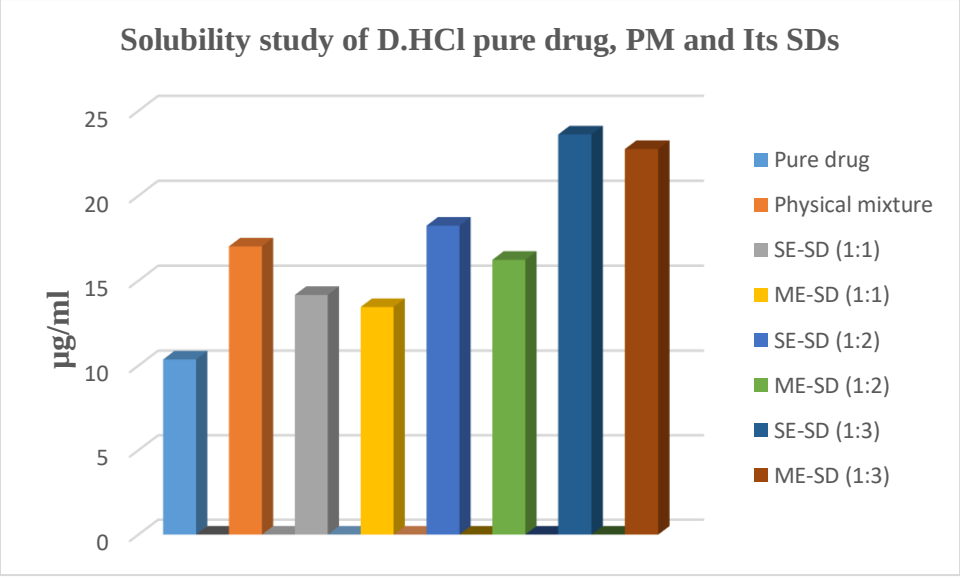

FIGURE: 6.19 SOLUBILITY STUDY OF D.HCL PURE DRUG, PM AND ITS SDs

2. In-Vitro Dissolution Studies:

Drug release studies conducted in a laboratory setting demonstrate a significant enhancement in the rate at which Duloxetine Hydrochloride dissolves when it is in the form of SDs, as compared to the pure drug. The dissolution rate increases in the following order: 1:3 > 1:2 > 1:1 > pure drug. Depending on the concentration ratio of Soluplus®, the dissolution rate of Duloxetine Hydrochloride in SDs can vary greatly. The rate of solubility increased as the carrier concentration in the SDs was raised.

Batch D3 showed the best results among all the other batches with a drug release of 97%. Similar results were shown in a study performed by Aroon A et al., (2023) [83]

(TABLE: 6.5) DISSOLUTION PROFILE OF DULOXETINE HCL, ITS PHYSICAL MIXTURE, AND ITS SDS

Time (min)	Percentage drug released (%)							
	Pure drug (%)	Physical mixture (1:3)	SE-SD (1:1) (D1)	SE-SD (1:2) (D2)	SE-SD (1:3) (D3)	ME-SD (1:1) (D4)	ME-SD (1:2) (D5)	ME-SD (1:3) (D6)
0	0	0	0	0	0	0	0	0
10	1.74	10.1515	6.25	8.27	14.67	5.95	9.1	12.45
20	4.94	14.671	10.67	12.65	21.72	9.53	13.43	19.34
30	9.73	23.45	14.83	20.11	28.51	12.38	21.64	26.56
40	16.52	29.312	19.91	25.05	36.90	17.63	28.49	34.67
50	24.51	37.015	26.02	32.2	44.49	24.32	36.24	42.78
60	29.71	45.23	33.37	39.45	52.88	30.83	43.35	50.89
70	38.90	54.245	40.58	47.59	59.68	38.61	51.89	57.19

80	44.49	65.951	47.58	56.36	68.47	44.74	60.03	65
90	50.49	70.1052	55.12	65.49	76.86	52.86	68.2	71.22
100	58.88	78.69	63.85	74.26	84.05	61.36	76.14	79.31
110	63.27	82.3	71.45	78.11	95.24	68.47	80.67	86.44
120	64.51	86.12	73.35	82.31	**97.24**	70.1	83.66	**93.91**

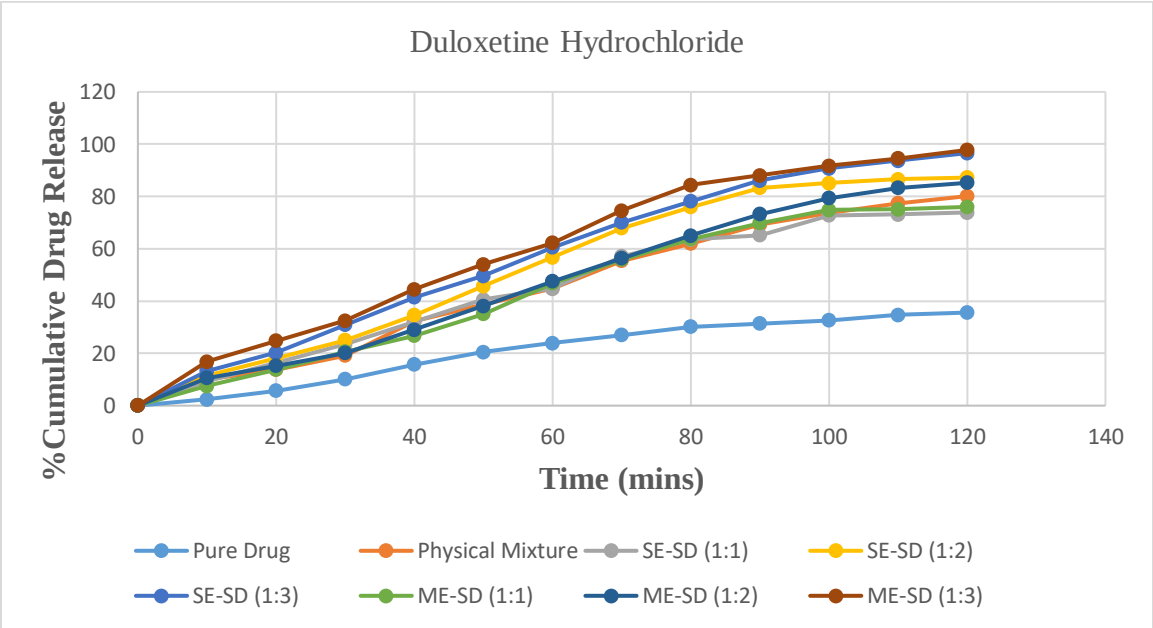

FIGURE: 6.20 CUMULATIVE % RELEASE STUDIES DULOXETINE HYDROCHLORIDE, ITS PHYSICAL MIXTURE, AND ITS SDS

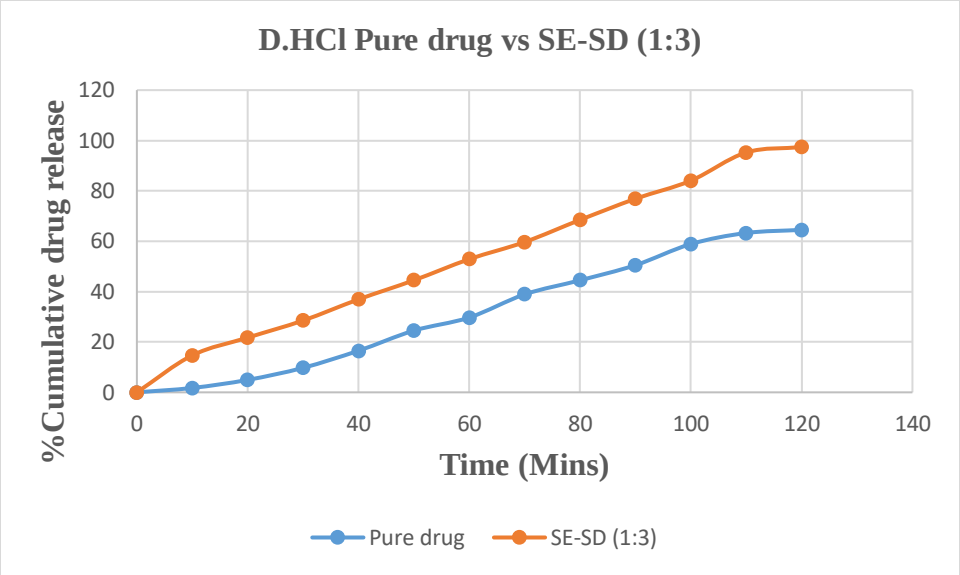

FIGURE: 6.21 RELEASE STUDIES OF D.HCl VS FORMULATION (SE-SD 1:3)

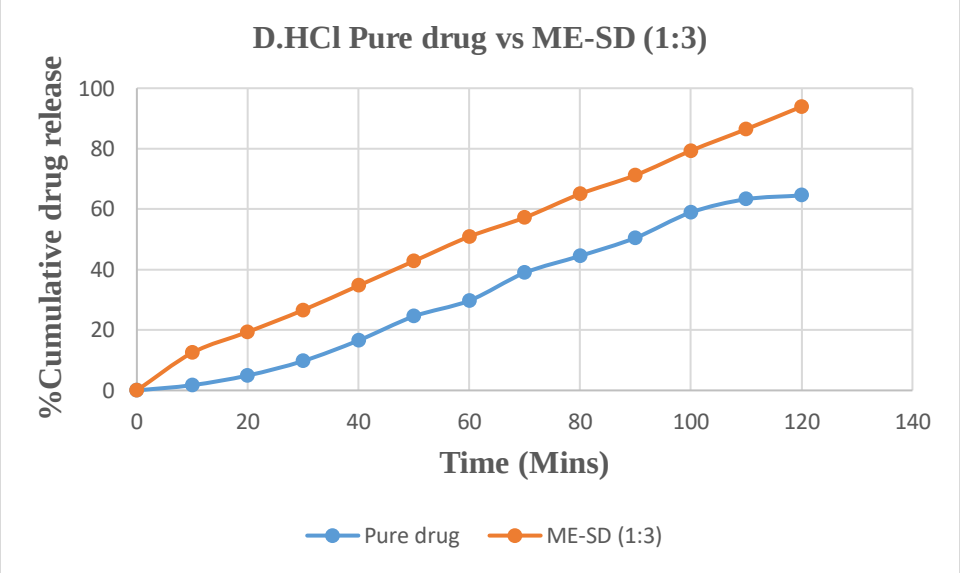

FIGURE: 6.22 RELEASE STUDIES OF D.HCl VS FORMULATION (ME-SD 1:3)

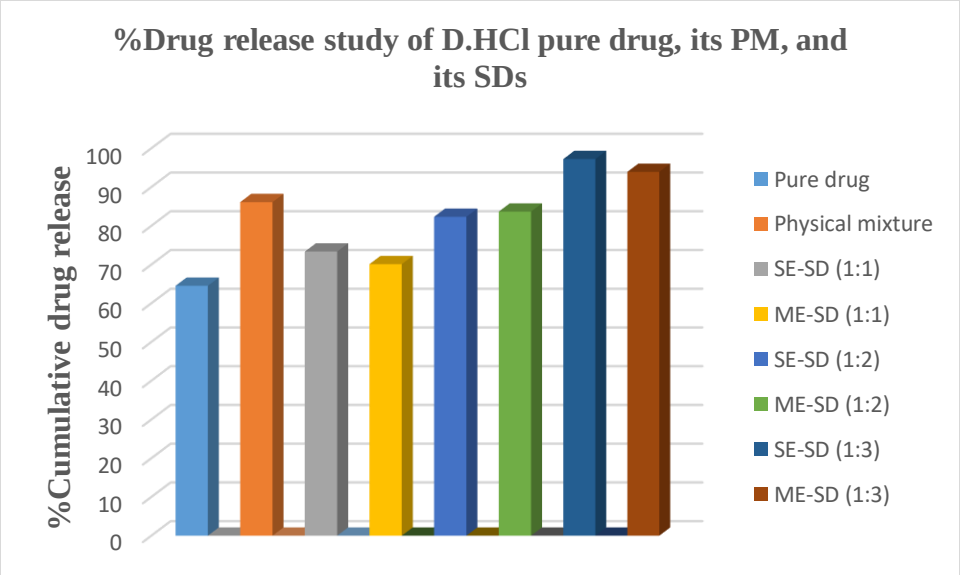

FIGURE: 6.23 %DRUG RELEASE STUDY OF D.HCL PURE DRUG, ITS PM, AND ITS SDs

3. **FT-IR:** There was no interaction between polymer and drug when the peaks of the drug (Figure 6.24) and physical mixture (Figure 6.25) were compared as shown in Table 6.6. However, as shown in Figure 6.26 & 6.27 some peaks were missing from the formulations due to the formation of bonds. Similar results were shown in a study performed by Aroon A et al., (2023) **[83]**

TABLE: 6.6 COMPARISON OF FTIR WAVELENGTHS OF DULOXETINE HCL AND ITS PHYSICAL MIXTURE

Functional groups (cm^{-1})	**Pure drug**(cm^{-1})	**Physical mixture**(cm^{-1})
C=O (1760-1605)	1735.62	1735.62
C-S (1450-1375)	1396.21	1396.21
N-H (1640-1550)	1581.34	1585.2
C-H (2850-3000)	2977.55	2973.7

