FORMULATION AND EVALUATION OF SOLID DISPERSION CAPSULES CONTAINING ERYTHROMYCIN STEARATE

A thesis presented to the school of Graduate Studies of Addis Ababa University in partial fulfillment of the requirements of the Degree of Master of Science in Pharmaceutics

By

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ADDIS ABABA UNIVERSITY

SCHOOL OF GRADUATE STUDIES

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DEPARTMENT OF PHARMACEUTICS

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Abstract

Erythromycin stearate is a macrolide and belong to one of the most commonly used families of clinically important antibiotics used to treat infections caused by Gram-positive bacteria such as *Staphylococcus aureus, Streptococcus pneumonia and Streptococcus pyogenes*.

The objective of this study was to increase the solubility of the poorly water soluble drug erythromycin stearate, by the formation of solid dispersion. Solubility is an important physicochemical factor affecting absorption of drug and its therapeutic effectiveness. In the present investigation, an attempt was made to improve the solubility and dissolution rate of a poorly soluble drug, Erythromycin stearate. The dispersion carriers used for the study were PEG4000, PEG 6000 and PVP K30. Fusion method, Solvent Evaporation method and Kneading methods in 2:1, 1:1 and 1:2 ratios of drug to polymer were used to prepare the solid dispersion.

The formulation were characterized for drug-polymer interaction using FTIR spectrum and DSC, solubility parameters, drug content studies, drug release studies. The interaction studies showed no interaction between the drug and the polymers. Formulations containing 1:2 ratio of drug: PEG4000, drug:PEG6000 prepared by fusion method showed the best release with a cumulative release of 97.55% and 101.78% respectively as compared to 54.62% for the pure drug. The flow property studies like angle of repose , hausner's ratio and carr's index showed the solid dispersion preparation had good flow.

The practical yield was found to be above 90% for all the formulations. Similarly the drug content was also above 90% for all the formulation except, the solid dispersion prepared by kneading method. The XRD studies showed the crystallinity of the solid dispersion reduced compared to the drug alone. Drug to PVPK30 1:2 ratio prepared by solvent evaporation method showed cumulative release of 96.31%. The results of short term stability studies showed good stability within the studied period of 3 months at the temperature 40°C and relative humidity of 75%.

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Above all, I magnify The Almighty- for Everything, nothing in this universe moves without His consent and I shall remain grateful Towards Him -

Happiness while playing is never about the winning but the playing itself. Likewise getting degree is even more meaningful if knowledge is gained in a right direction and not just achieving the degree. It's fact that every mission needs a spirit of hard work and dedication but it needs to be put on the right path to meet its destination and in my case these credits goes to my esteemed guide, Dr. Fitsum Feleke Sahle and Dr. Nisha Mary Joseph, Department of Pharmaceutics, School of Pharmacy, Addis Ababa University. By virtue of their invaluable scholastic suggestion, I have been able to look at things in a better way.

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Shweta Mehta

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Acronyms

BCS	Biopharmaceutical Classification System
CAP	Cellulose Acetate Phthalate
CMEC	Carboxymethyl Cellulose
DSC	Differential Scanning Colorimeter
ES	Erythromycin Stearate
FM	Fusion Method
FTIR	Fourier Transform Infrared
G.A.A	Glacial Acetic Acid
GIT	Gastro Intestinal Tract
HDSC	Hyper Differential Scanning Colorimeter
HPC	Hydroxy Propyl Cellulose
HPLC	High Performance Liquid Chromatography
HPMC	Hydroxy Propyl Methyl Cellulose
HPMCP	Hydroxypropyl Methyl Cellulose Phthalate
ITC	Isothermal Titration Calorimeter
KM	Kneading Method
MC	Methyl Cellulose
MOA	Mechanism of Action
MP	Melting Point
PDE	Permitted Daily Dose
PEG	Polyethylene Glycol
PHEMA	Poly(2-hydroxyethylmetha acrylate)
PVP	Polyvinyl Pyrolidone
PXM	Poloxamers

RH	Relative Humidity
SD	Solid Dispersion
SEM	Scanning Electron Microscopy
Tg	Glass Transition Temperature
UV	Ultraviolet
XRPD	X-Ray Powder Diffraction

DECLARATION

I, the undersigned, declare that this is my original work and has not been persecuted for a degree in any university.