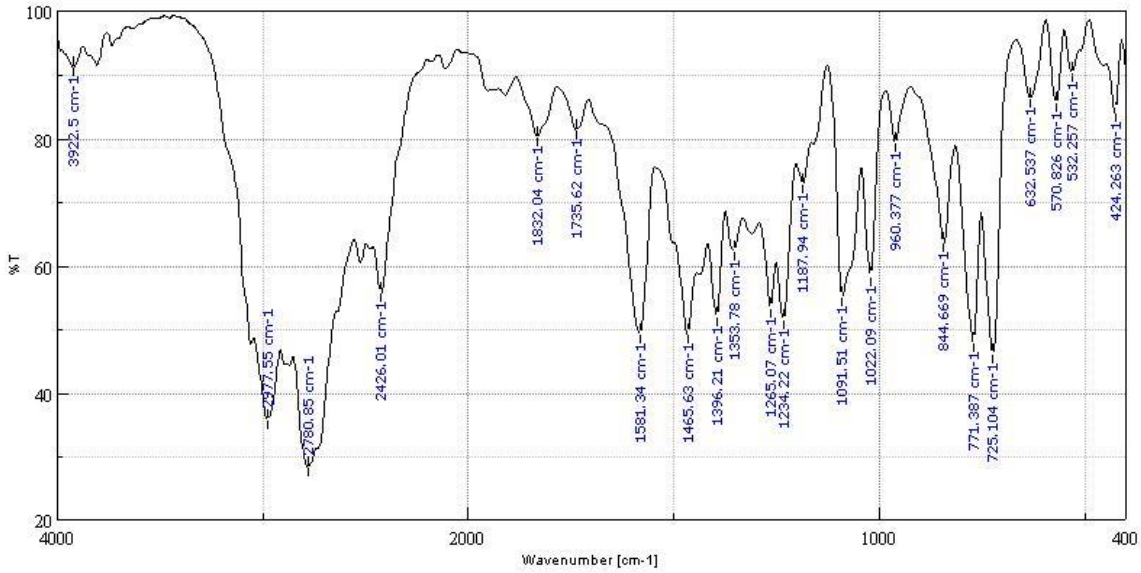

FIGURE: 6.24 FTIR SPECTRA OF DULOXETINE HYDROCHLORIDE

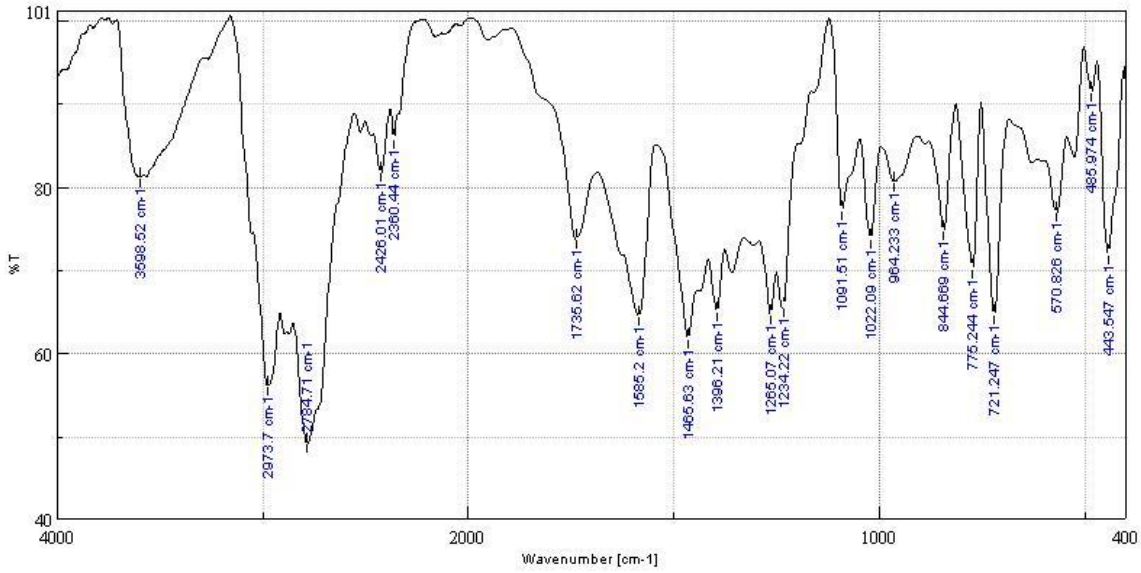

FIGURE: 6.25 FTIR SPECTRA OF DULOXETINE HYDROCHLORIDE PHYSICAL MIXTURE

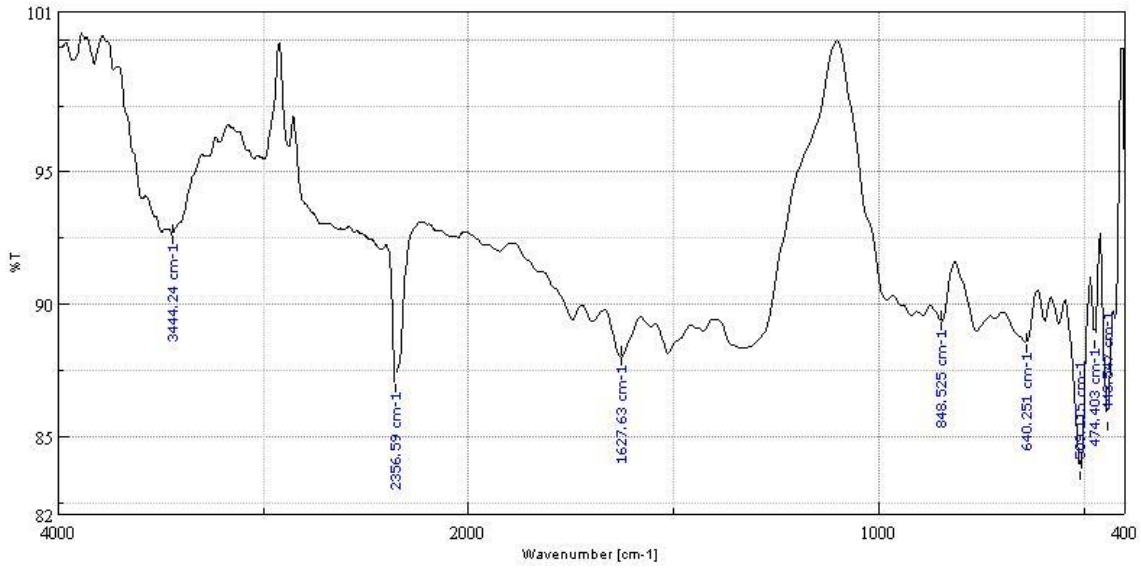

FIGURE: 6.26 FTIR SPECTRA OF DULOXETINE HYDROCHLORIDE FORMULATION D3 (SE-SD 1:3)

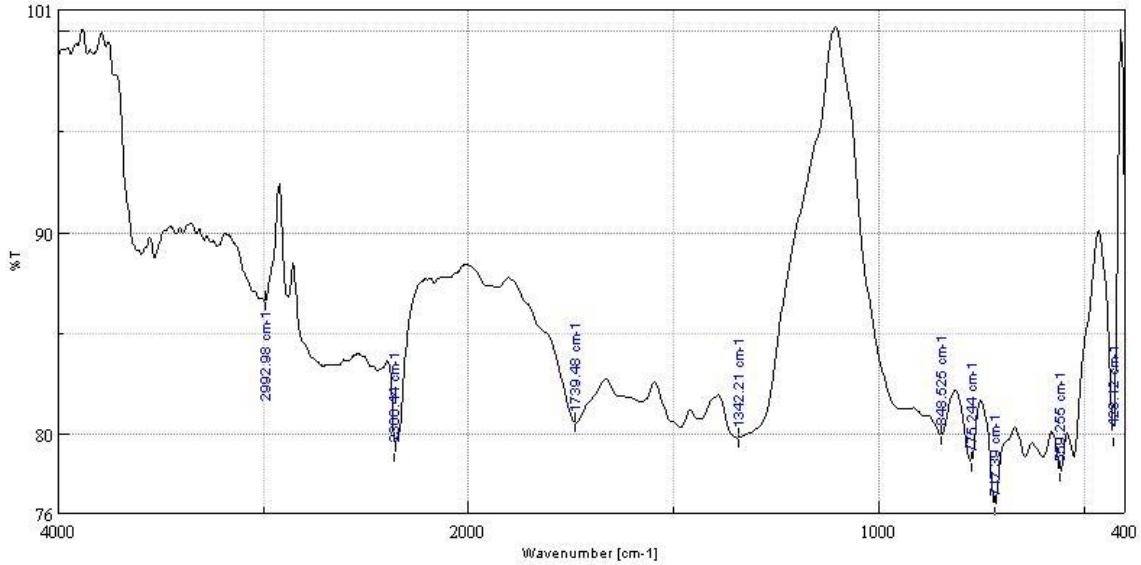

FIGURE: 6.27 FTIR SPECTRA OF DULOXETINE HYDROCHLORIDE FORMULATION D3 (ME-SD 1:3)

4. **DSC:** Thermal analysis of Duloxetine Hydrochloride and its SDs was done. The endothermic peak shown in Figure 6.28 corresponds to its melting point. The physical mixture and formulations showed the disappearance of the exothermic peak and shifting of the endothermic peak towards higher temperatures as shown in Figures 6.29, 6.30, and 6.31. Similar results were shown in a study performed by Nijhawan M et al., (2024) [72]

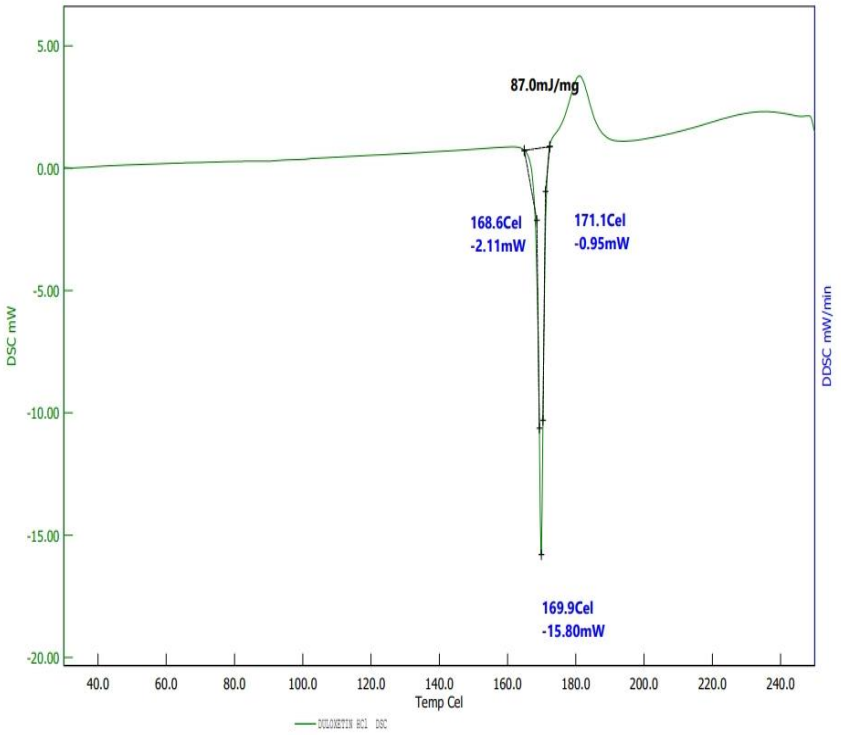

FIGURE: 6.28 DSC THERMOGRAM OF DULOXETINE

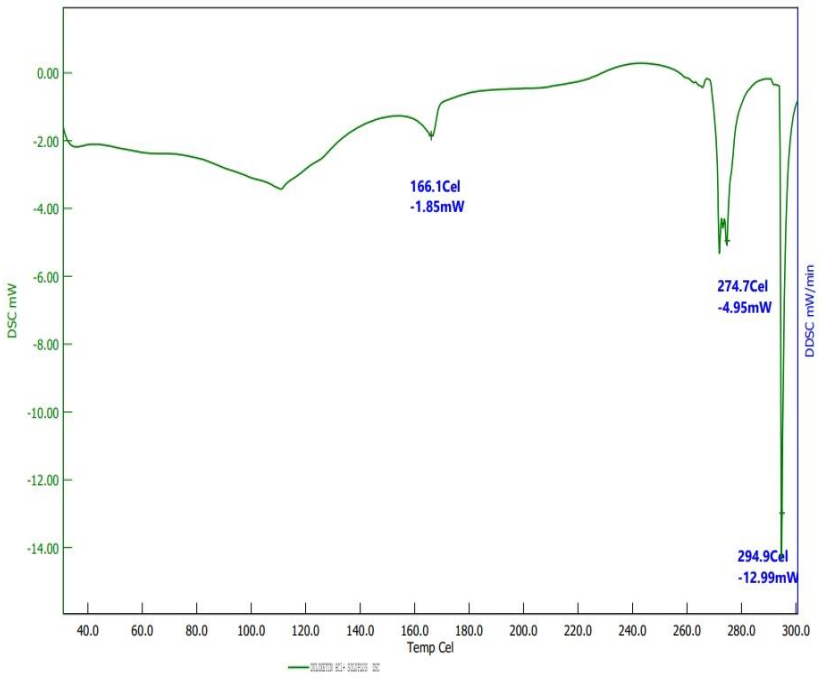

FIGURE: 6.29 DSC THERMOGRAM OF DULOXETINE HYDROCHLORIDE PHYSICAL MIXTURE

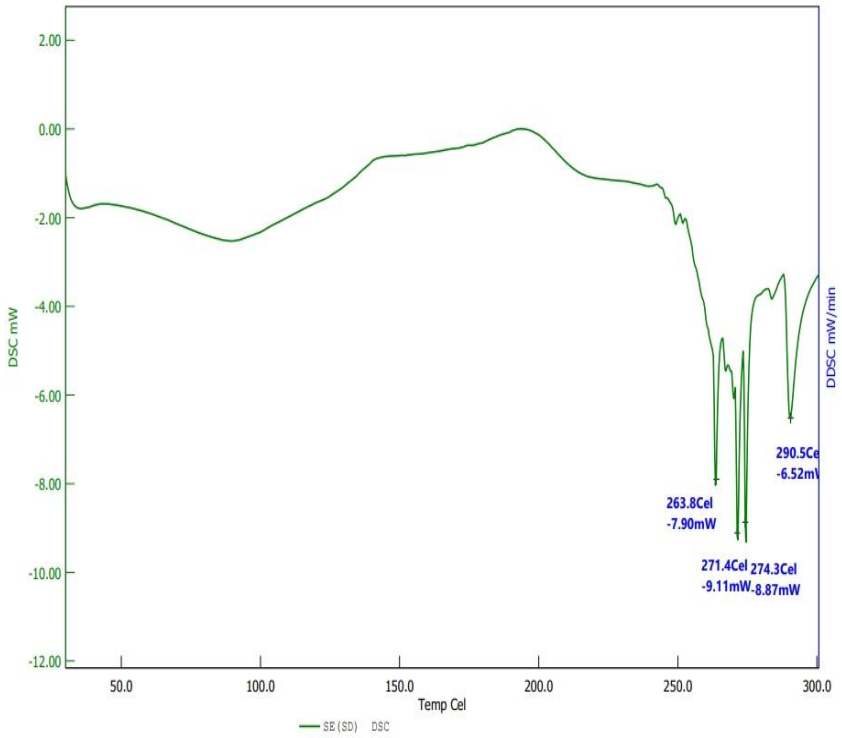

FIGURE: 6.30 DSC THERMOGRAM OF DULOXETINE HYDROCHLORIDE FORMULATION D3 (SE-SD 1:3)