Shweta Mukesh Mehta

Signature: _____

This thesis has been submitted for examination with our approval as advisors

Dr. Fitsum Feleke Sahle

Signature: _____

Dr. Nisha Mary Joseph

Signature: _____

1. INTRODUCTION

Therapeutic effectiveness of a drug product depends upon its bioavailability which depends on the solubility of drug and penetration through the biological membrane (Nokhodchi et al., 2007). Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for pharmacological response (Nagabandi et al., 2011). Nonetheless, solubility of the drug in the gastric media is a major problem with most drugs. Other factors that affect bioavailability of the drug other than dissolution and permeability includes pre-systemic metabolism of the drug in any other organ and susceptibility to efflux mechanism (Sridhar., 2013).

Solubility or dissolution enhancement techniques remain one of the most vibrant field for the researchers in formulation science. Solubility and dissolution are the core concepts of any physical or chemical science including biopharmaceutical and pharmacokinetic considerations in therapy of any field of medicine (Thorat et al., 2011).

The dissolution rate is often the rate determining step in drug absorption (Nagabandi et al., 2011). An ideal drug delivery system should be able to deliver an adequate amount of drug, preferably for an extended period of time for its optimum therapeutic activity. Most drugs are inherently not long lasting in the body and require multiple daily dosing to achieve the desired blood concentration to produce therapeutic activity (Ruchi Tiwari, Gaurav Tiwari et al. 2009). Over the years, tools of drug discovery have caused a perceptible shift in biopharmaceutical properties (Thorat et al., 2011).

Currently only 8% of new drug candidates have both high solubility and permeability (Pedada et al., 2013). Low solubility has been the major problem hampering the release of new chemical entities into the market. Every year more than 50% of the potentially active pharmaceutical ingredients get rejected due to the above stated problems (Patel., 2011). A review of new monograph in European Pharmacopoeia shows more than 40% of the drug candidates have aqueous solubility below 1mg/ml and 32% have an aqueous solubility below 0.1mg/ml (Aggarwal et al., 2010). The synthetic approaches are growing successfully to deliver many promising lead compounds for most of the pharmacological categories, and are also taking the molecules towards bulkier structures. Therefore, pharmaceutical companies are focusing on finding a technology by which they can enhance the aqueous solubility and bioavailability of the drug (Patel., 2011).

The biopharmaceutical classification system (BCS) divides drugs in four classes depending on *in vitro* solubility and *in vivo* permeability data (Sapkal et al., 2013).The large percentage of Class II drugs with solubility-limited bioavailability underscores the importance of developing new manufacturing strategies to increase the apparent solubility of potential drug molecules. Class II drugs, with low solubility but high permeability, are the most likely BCS class of drugs to benefit from solubility enhancement (Calahan., 2011). By enhancing the drug release profile of these drugs, it is possible to enhance their bioavailability and reduce side effects (Vasconcelos et al., 2007). Therefore, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS class II drugs (Dewan et.al., 2012).

1.1. Strategies to improve aqueous solubility of poorly water soluble drugs

Enhancement of oral bioavailability of poorly water soluble drug remains one of the most challenging aspects of drug development. There are several pharmaceutical strategies available to improve the aqueous solubility of poorly soluble drugs: solid dispersion, solubilization using surfactants, the use of cosolvents, reduction of particle size, hydrotrophy and the use of aqueous soluble derivative or salts (Sapkal et al., 2013; Bobe et.al., 2011). Among these methods, salt formation, solubilization and particle size reduction are commonly used methods to increase dissolution rate and thus increase the oral absorption and bioavailability of such drugs. However, there are practical limitations of these techniques. The salt formation is not feasible for neutral compounds and the synthesis of appropriate salt form of drugs that are weakly acidic or weakly basic may often not be practical. Besides, even when salt can be prepared, an increased dissolution rate in GIT may not be achieved in many cases because of the reconversion of salts into aggregates to their respective acid or base form (Aleem., 2006).

The solubilization of the drug into organic solvents or in aqueous media with the help of surfactant and co-solvents leads to liquid formulations that are not desirable commercially and with reduced patient compliance. Although particle size reduction is commonly used to increase the dissolution rate, there is practical limit to how much size reduction can be achieved by the commonly used method such as controlled crystallization, grinding etc. The use of very fine powder in the dosage form may be problematic due to poor wettability and difficulty in handling the powder (Aleem., 2006). Due high surface charge on discrete small particles, there is a strong tendency for particle agglomeration (Luhadia and Agrawal, 2012). However, Solubility of such

drugs can be improved by incorporating the drug in a hydrophilic carrier material obtaining a product called solid dispersion(Patidar et al., 2011). Solid dispersion techniques have been used to enhance the dissolution and oral bioavailability of many poorly soluble drugs(Sapkal et al., 2013).