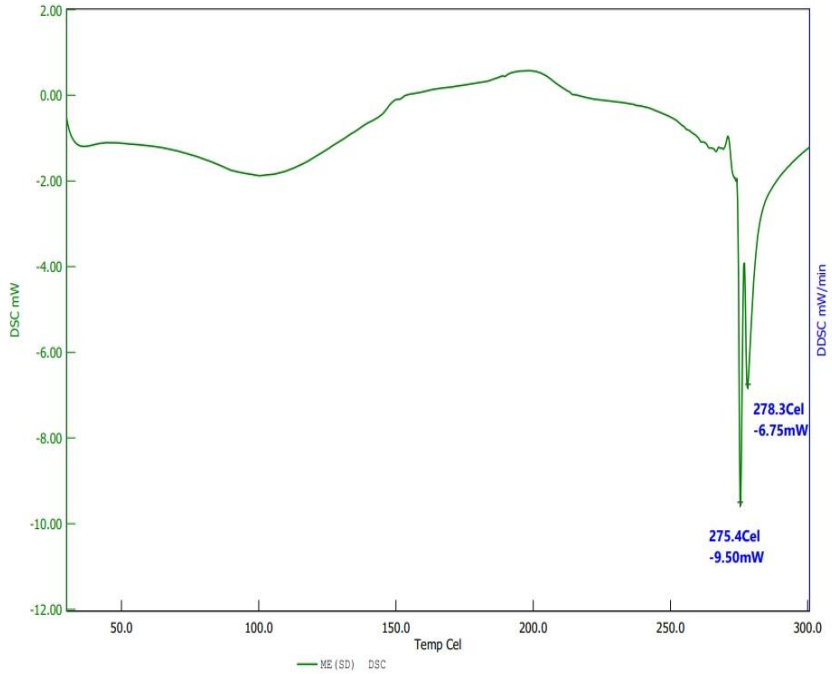

FIGURE: 6.31 DSC THERMOGRAM OF DULOXETINE HYDROCHLORIDE FORMULATION D6 (ME-SD 1:3)

5. **XRD:** The peaks of Duloxetine Hydrochloride are sharp as shown in Figure 6.32 while most of these peaks are absent, the present peaks appear to be broad in formulations as shown in Figure 6.33 and 6.34. Similar results were shown in a study performed by Aroon A et al., (2023) **[83]**

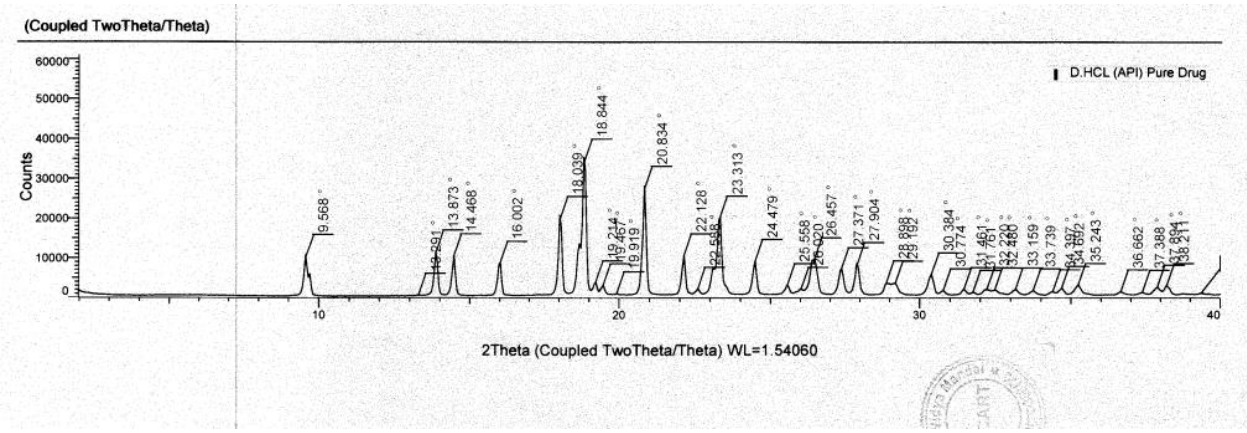

FIGURE: 6.32 XRD SPECTRA OF DULOXETINE HYDROCHLORIDE

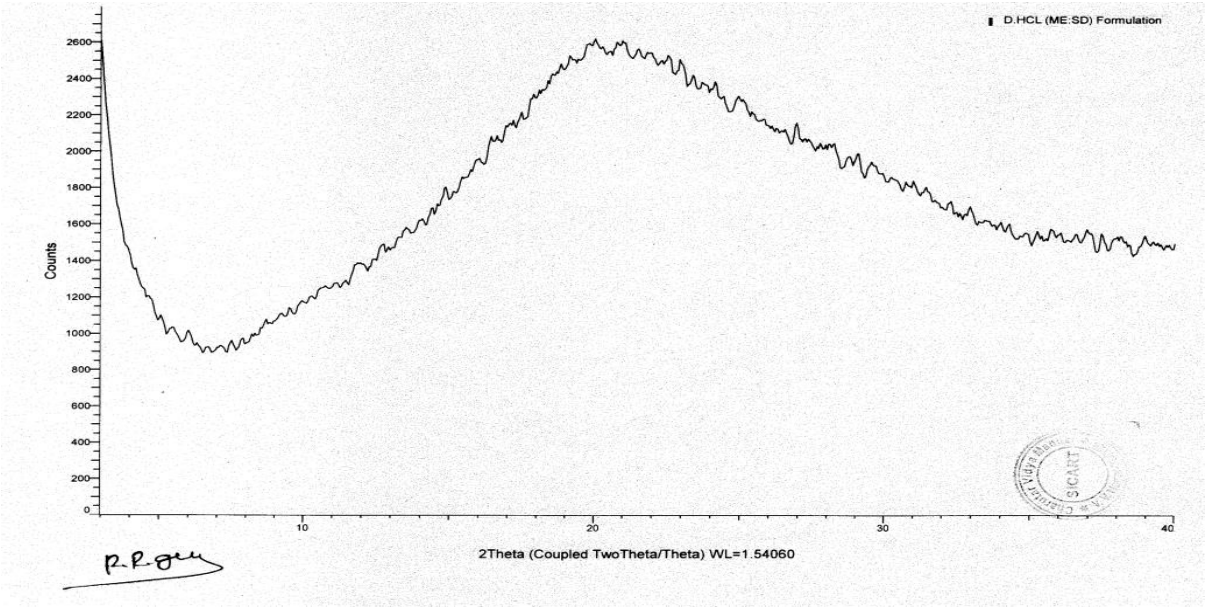

FIGURE: 6.33 XRD SPECTRA OF DULOXETINE HYDROCHLORIDE FORMULATION D3 (SE-SD 1:3)

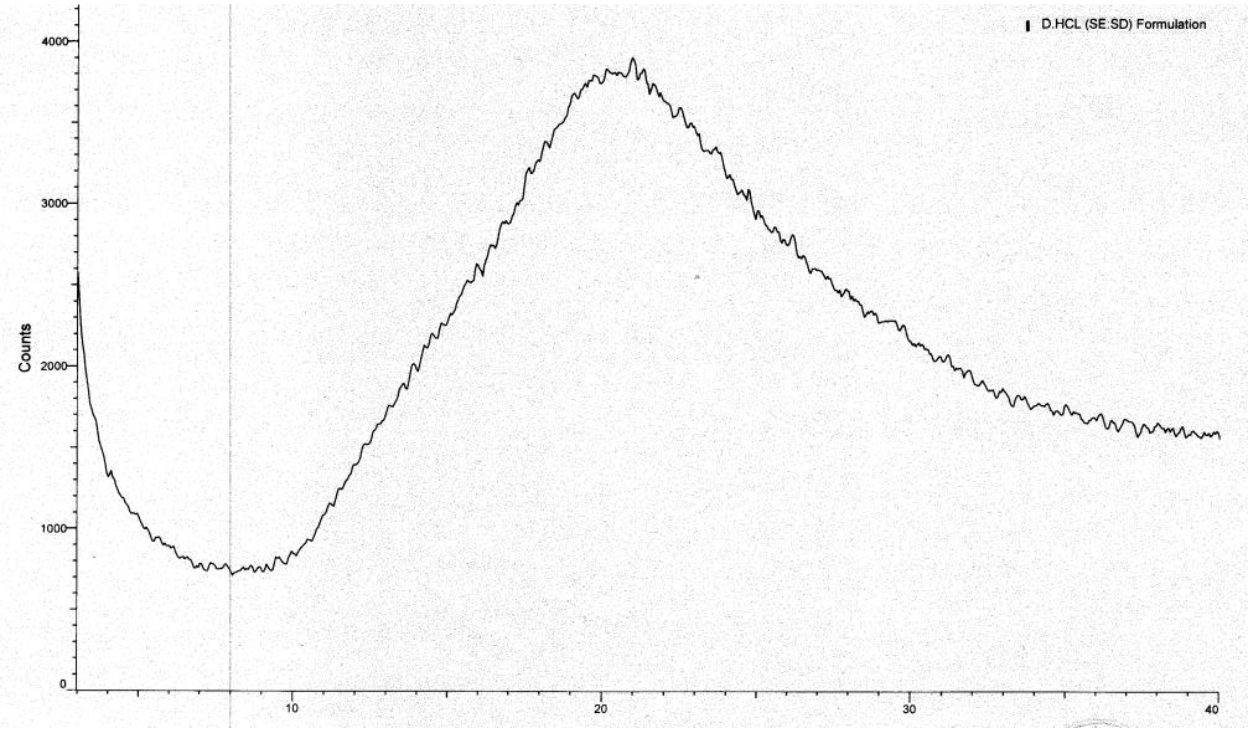

FIGURE: 6.34 XRD SPECTRA OF DULOXETINE HYDROCHLORIDE FORMULATION D6 (ME-SD 1:3)

6.1.3 Abiraterone Acetate

1. %Drug Content, %Yield and Solubility:

TABLE: 6.7 CHARACTERIZATION OF ABIRATERONE ACETATE, ITS PHYSICAL MIXTURE, AND ITS SDs

Name	%Drug content	%Yield	Solubility (µg/ml)
Pure drug	-	-	5.23 ±0.15
Physical mixture	81.57 ±0.9	-	37.45 ±0.36
(SE-SD 1:1) A1	76.88 ±0.65	84.25	24.3 ± 0.54
(SE-SD 1:2) A2	82.15 ±0.78	86.61	40.75 ± 0.26
(SE-SD 1:3) A3	89.24 ±0.59	85.17	60.12 ± ±0.30
(ME-SD 1:1) A4	85.63 ±0.47	86.43	27.63 ± 0.18
(ME-SD 1:2) A5	86.63 ±0.88	85.68	41.95 ± 0.23
(ME-SD 1:3) A6	90.44 ±0.68	88.04	65.54 ± 0.12

*All values are in mean ± SD (n=3)

The drug content of all the batches was found between 76-90% and out of those batches A6 and A3 showed the best results. Batch A6 showed an increase in solubility along with drug content (90.44) and yield (89.04%). The solubility of formulation showed multiple folds of increase, A1 & A4 showed 5 times increase in solubility while the best batches showed more than 10 times increase in solubility which shows that the carrier Soluplus® has the capability of enhancing the solubility of this drug.

Solubility increased with the increase in polymer concentration: 1:3>1:2>1:1. Similar results were obtained from study conducted by Gala et al. (2020)[104]

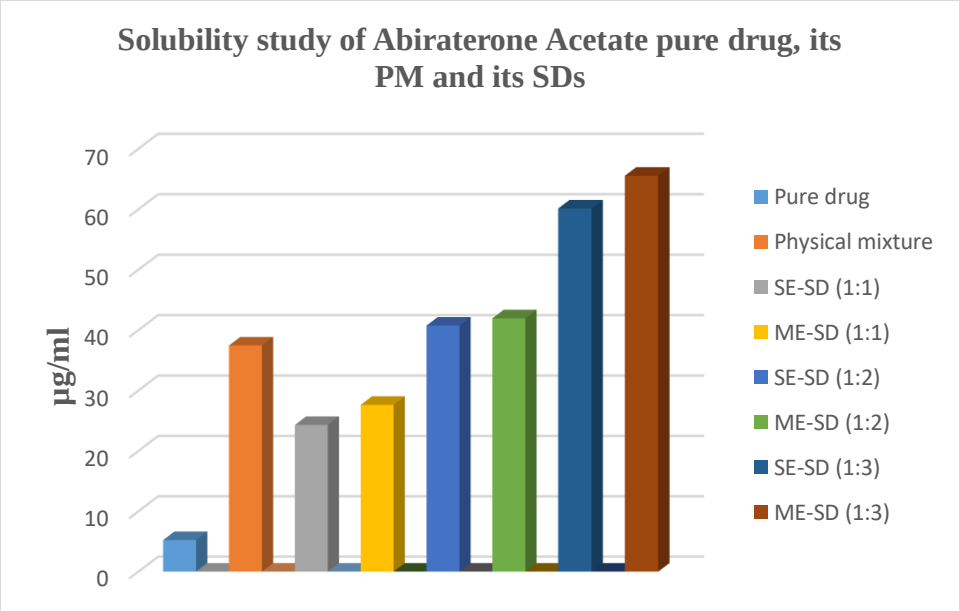

FIGURE: 6.35 SOLUBILITY STUDY OF ABIRATERONE ACETATE PURE DRUG, ITS PM AND ITS SDs

2. In-Vitro Drug Release

From the dissolution data, it was observed that the prepared SDs showed an enhanced dissolution rate when compared to pure drug. The probable reason is the crystalline drug was converted to the amorphous form. The amorphous solid has high free energy, due to which in the process of stabilization, they form hydrogen bonds with the water molecules and get converted into the solution form.

Among all the batches A3 and A6 showed greater dissolution rate release up to 62.8% and 63.59% of the drug.