1.2. Solid Dispersion

In 1961, Sekiguchi and Obi developed a practical method whereby many of the limitations with the bioavailability enhancement of poorly water-soluble drugs can be overcome. This method, which was later termed solid dispersion, involved the formation of eutectic mixtures of drugs with water-soluble carriers by melting of their physical mixtures. Sekiguchi and Obi suggested that the drug was present in a eutectic mixture in a microcrystalline state (Serajuddin., 1999).

Later, Goldberg et al. demonstrated that the entire drug in a solid dispersion might not necessarily be present in a microcrystalline state; a certain fraction of the drug might be molecularly dispersed in the matrix, thereby forming a solid solution. In either case, once the solid dispersion was exposed to aqueous media the carrier dissolves and the drug was released as very fine, colloidal particles. Because of this greatly enhanced surface area is obtained. Thus the dissolution rate and the bioavailability of poorly water-soluble drugs were expected to be high (Serajuddin., 1999).

The term solid dispersion was introduced in the early 1970s, referring to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug (Arora et al., 2010). It represents a useful pharmaceutical technique for increasing the dissolution, absorption and therapeutic efficacy of drugs in dosage form. The properties, performance and practical applications of solid dispersion depends on factors such as the method of preparation, composition, selection of a suitable carrier and physicochemical properties (Vyas et. al., 2012)

Chiou and Riegelman defined the term solid dispersion as “a dispersion of active ingredients in an inert carrier at solid state prepared by melting, solvent or melting-solvent method. Dispersion obtained through the fusion process is often called melts, and those obtained by solvent method are frequently referred as co precipitates or co- evaporates”. They classified solid dispersions in-

to the following types: a) Simple eutectic mixtures, b)solid solutions, c) glass solutions and glass suspensions, and d) amorphous precipitations in a crystalline carrier (Santhosh et al., 2011).

Solid Dispersion technique includes complete removal of drug crystallinity, and molecular dispersion of the poorly soluble compound in a hydrophilic polymeric carrier (Janssens and Mooter., 2009). Solid dispersion is a promising approach to improve the dissolution and bioavailability of hydrophobic drugs (Liu and Wang., 2007). The preparation and storage conditions of solid dispersions are crucial since changes may alter the dissolution characteristics of the active ingredients (Papageorgiou et al., 2006).

The development of solid dispersions is a practically viable method to enhance bioavailability of poorly water soluble drugs and to overcome the limitations of previous approaches such as salt formation, solubilization by co solvents, and particle size reduction. Among various approaches to increase dissolution rate, solid dispersion has shown promising results in improving solubility, wettability, dissolution rate of drug and subsequently its bioavailability. Only a few solid dispersion products are however commercially available due to its drawback of poor scale up. The surface solid dispersions can overcome some of the shortcomings of the conventional solid dispersions. The carriers used in surface solid dispersion are water-insoluble, porous materials and hydrophilic in nature (Kiran et al., 2009).

In conventional capsules and tablets, the dissolution rate is limited by the size of the primary particles formed after the disintegration of the dosage forms. In this case, an average particle size of 5 μm is usually the lower limit, although higher particle sizes are preferred for ease of handling, formulation, and manufacturing. On the other hand, if a solid dispersion or a solid solution is used, a portion of the drug dissolves immediately to saturate the gastrointestinal fluid, and the excess drug precipitates out as fine colloidal particles or oily globules of submicron size. Because of such work done in the bioavailability enhancement of poorly water-soluble drugs, solid dispersion has become one of the most active areas of research in the pharmaceutical field (Serajuddin., 1999).

1.2.1. Advantages and Disadvantages of Solid Dispersion

Generally solid dispersion are formulated with the advantage of rapid dissolution rates that result in an increase in the rate and extent of the absorption which further results in reduction in pre-

systemic drug metabolism and reduction of the administered dose. Bioavailability of anti cancer drug has been improved by incorporating them in solid dispersion (Khatry et al., 2013). The Other advantages of formation of solid dispersion include:

i) Transformation of the liquid form of the drug into a solid form (e.g., clofibrate and benzoyl benzoate can be incorporated into PEG 6000 to give a solid, avoidance of polymorphic changes and thereby bio-availability problems) (Sakharam et al., 2012).

ii) Particles in solid dispersions have been found to have a higher degree of porosity. The increased porosity of solid dispersion particles accelerates the drug release profile. Increased porosity also depends on the carrier properties (Saffoon et al., 2011).

iii) Homogeneous distribution of small amount of drug at solid state is possible to attain.

iv) Enhancement of the active agent bioavailability to a desirable extent (Kapoor et al., 2012).

Disadvantage

Despite extensive expertise with solid dispersions, they are not broadly used in commercial products, mainly because there is the possibility that during processing or storage the amorphous state may undergo crystallization and dissolution rate decreases with ageing. The effect of moisture on the storage stability of amorphous pharmaceuticals is also a significant concern, as it may increase drug mobility and promote drug crystallization (Tiwari, et al., 2009).

1.2.2. Types of Solid Dispersion

A. Simple Eutectic mixtures

These are prepared by rapid solidification of the fused melt of two component that show complete liquid miscibility and negligible solid-solid solubility. Thermodinamically, such system is an intimately blended physical mixture of its two crystalline component. Thus, the X-ray diffraction pattern of eutectic constitutes an additive composite of two components. Ex chloremphenicol-urea, griseofulvin and tolbutamide with PEG 2000 (Argade et al., 2013).

B. Solid solution

It consists of a solid solute dissolved in solid solvent. A mixed crystal is formed because the two components crystallized together in a homogenous one-phase system. Hence, this system would be expected to yield much higher rate of dissolution than simple eutectic system (Varma et.al., 2012).

C. Glass solution and suspensions

They are homogeneous glassy system in which solute dissolves in glass carrier. Glass suspensions are mixture in which precipitated particles are suspended in glass solvent (Kumar et al., 2010). The main advantage of glass solution is that they do not possess strong lattice as true solid solutions and hence they do not present this barrier to rapid dissolution. The disadvantage is that the glassy state is metastable compared to the crystalline state (Sharma P et al., 2012). Eg. Carriers for glass solution and suspension - citric acid, sugars (dextrose, sucrose, galactose), PVP, PEG, urea (Kannao et al., 2014).

D. Amorphous precipitation in crystalline matrix

This is similar to simple eutectic mixtures. However it differs from simple eutectic mixture by that the drug is precipitated out in amorphous form (Kumar et al., 2010). E.g. Sulfathiazole was precipitated in the amorphous form un crystalline urea.

1.2.3. Quality attributes of solid dispersions

A. Particles with reduced particle size

Molecular dispersion represents the last stage of particle size reduction, solid dispersion uses this principle where the drug is molecularly dispersed in the dissolution medium after the dissolution of the carrier. As a result high surface area is formed and thus increased dissolution and consequently improved bioavailability of poorly water soluble drug (Kumar. S et al., 2011).

B. Particles with improved wettability

A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions. It was observed that even carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity, such as cholic acid and bile salts, when used, can significantly increase the wettability properties of drugs.

C. Particles with high porosity

Particles in solid dispersions have been found to have a high degree of porosity. The increase in porosity relies on the properties of carriers used, for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate and hence bioavailability (Mohanachandran et al., 2010).

D. Particles in amorphous state

Poorly water-soluble crystalline drugs, when in the amorphous state tend to have higher degree of solubility. Drug in its amorphous state shows higher drug release because no energy is required to break up the crystal lattice during the dissolution process (Dhirendra et al., 2009).

1.2.4. Carriers Used for the Preparation of Solid Dispersion

Initially, in order to increase the dissolution rate of the drug, hydrophilic or water soluble carriers are used in solid dispersion. The properties of a carrier have a major influence on the dissolution characteristics of the dispersed drug. Carriers which are soluble and dissolve in water at a fast rate are widely used in pharmaceutical formulation to enhance dissolution of drugs. A carrier should meet the following criteria to be suitable for increasing the dissolution rate of the drug.

1.2.4.1. Ideal Properties of Carriers used in Solid Dispersion

Selection of carrier for solid dispersion should be based on the following criteria:

i. Solubility in various solvent: a carrier that is soluble in a variety of solvents and pass through a vitreous state upon solvent evaporation is necessary to prepare solid dispersion using solvent method (Sharma et al., 2011).
ii. Water solubility: water solubility improves wettability and dissolution.
iii. Glass transition point: a high glass transition point improves stability of the formulation.
iv. Water uptake: minimal water uptake by the carrier produces a stable formulation
v. Melting point: a low melting point of the carrier is required for a stable formulation.
vi. Solubility parameters: the carrier should have the solubility parameter similar to that of the drug and must be capable of forming a solid dispersion (Khatry et al., 2013).

1.2.4.2. Types of Carriers used for the Formulation of Solid Dispersion

A. First generation carriers

This class of carriers includes crystalline carriers: urea, sugars, and organic acids. They have the disadvantage of forming a more thermodynamically stable crystalline solid dispersion that do not release the drug quickly (Kapoor B et al., 2012).