Other batches also show increased dissolution compared to pure drug which proves that formulation of SDs with Soluplus® enhances the dissolution rate of this drug. Similar results were obtained from a study conducted by Nakka VN et al., (2024) [77]

TABLE: 6.8 DISSOLUTION PROFILE OF ABIRATERONE ACETATE, ITS PHYSICAL MIXTURE AND ITS SDS

Time (min)	Percentage drug released (%)							
	Pure drug (%)	Physical mixture (1:3)	SE-SD (1:1) A1	SE-SD (1:2) A2	SE-SD (1:3) A3	ME-SD (1:1) A4	ME-SD (1:2) A5	ME-SD (1:3) A6
0	0	0	0	0	0	0	0	0
10	2.05	6.29	5.839	5.848	8.16	4.692	6.787	7.25
20	3.14	11.15	8.593	8.421	15.24	9.604	8.136	13.36
30	5.37	16.38	10.261	14.087	19.37	12.563	12.180	19.87
40	7.82	22.5	14.575	21.428	25.61	15.781	16.806	27.61
50	8.91	26.41	21.569	27.437	32.78	18.611	21.452	34.75
60	11.47	31.96	23.579	32.096	36.97	22.714	26.782	39.98
70	12.59	34.37	26.715	36.775	44.32	23.892	32.159	46.47
80	14.23	38.24	30.435	40.62	48.74	26.253	38.45	51.63
90	16.85	41.05	33.64	44.466	53.49	29.004	42.68	55.41
100	17.23	45.63	37.23	50.026	57.54	33.571	47.310	57.35
110	17.31	47.97	39.10	53.853	60.21	36.23	50.005	59.84
120	17.38	49.78	40.35	54.63	**62.82**	38.95	52.807	**63.59**

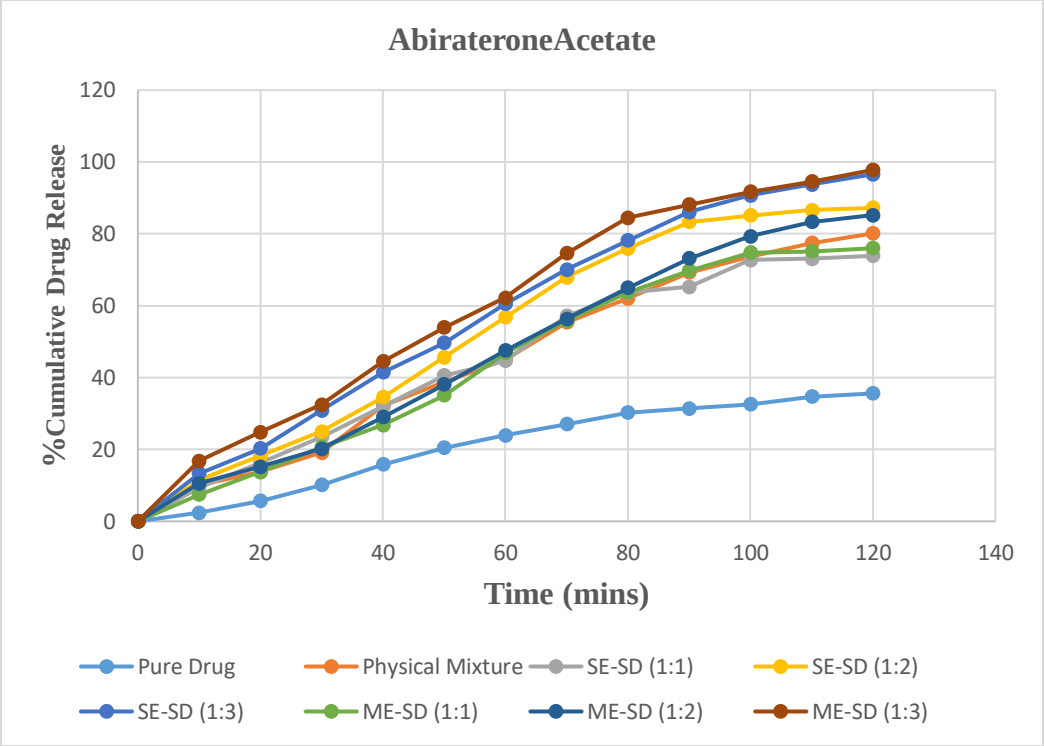

FIGURE: 6.36 CUMULATIVE % RELEASE STUDIES OF ABIRATERONE ACETATE, ITS PHYSICAL MIXTURE, AND ITS SDs

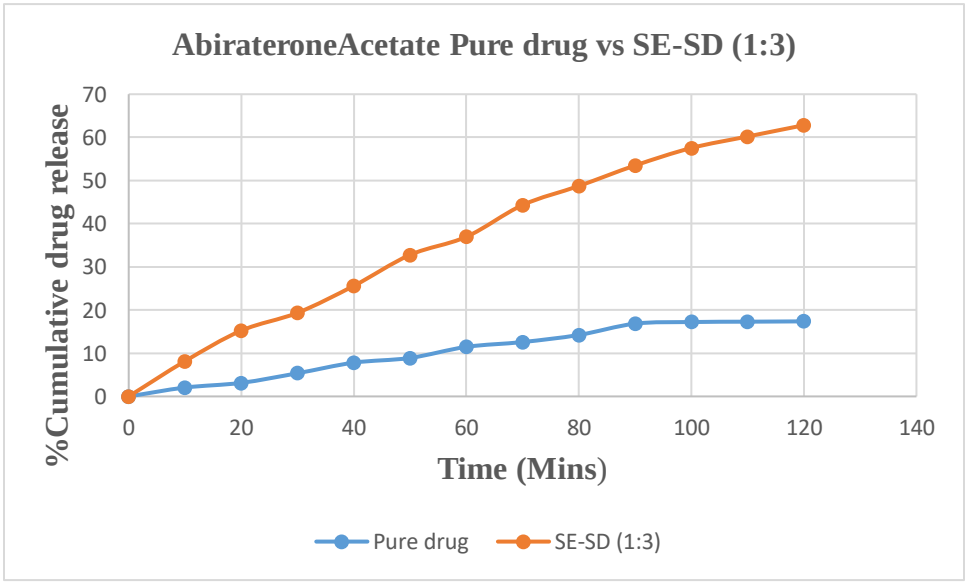

FIGURE: 6.37 RELEASE STUDIES OF ABIRATERONE ACETATE VS FORMULATION (SE-SD 1:3)

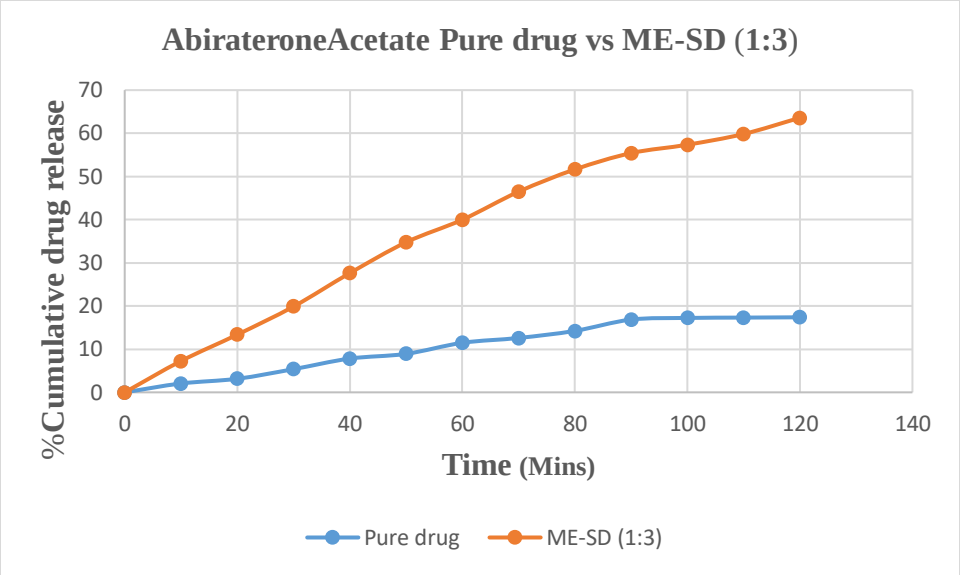

FIGURE: 6.38 RELEASE STUDIES OF ABIRATERONE ACETATE VS FORMULATION (ME-SD 1:3)

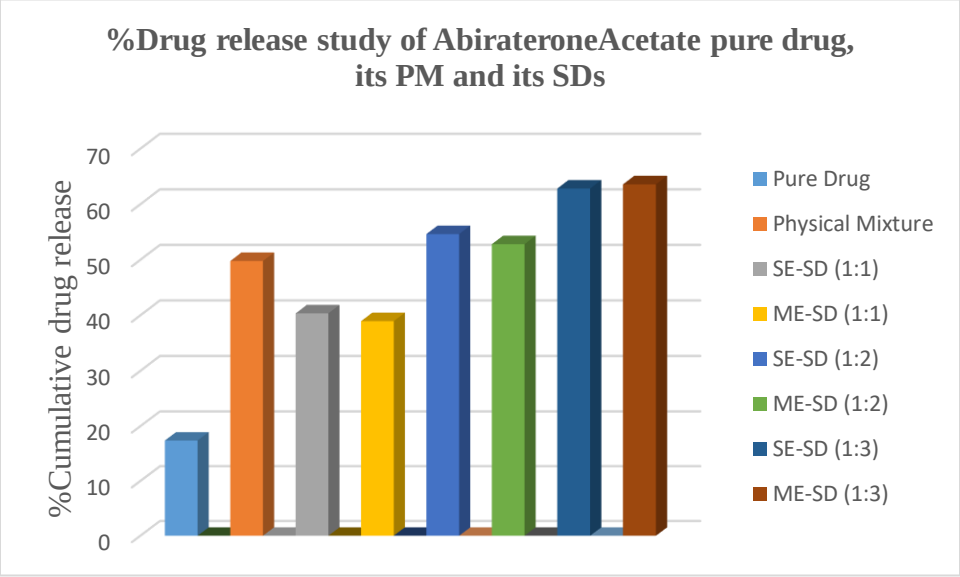

FIGURE: 6.39 %DRUG RELEASE STUDY OF ABIRATERONE ACETATE PURE DRUG, ITS PM AND ITS SDS

3. **FTIR:** Upon comparing Figures 6.40 and 6.41, no interaction was observed that indicated compatibility between the drug and polymer. The formulations also show respective functional

group wavelengths when compared with the wavelength of the pure drug as shown in Table 6.9. Similar results were obtained from a study conducted by Thawani LM, (2023) [73]

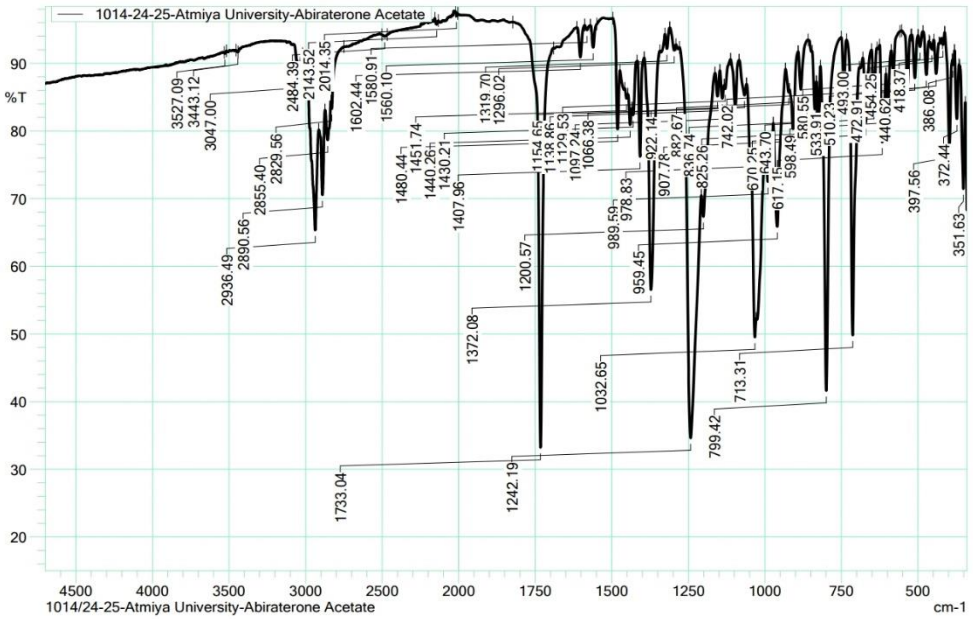

FIGURE: 6.40 FTIR SPECTRA OF ABIRATERONEACETATE

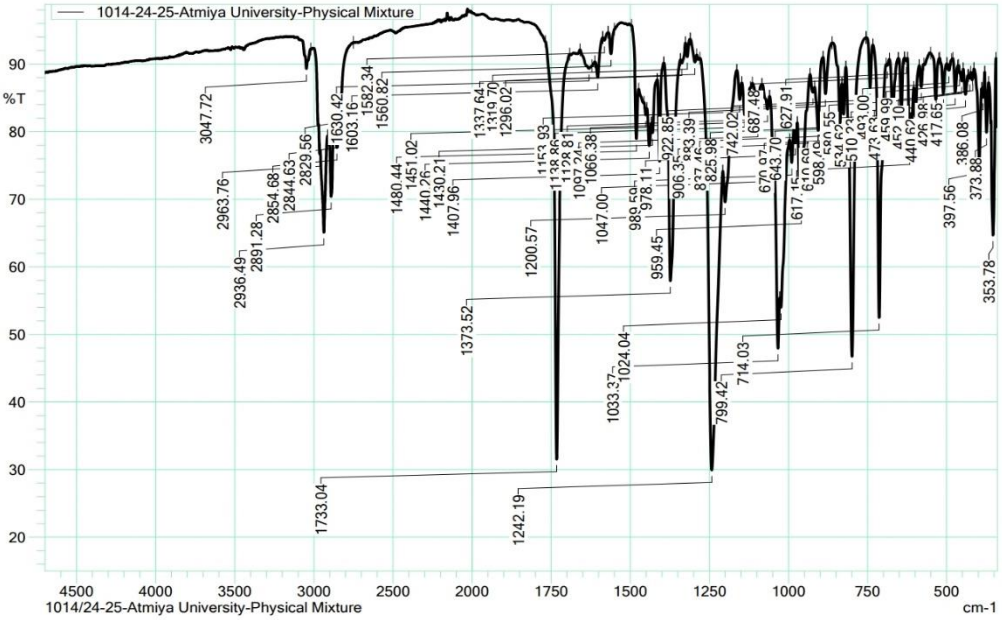

FIGURE: 6.41 FTIR SPECTRA OF ABIRATERONE ACETATE PHYSICAL MIXTURE

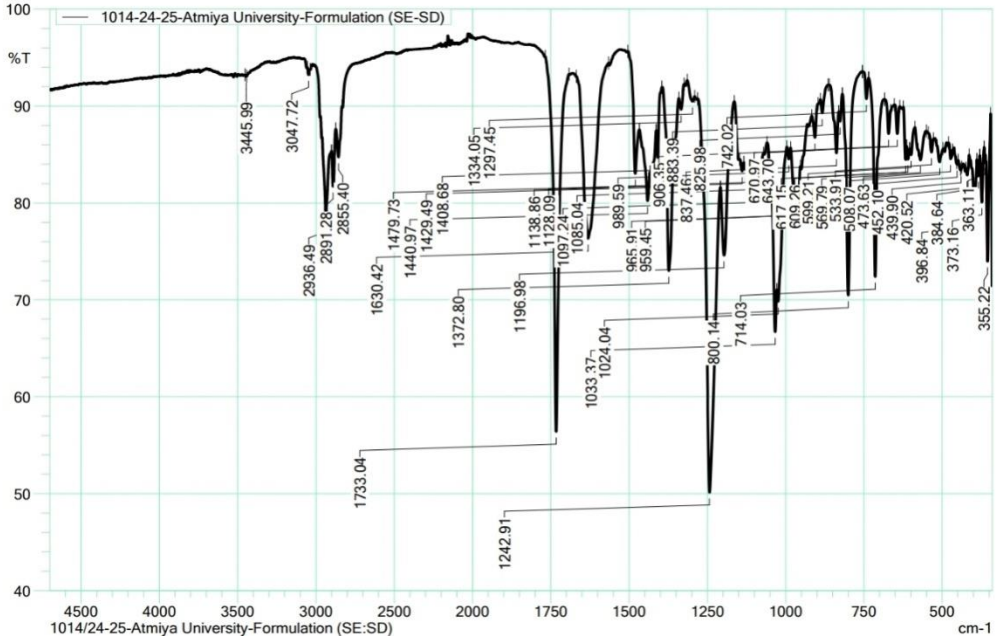

FIGURE: 6.42 FTIR SPECTRA OF ABIRATERONE ACETATE FORMULATION A3 (SE-SD 1:3)

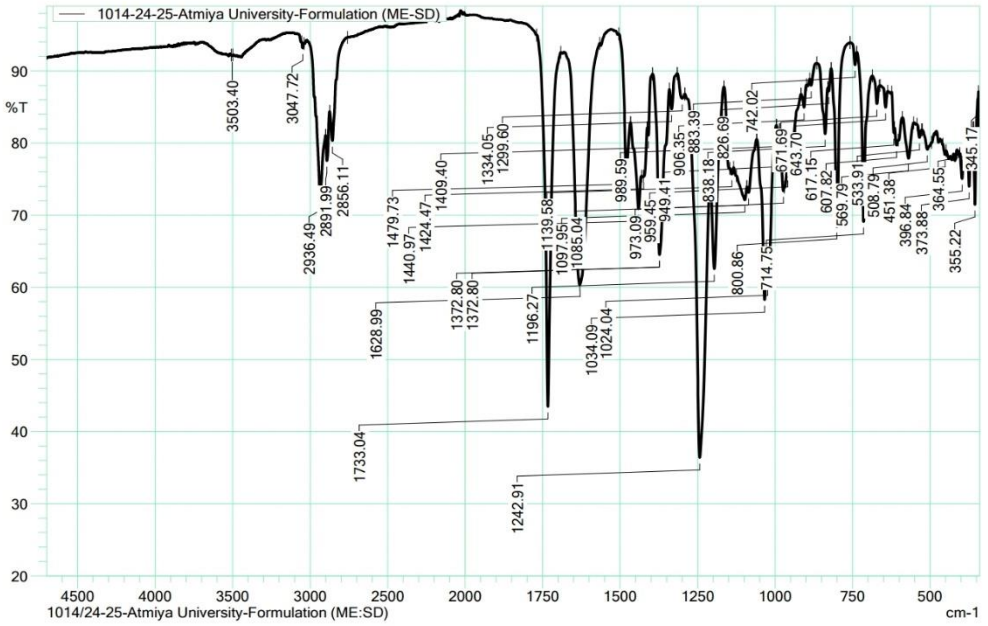

FIGURE: 6.43 FTIR SPECTRA OF ABIRATERONE ACETATE FORMULATION A6 (ME-SD 1:3)

TABLE: 6.9 COMPARISON OF FTIR WAVELENGTHS OF ABIRATERONE ACETATE, ITS PHYSICAL MIXTURE, AND ITS SDS

Functional groups with wavelength	Pure drug (cm^{-1})	Physical mixture (cm^{-1})	A3 (cm^{-1})	A6 (cm^{-1})
(SB) C-H Stretching 2850-3000 cm^{-1}	2855.40	2854.68	2855.40	2856.11
	2890.56	2891.28	2891.28	2891.99
	2936.49	2936.49	2936.49	2936.49
(SB) C=O Stretching 1700-1750 cm^{-1}	1733.04	1733.04	1733.04	1733.04
(PR)C-H Stretching 3020-3100cm^{-1}	3047.00	3047.72	3047.72	3047.72
(PR) C=C Stretching 1600-1680 cm^{-1}	1602	1603.16	1630.42	1628.99
(AE) C=O Stretching Around 1240 cm^{-1}	1242.19	1242.19	1242.91	1242.91
(TBDMS) Si-C Stretching 1250-1300 cm^{-1}	1296.02	1296.02	1297.45	1299.60

SB- Steroidal Backbone

PR- Pyridine ring

AE- Acetate Ester group

TBDMS- Tert-Butyldimethylsilyl

4. **DSC:** The DSC of pure Abiraterone Acetate showed the endothermic peak at 144.98°C as shown in Figure 6.44, which corresponds to the reported melting point of the drug. There is a reduction in the exothermic peak of the physical mixture as shown in Figure 6.45 which indicates that there is a reduction in crystallinity. The formulation showed a reduction in the intensity of the exothermic peak as shown in Figure 6.46. Similar results were obtained from a study conducted by Liu et al. (2022) **[86]**

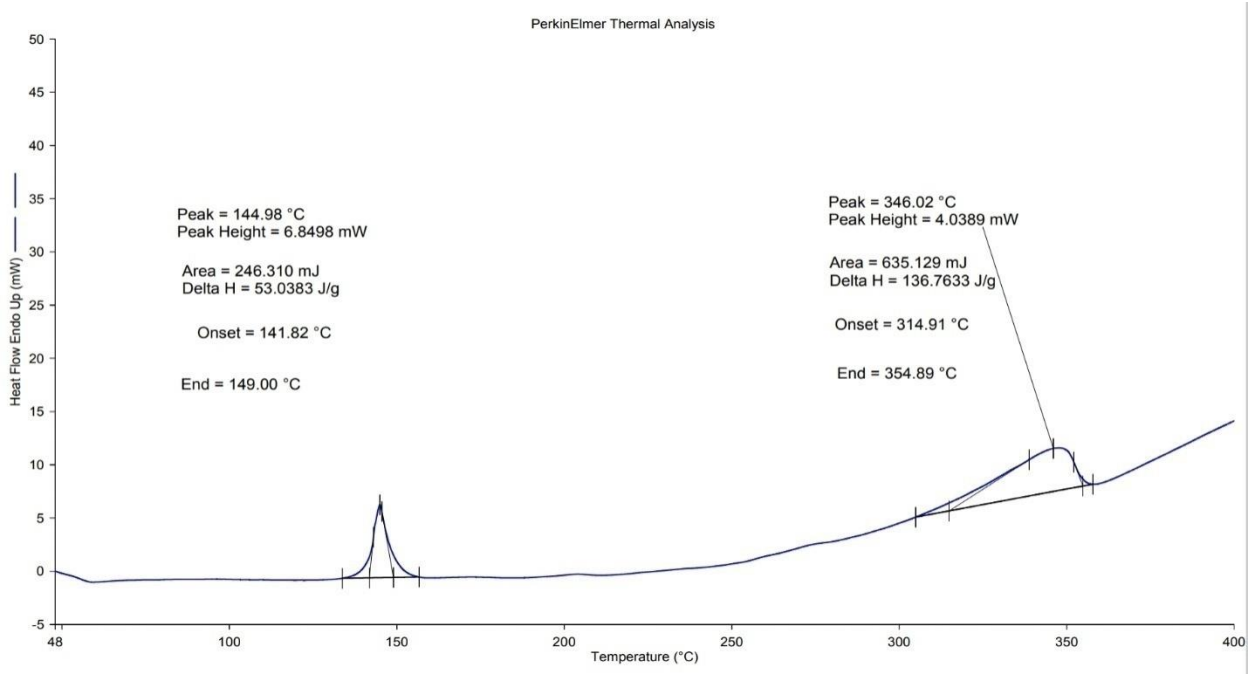

FIGURE: 6.44 DSC THERMOGRAM OF ABIRATERONE ACETATE

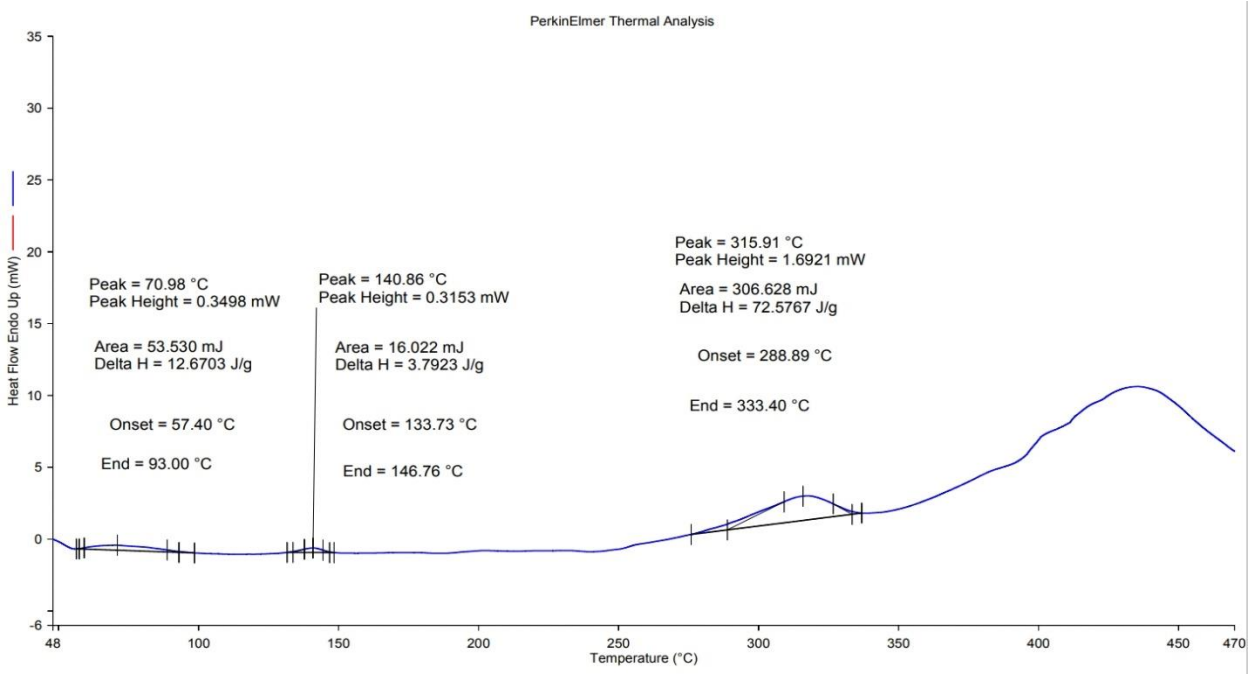

FIGURE: 6.45 DSC THERMOGRAM OF ABIRATERONE ACETATE PHYSICAL MIXTURE

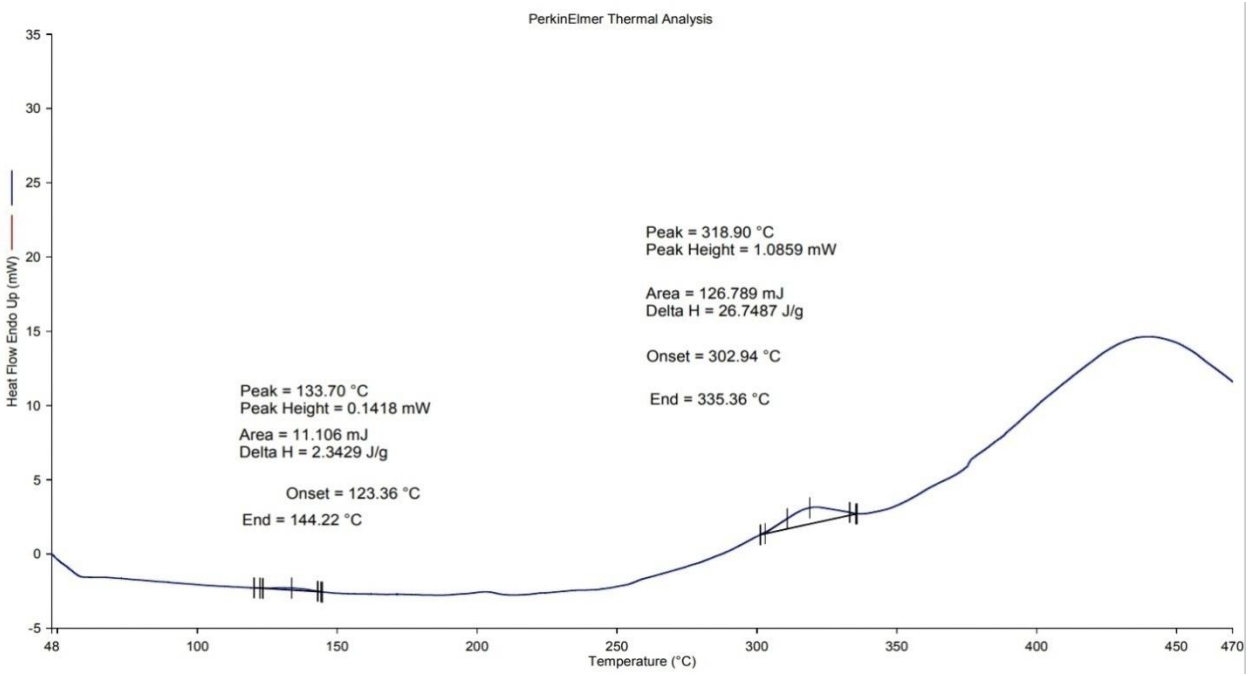

FIGURE: 6.46 DSC THERMOGRAM OF ABIRATERONE ACETATE FORMULATION A6 (ME-SD 1:3)

5. **XRD:** The pure drug showed sharp peaks in XRD as shown in Figure 6.47 which corresponds to its crystalline nature. The formulation showed a reduction in intensity of peak when compared with pure drug as shown in Table 6.10). There is a drop in the intensity of the peak, indicating a loss in crystallinity. Out of the two batches, A3 (Figure 6.48) and A6 (Figure 6.49), A6 has superior results in reducing peak intensity. The reduction in the magnitude of peaks indicates the amorphous characteristics of the created SDs. Similar results were obtained from a study conducted by Liu et al. (2022) **[86]**

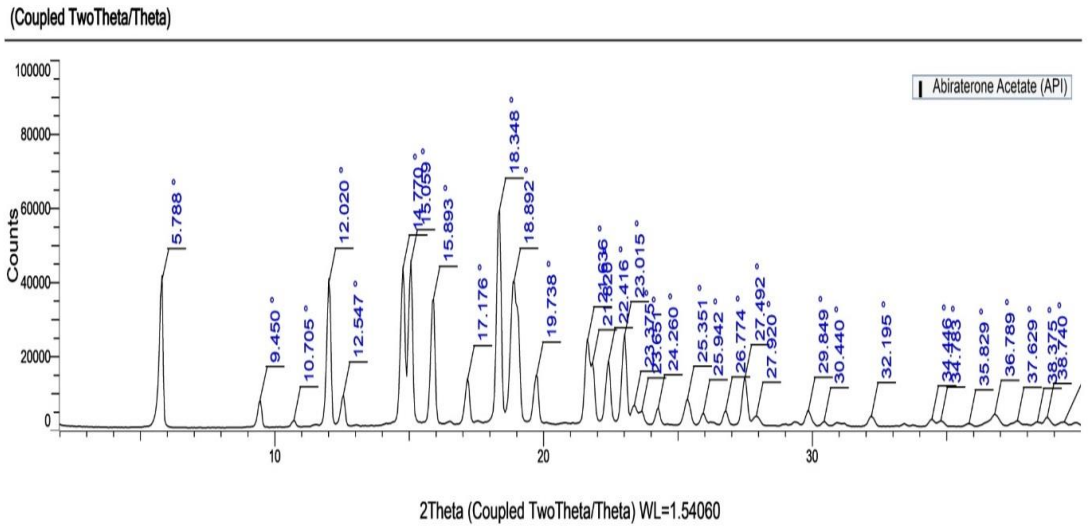

FIGURE: 6.47 XRD SPECTRA OF ABIRATERONE ACETATE

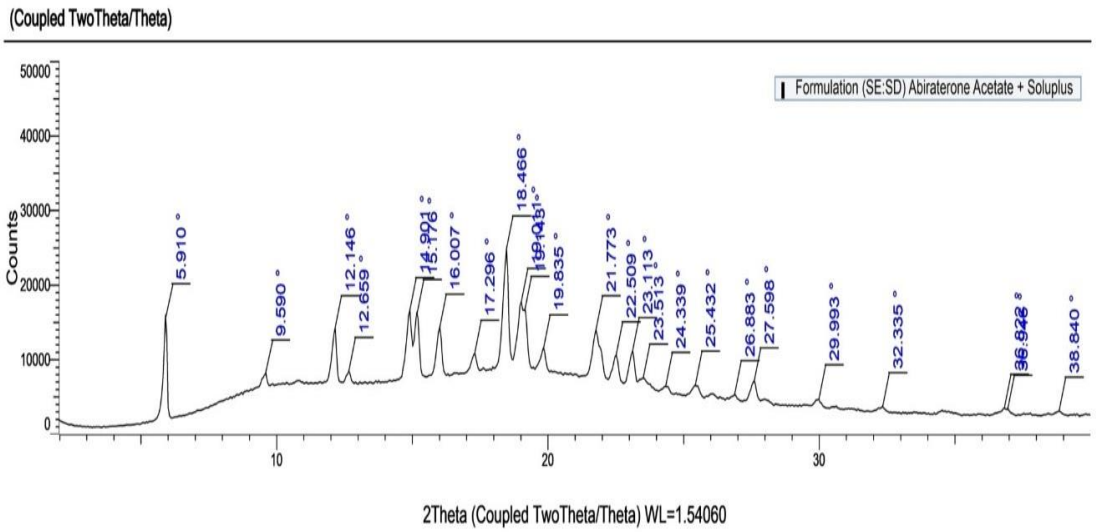

FIGURE: 6.48 XRD SPECTRA OF ABIRATERONE ACETATE FORMULATION A6 (SE-SD 1:3)

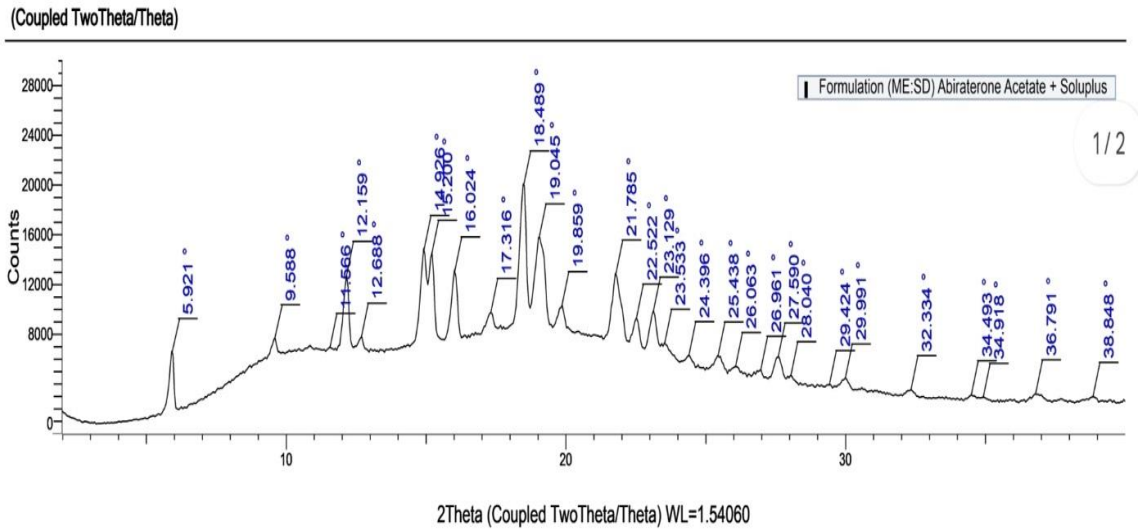

FIGURE: 6.49 XRD SPECTRA OF ABIRATERONE ACETATE FORMULATION A6 (ME-SD 1:3)

TABLE: 6.10 XRD PEAK INTENSITY COMPARISON OF ABIRATERONE ACETATE AND ITS SDs

Angle° 2Ɵ	Pure drug (intensity)	Angle° 2Ɵ	A3 Intensity	Angle° 2Ɵ	A6 (intensity)
5.788	39136.890	5.910	13788.340	5.921	4873
12.020	38884.290	12.146	9959.945	12.159	8996
14.770	42100.910	14.901	11835.300	14.926	10488
15.059	43478.340	15.176	11538.720	15.200	10083.420
15.893	33531.370	16.007	9434.891	16.025	8610.174
18.348	57186.800	18.466	19697.470	18.489	15295.730
18.892	38199.080	19.011	12656.630	19.045	1019.820

CHAPTER 7
SUMMARY AND CONCLUSION

7. SUMMARY AND CONCLUSION

Nowadays, various routes of administration have been explored for the effective delivery of the drug. The oral route is considered the most convenient for the administration of the medications to patients. Poor water solubility is widely recognized as the main reason for the poor oral absorption of many new chemical entities. Many new approaches have been developed to enhance the solubility of poorly soluble drugs and among them SDs are considered to be quite an effective method.

The present investigation aimed to develop SDs of Rifampicin (BCS Class-2), Duloxetine Hydrochloride (BCS Class-2), and Abiraterone Acetate (BCS Class-4). Rifampicin is a drug used in the treatment of tuberculosis, Duloxetine Hydrochloride in major depressive disorder, and Abiraterone acetate in treatment of Prostate cancer. So, by formulating SDs of these drugs solubility can be increased.

SDs are defined as group of solid products consisting of a hydrophobic drug dispersed in at least one hydrophilic carrier, resulting in increased surface area and, enhanced drug solubility and dissolution rate.

Preliminary trials were performed to determine the methods and solventthat were used for further research work. The drugs and polymer were evaluated with FT-IR to determine the compatibility of the drug and polymer, with DSC the melting point of the drug was determined along with its thermal behavior.

The FT-IR of the drug and physical mixture were compared, and no interaction was found. The DSC performed for the drugs shows the endothermic peak at temperatures which corresponds with their melting point.

All the drugs were formulated into SDs using solvent evaporation and melt evaporation technique with each drug having 6 batches of formulation. Each method had 3 batches with the drug to polymer ratio of 1:1, 1:2, and 1:3. The formulated batches were then subjected to different evaluation parameters.

Formulated batches were evaluated for %drug content, %yield, solubility studies, and in vitro-dissolution studies. Among those batches, the batches with good solubility and in vitro dissolution were then evaluated with FT-IR, DSC, and XRD.

For Rifampicin: The DSC of formulation SE-SD (1:3) showed a reduction in melting point and formulation ME-SD (1:3) showed perfect encapsulation of the drug in the polymer

The XRD report showed favorable results in both formulations with no sharp peaks observed which were found in the XRD of Pure drug

For Duloxetine Hydrochloride: The DSC formulation SE-SD (1:3) and ME-SD (1:3) showed a reduction of melting peak and shifting of endothermic peak to a higher temperature which shows changes in composition and formation of a complex.

The XRD shows no sharp peak in both formulations which shows they changed from crystalline to amorphous state

For Abiraterone Acetate: The DSC of formulation shows perfect encapsulation of the drug in polymer and for another formulation shows a reduction in melting peak which corresponds to a reduced crystalline nature.

Conclusion:

The polymer Soluplus® was utilized to create a SDs formulation, increasing the solubility of the drugs and thus improving the dissolving rate. The solubility of drugs rises with the increase in concentration of polymer, as demonstrated by the batch SE-SD (1:3) and ME-SD (1:3) in each drug formulation [Rifampicin (R3 and R6), Duloxetine Hydrochloride (D3 and D6), and Abiraterone acetate (A3 and A6)]. Between the two techniques, melt evaporation is slightly superior to solvent evaporation. However, both procedures were successful in producing batches that may be subsequently used for solid or liquid formulation. The solubility enhanced by the polymer Soluplus Showed more than Two-fold in Rifampicin and Duloxetine HCl and more than 10-fold in Abiraterone Acetate

The research study determined that Soluplus® can increase the solubility of Rifampicin, Duloxetine Hydrochloride, and Abiraterone acetate in water.

The dissolving rate of SDs was improved when compared to pure medicines through the formulation of SDs using Soluplus®. The drug release percentage was greater than 90% for Rifampicin, greater than 90% for Duloxetine HCL, and greater than 60% for Abiraterone Acetate.

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8. REFERENCES

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ANNEXURE

9. ANNEXURE

9.1 Standard curves of drugs: The standard curves of drugs (Rifampicin, Duloxetine Hydrochloride, and Abiraterone Acetate) were prepared in distilled water, methanol, and phosphate buffer (7.4, 6.8, 4.5) respectively.

9.1.1 Rifampin

The standard curves for Rifampicin were prepared in distilled water, methanol, and phosphate buffer (6.8)

1. **Distilled water:** The **λmax** of the Rifampicin was found to be 472nm as shown in Figures 9.1 and 9.2. Different concentrations of Rifampicin from 10 to 50µg/ml were prepared and the absorbance was taken at 472 nm using a UV spectrophotometer. The graph was plotted between Concentration vs Absorbance

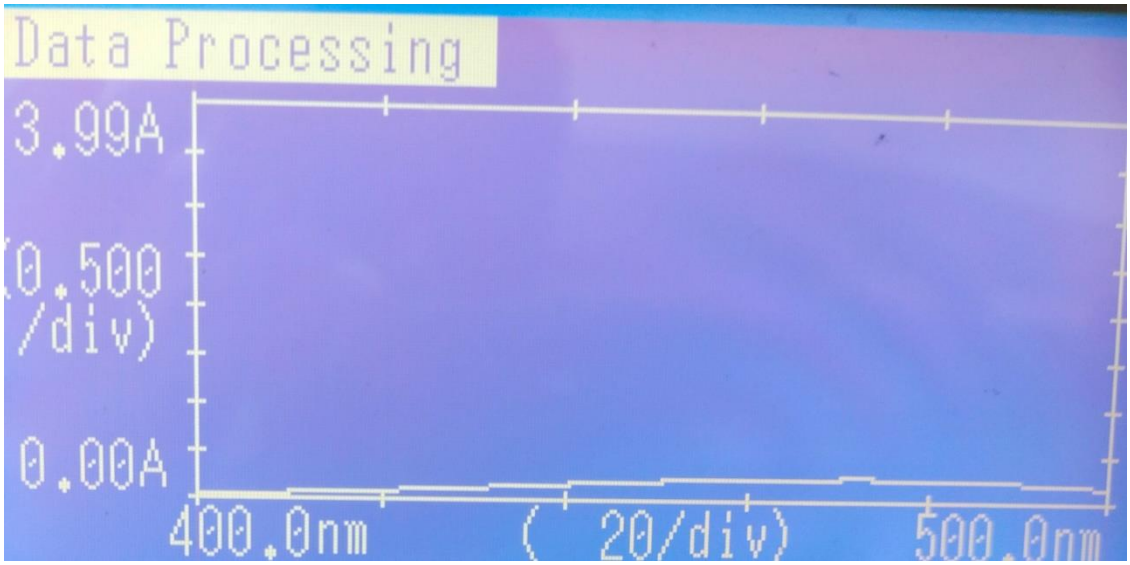

FIGURE: 9.1 λmax OF RIFAMPICIN

FIGURE: 9.2 λmax OF RIFAMPICIN

TABLE: 9.1 STANDARD CURVE OF RIFAMPICIN IN WATER

S. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.132 ± 0.021
3	15	0.192 ± 0.041
4	20	0.274 ± 0.012
5	25	0.356 ± 0.063
6	30	0.428 ± 0.054
7	35	0.524 ±0.045
8	40	0.624 ±0.036
9	45	0.715 ± 0.021
10	50	0.829 ± 0.031

*All values are in mean ± SD (n=3)

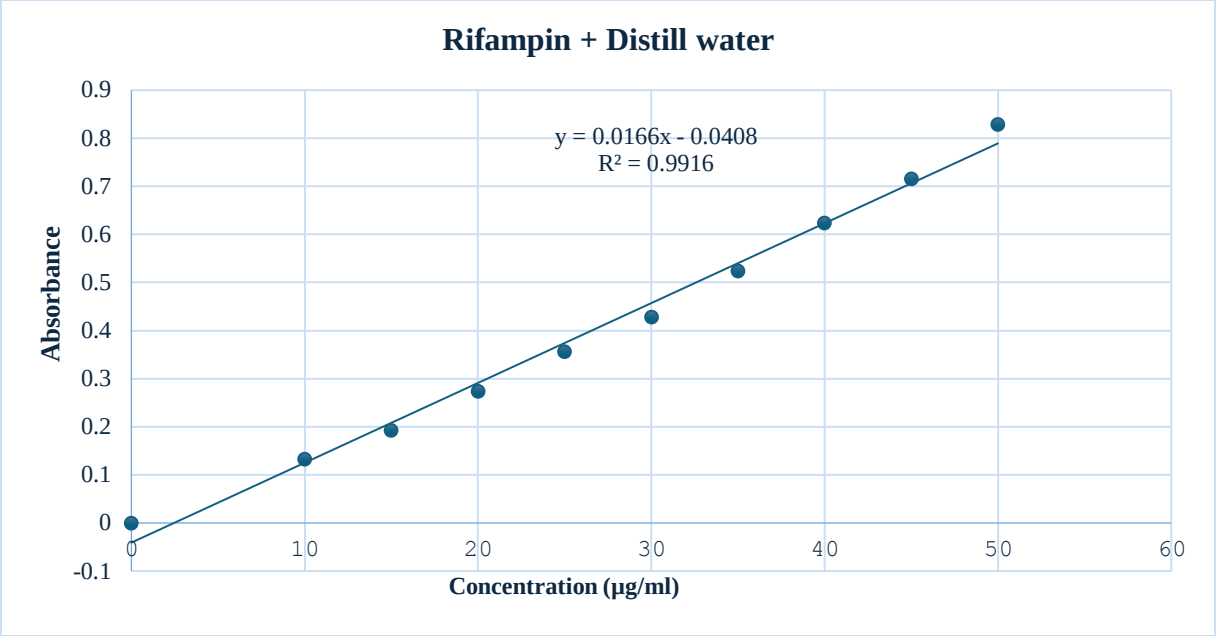

FIGURE: 9.3 STANDARD CURVE OF RIFAMPICIN IN WATER

2. **Methanol**: The **λmax** of the Rifampicin was found to be 472nm as shown in Figures 9.1 and 9.2. Different concentrations of Rifampicin from 10 to 100µg/ml were prepared and the absorbance was taken at 472 nm using a UV spectrophotometer. The graph was plotted between Concentration vs Absorbance.

TABLE: 9.2 STANDARD CURVE OF RIFAMPICIN IN METHANOL

S. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.253 ± 0.015
3	20	0.465 ± 0.021
4	30	0.653 ± 0.046
5	40	0.875 ± 0.054
6	50	1.181 ± 0.041
7	60	1.341 ± 0.21
8	70	1.62 ± 0.36
9	80	1.919 ± 0.39
10	90	2.21 ± 0.41
11	100	2.45 ± 0.048

*All values are in mean ± SD (n=3)

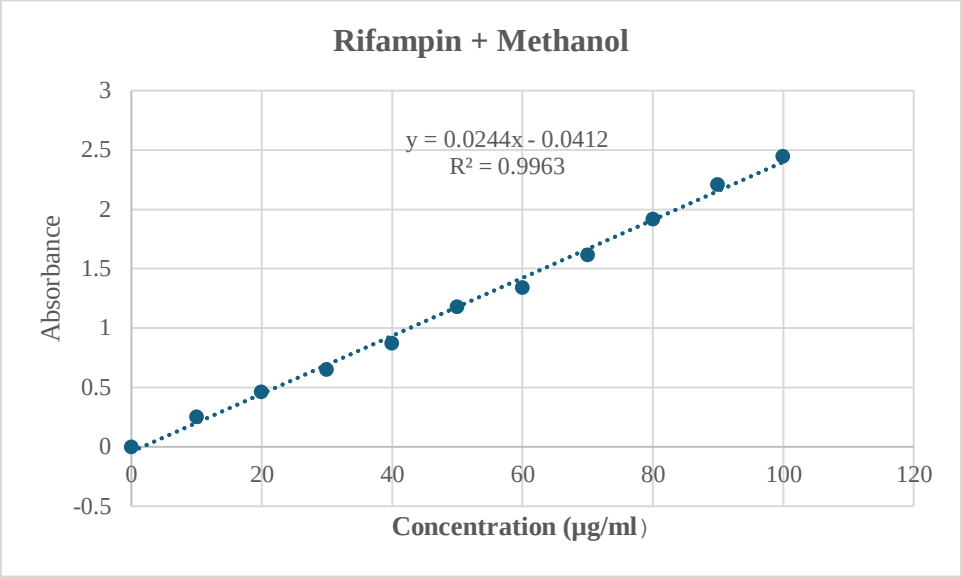

FIGURE: 9.4 STANDARD CURVE OF RIFAMPICIN IN METHANOL

3. **Phosphate buffer (7.4):** The **λmax** of the Rifampicin was found to be 472nm as shown in Figures 9.1 and 9.2. Different concentrations of Rifampicin from 10 to 100µg/ml were prepared the absorbance was taken at 472 nm using a UV spectrophotometer. The graph was plotted between Concentration vs Absorbance.

TABLE: 9.3 STANDARD CURVE OF RIFAMPICIN IN PHOSPHATE BUFFER

Sr. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.157 ± 0.031
3	20	0.311 ±0.014
4	30	0.442 ±0.055
50	40	0.587 ±0.032
6	50	0.761 ±0.016
7	60	0.972 ±0.025
8	70	1.078 ±0.041
9	80	1.185 ±0.039
10	90	1.354 ± 0.023
11	100	1.536 ± 0.019

*All values are in mean ± SD (n=3)

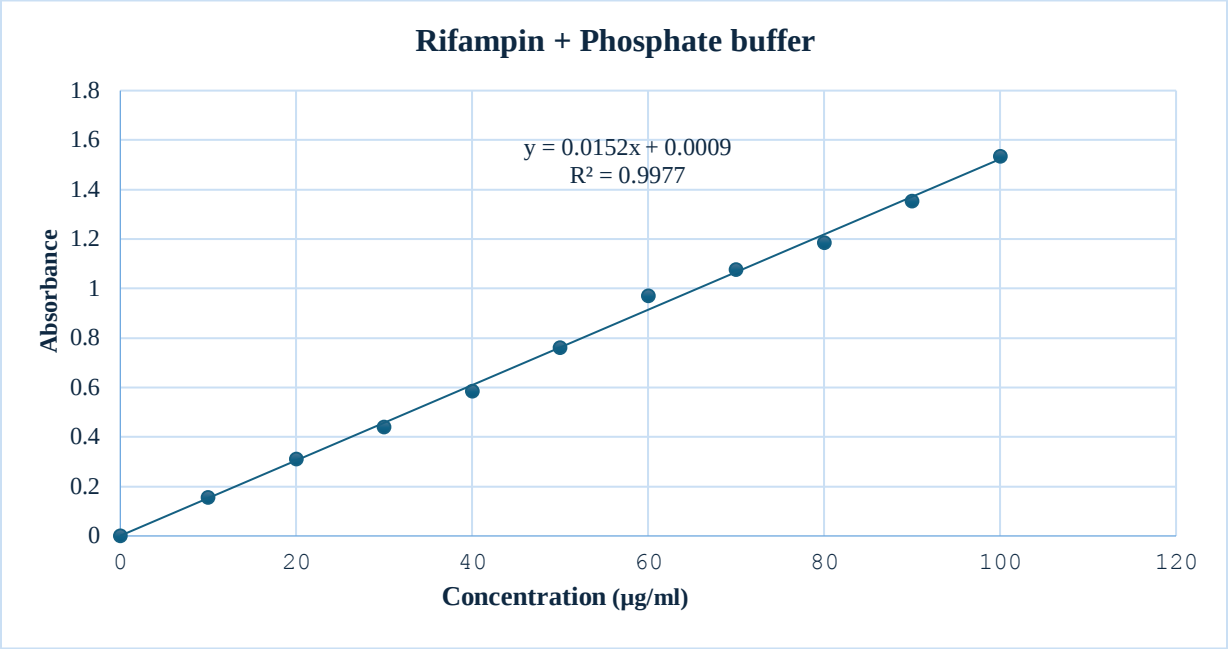

FIGURE: 9.5 STANDARD CURVE OF RIFAMPICIN IN PHOSPHATE BUFFER

9.1.2 Duloxetine Hydrochloride

The standard curves for Duloxetine HCl were prepared in Distilled water, Methanol, and Phosphate Buffer (6.8)

1. **Distilled water:** The **λmax** of Duloxetine HCl was found to be 289.6 nm as shown in Figures 9.6 and 9.7. Different concentrations of Duloxetine HCl from 10 to 100µg/ml were prepared and the absorbance was taken at 289.6 nm using a UV spectrophotometer. The graph was plotted between Concentration vs Absorbance.

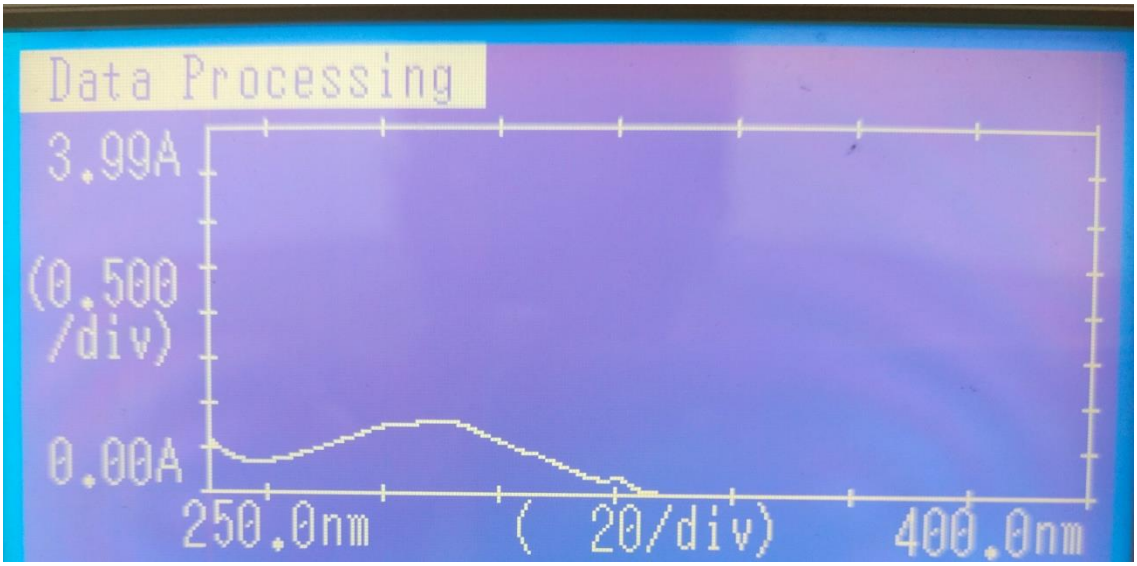

FIGURE: 9.6 λmax OF DULOXETINE HYDROCHLORIDE

FIGURE: 9.7 λmax OF DULOXETINE HYDROCHLORIDE

TABLE: 9.4 STANDARD CURVE OF D.HCl IN WATER

Sr. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.165 ± 0.016
3	20	0.333 ± 0.0010
4	30	0.434 ± 0.028
50	40	0.686 ± 0.031
6	50	0.816 ± 0.028
7	60	0.959 ± 0.033
8	70	1.094 ± 0.043
9	80	1.246 ± 0.031
10	90	1.336 ±0.025
11	100	1.483 ± 0.044

*All values are in mean ± SD (n=3)

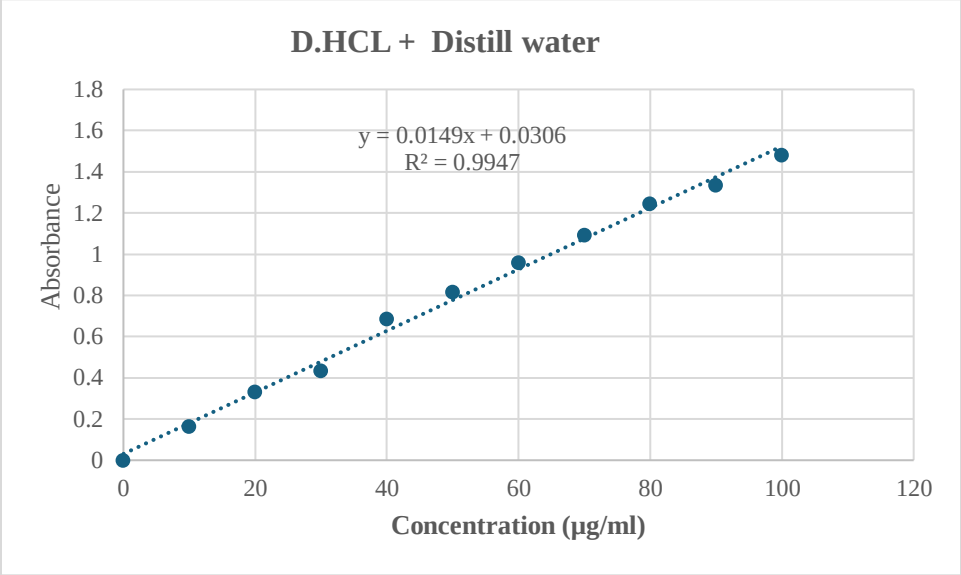

FIGURE: 9.8 STANDARD CURVE OF D.HCl IN WATER

2. **Methanol:** The **λmax** of Duloxetine HCl was found to be 289.6 nm as shown in Figures 9.6 and 9.7**.** Different Concentrations of Duloxetine Hydrochloride from 5 to 50µg/ml were

prepared and the absorbance was taken at 289.6 nm using a UV spectrophotometer. The graph was plotted between Concentration vs Absorbance.

TABLE: 9.5 STANDARD CURVE OF D.HCL IN METHANOL

Sr. No.	Concentration(µg/ml)	Absorbance
1	0	0
2	5	0.095 ± 0.005
3	10	0.201 ± 0.002
4	15	0.299 ± 0.009
5	20	0.410 ± 0.003
6	25	0.508 ± 0.004
7	30	0.619 ± 0.013
8	35	0.705 ± 0.007
9	40	0.811 ± 0.008
10	45	0.915 ± 0.015
11	50	1.010 ± 0.007

*All values are in mean ± SD (n=3)

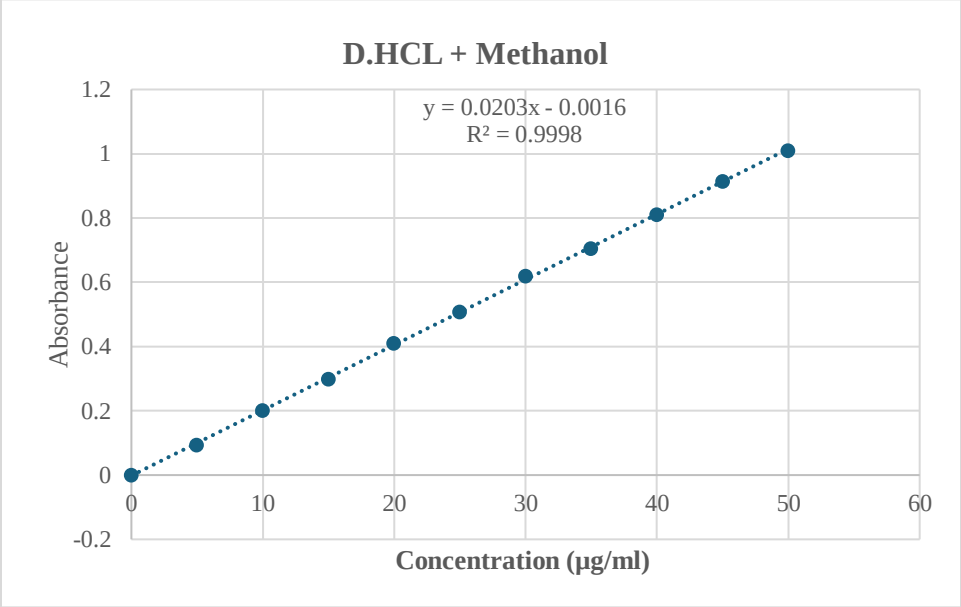

FIGURE: 9.9 STANDARD CURVE OF D.HCL IN METHANOL

3. **Phosphate buffer (6.8):** The **λmax** of Duloxetine HCl was found to be 289.6 nm as shown in Figures 9.6 and 9.7 Different concentrations of Duloxetine HCl from 10 to 100µg/ml were prepared and the absorbance was taken at 289.6 nm using a UV spectrophotometer. The graph was plotted between Concentration vs Absorbance.

TABLE: 9.6 STANDARD CURVE OF D.HCL IN PHOSPHATE BUFFER

Sr. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.162 ± 0.010
3	20	0.348 ± 0.011
4	30	0.515 ± 0.016
5	40	0.664 ± 0.015
6	50	0.852 ± 0.028
7	60	1.024 ± 0.031
8	70	1.232 ± 0.028
9	80	1.441 ± 0.04
10	90	1.651 ± 0.033
11	100	1.924 ± 0.043

*All values are in mean ± SD (n=3)

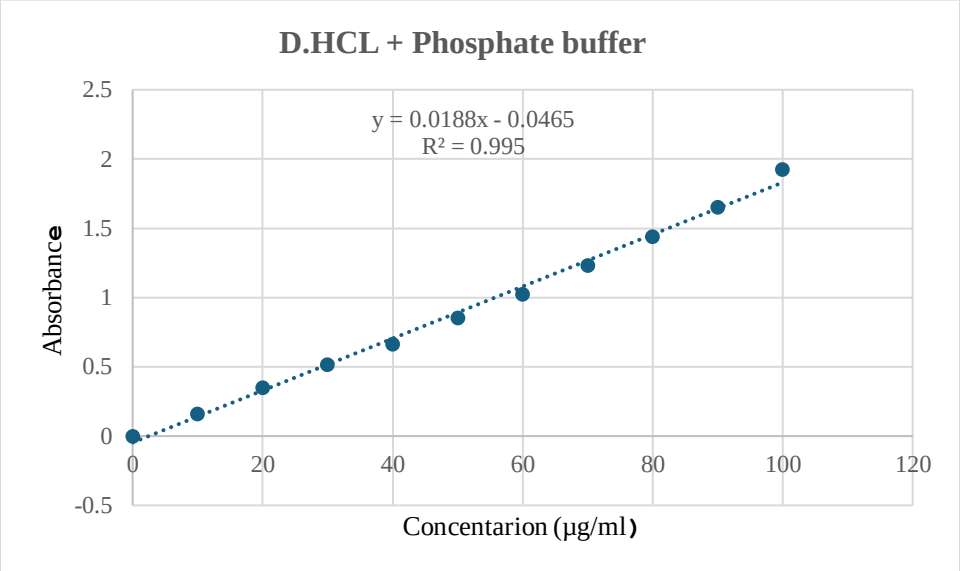

FIGURE: 9.10 STANDARD CURVE OF D.HCL IN PHOSPHATE BUFFER

9.1.3 Abiraterone Acetate

The standard curves for Abiraterone Acetate were prepared in Methanol, Distilled Water, and Phosphate Buffer (4.5)

Methanol: The **λmax** of Abiraterone Acetate was found to be 254 nm as shown in Figures 9.11 and 9.12. Different concentrations of Abiraterone Acetate from 10 to 50µg/ml were prepared and the absorbance was taken at 254 nm using a UV spectrophotometer. The graph was plotted between Concentration vs Absorbance.

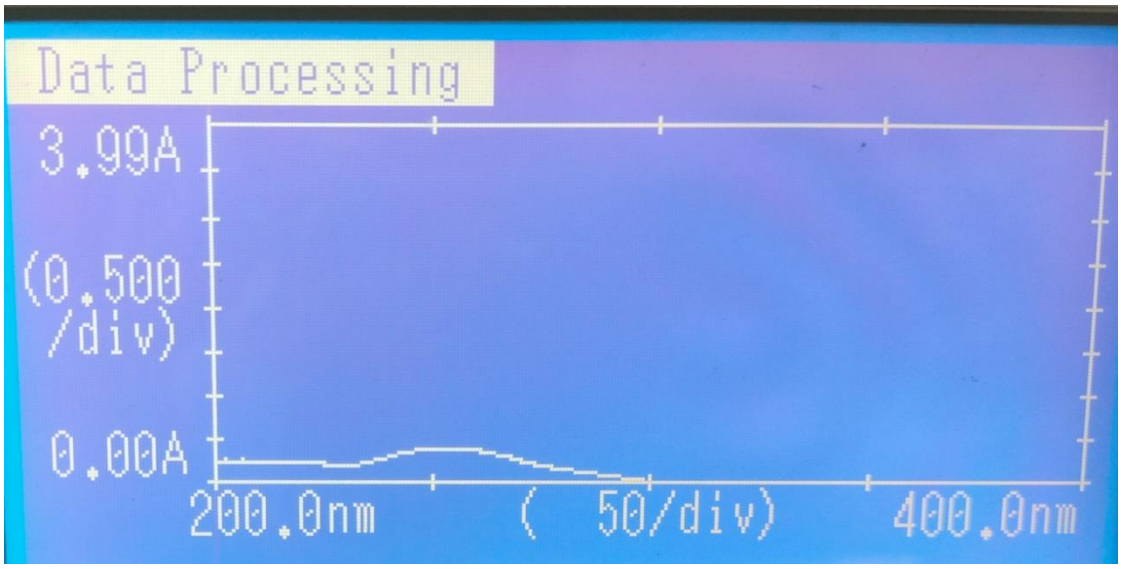

FIGURE: 9.11 λmax OF ABIRATERONE ACETATE

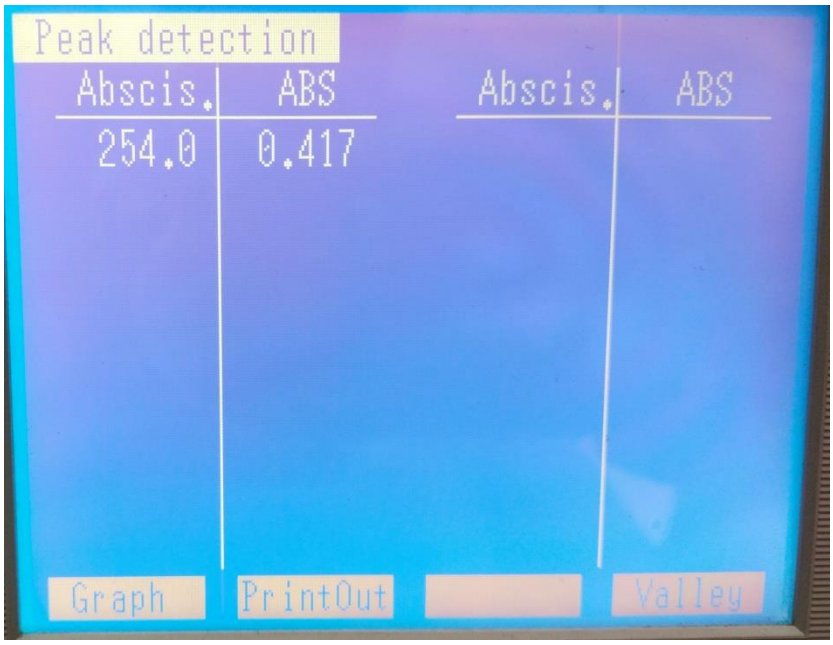

FIGURE: 9.12 λmax OF ABIRATERONE ACETATE

Table: 9.7 standard curve of abiraterone acetate in methanol

Sr. No.	Concentration(µg/ml)	Absorbance
1	0	0
2	10	0.263 ± 0.005
3	15	0.395 ± 0.002
4	20	0.549 ± 0.001
5	25	0.701 ± 0.009
6	30	0.8745 ± 0.003
7	35	1.011 ± 0.012
8	40	1.2 ± 0.008
9	45	1.326 ± 0.007
10	50	1.573 ± 0.013

*All values are in mean ± SD (n=3)

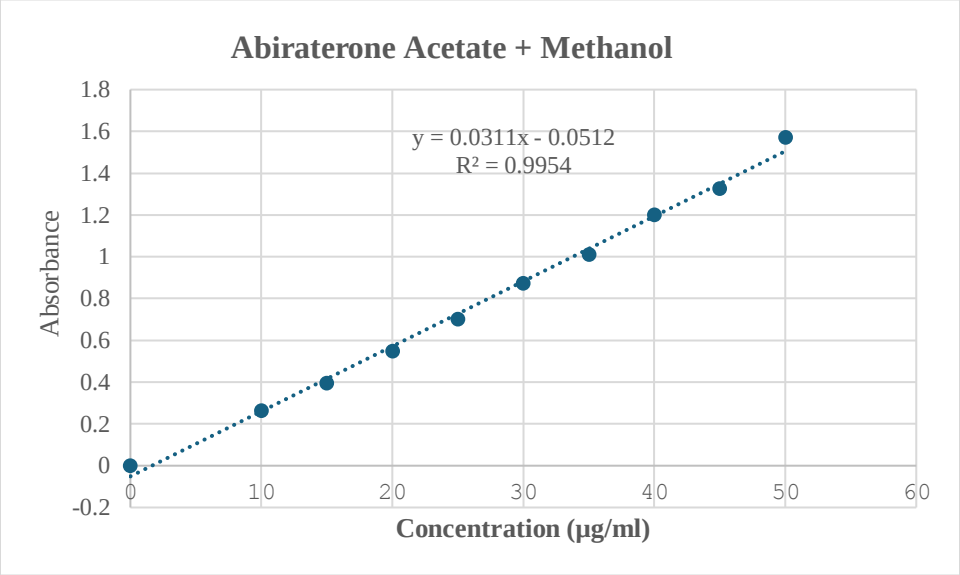

FIGURE: 9.13 STANDARD CURVE OF ABIRATERONE ACETATE IN METHANOL

2. **Distilled water:** The **λmax** of Abiraterone Acetate was found to be 254 nm as shown in Figures 9.11 and 9.12 Different concentrations of Abiraterone Acetate from 20 to 200µg/ml were

prepared and the absorbance was taken at 254 nm using a UV spectrophotometer. The graph was plotted between Concentration vs Absorbance.

TABLE: 9.8 STANDARD CURVE OF ABIRATERONE ACETATE IN WATER

Sr. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	20	0.054 ± 0.003
3	40	0.092 ±0.005
4	60	0.125 ± 0.01
5	80	0.168 ± 0.002
6	100	0.210 ± 0.008
7	120	0.251 ± 0.02
8	140	0.308 ± 0.01
9	160	0.359 ± 0.02
10	180	0.412 ± 0.03
11	200	0.476 ± 0.02

*All values are in mean ± SD (n=3)

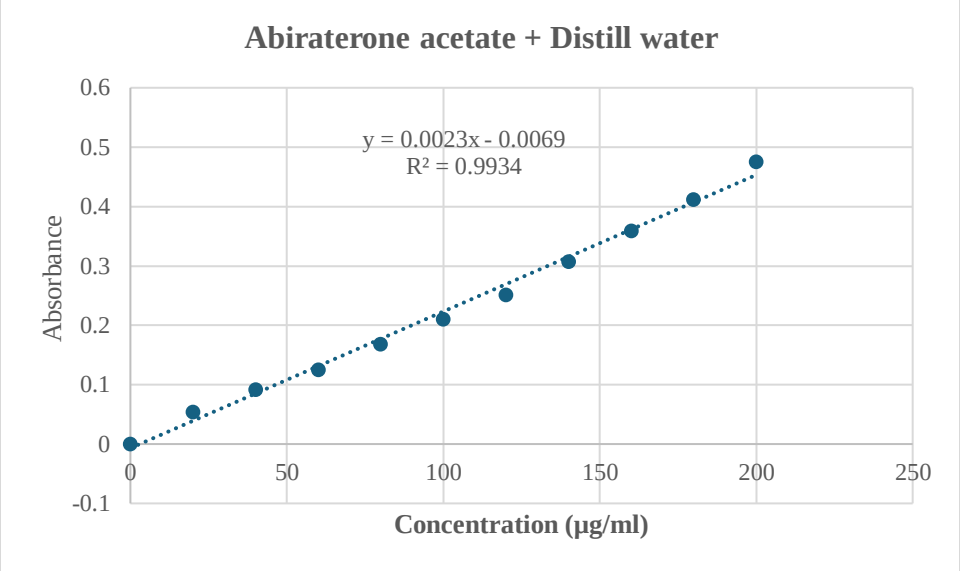

FIGURE: 9.14 STANDARD CURVE OF ABIRATERONE ACETATE IN WATER

3. Phosphate buffer (4.5): The **λmax** of Abiraterone Acetate was found to be 254 nm as shown in Figures 9.11 and 9.12 Different concentrations of Abiraterone Acetate from 20 to 200µg/ml

were prepared and the absorbance was taken at 254 nm using a UV spectrophotometer. The graph was plotted between Concentration vs Absorbance.

TABLE: 9.9 STANDARD CURVE OF ABIRATERONE ACETATE IN PHOSPHATE BUFFER

Sr. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	20	0.069 ±0.02
3	40	0.145 ± 0.05
4	60	0.225 ± 0.03
5	80	0.284 ± 0.04
6	100	0.367 ± 0.03
7	120	0.462 ± 0.06
8	140	0.564 ± 0.03
9	160	0.641 ± 0.04
10	180	0.759 ± 0.01
11	200	0.868 ± 0.05

*All values are in mean ± SD (n=3)

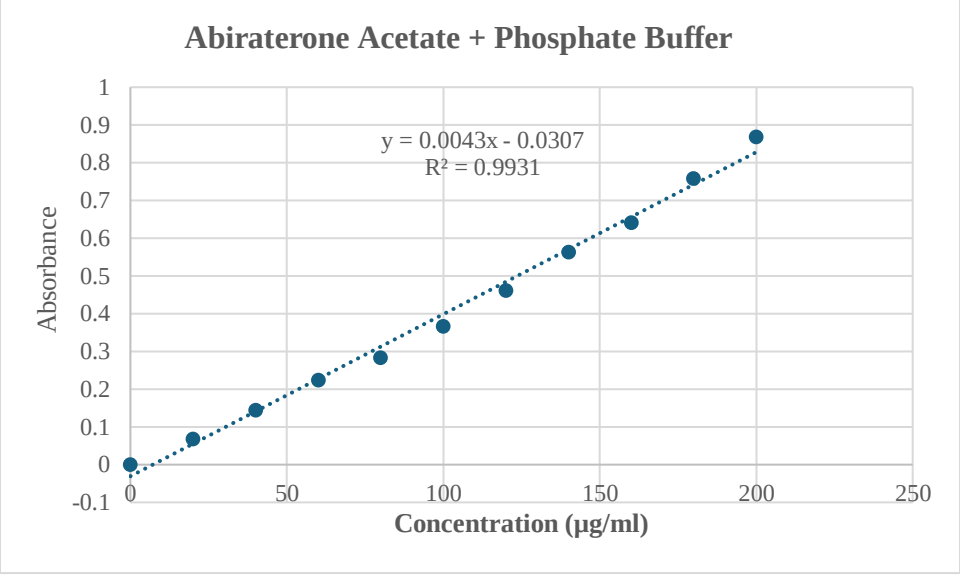

FIGURE: 9.15 STANDARD CURVE OF ABIRATERONE ACETATE IN PHOSPHATE BUFFER