B. Second generation carriers

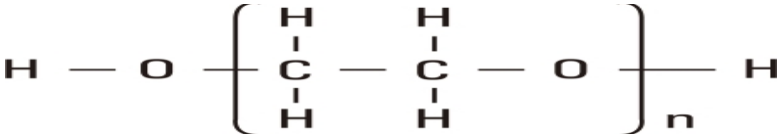
These classes of carriers are amorphous carriers, which are generally polymers. These mainly include: synthetic polymers such as povidone (PVP), polyethyleneglycols (PEG) and polymethacrylates and semi synthetic polymers derived from cellulose, such as hydroxypropy lmethyl cellulose (HPMC), ethylcellulose or hydroxypropylcellulose or starch derivates, like cyclodextrins (Vasconcelos et al., 2007).

C. Third generation carriers

Surfactant are introduced in the third generation. These carriers have surface activity and self-emulsifying properties. The use of surfactant such as inulin, gelucire 44/14 (Tiwari et al., 2009) and poloxamer 407 as carriers were shown to be effective in originating high polymorphic purity and enhanced in vivo bioavailability (Yadav and Tanwar et.al., 2015)

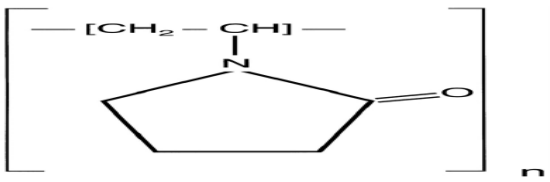
Description of commonly used carriers for the preparation of solid dispersion is given below.

i) Polyethylene Glycol (PEG)



Polyethylene glycols (PEGs) are polymers of ethylene oxide, with a molecular weight (MW) usually falling in the range 200-300000. For the manufacture of solid dispersions and solutions, PEGs with molecular weights of 1,500-20,000 are commonly employed. Their solubility in water is generally good, but reduces with MW. A meticulous advantage of PEGs for the solid dispersions is that they have good solubility in numerous organic solvents. The melting point of the PEGs of interest lies under 65 °C. Additional attractive features of the PEGs include their ability to solubilize some compounds and also to improve compound wettability. Even the dissolution rate of a relatively soluble drug like aspirin could be improved by formulating it as a solid dispersion in PEG 6000 (Nikghalb et al., 2012).

ii) Polyvinylpyrrolidone



Polymerization of vinylpyrrolidone leads to polyvinylpyrrolidone (PVP) of molecular weights ranging from 2,500 to 3,000,000. The glass transition temperature of a given PVP is dependent not only on its MW but also on the moisture content. In general, the glass transition temperature (Tg) is high; for example, PVP K25 has a Tg of 155°C. For this reason PVPs have only limited application for the preparation of solid dispersions by the hot melt method. However, due to their good solubility in a wide variety of organic solvents, they are particularly suitable for the preparation of solid dispersions by solvent method (Leuner and Dressman., 2000).

Similar to the PEGs, PVPs have good water solubility and can improve the wettability of the dispersed compound in many cases. Improved wetting and thereby an improved dissolution rate from a solid dispersion in PVP. The chain length of the PVP has a very significant influence on the dissolution rate of the dispersed drug from the solid dispersion. The aqueous solubility of the PVPs becomes poorer with increasing chain length and a further disadvantage of the high MW PVPs is their much higher viscosity at a given concentration (Leuner and Dressman., 2000).

iii) Cyclodextrin

Cyclodextrins are used to increase the solubility of water insoluble drugs, through inclusion complexation. Cyclodextrins are cyclic (α-1,4)-linked oligosaccharides of α-D glucopyranose, containing a relatively hydrophobic central and hydrophilic outer surface (Challa, et.al., 2005)

iv) Surfactants for Solid Dispersion

The utility of the surfactant systems in solubilization is well known. Surfactant reduces hydrophobicity of drug by reducing interfacial or surface tension. Recently a new class of surfactant known as Gelucires are introduced which identify by melting points and HLB values. Gelucire is widely used in the formulation of semi solid dispersions. Gelucire 44/14 is an inert semi solid waxy material, which is amphiphilic in nature. It has unique emulsifying properties that make it ideal for prompt release formulation. The suffixes 44 and 14 refer to its melting point and its HLB respectively (Dhalli., 2007). Some other surfactants such as tweens, and span can also be used (Chauhan, et al., 2005).

Poloxamers are a group of surface active compounds widely used in the pharmaceutical industry. The polymers are derived from the sequential polymerization of propylene oxide and

ethylene oxide. Due to the possibility to combine blocks of different molecular weights, the properties of the resulting polymers vary in a wide range. Generally, these are waxy, white granules of free-flowing nature and are practically odorless and tasteless. Aqueous solutions of pluronic in presence of acids, alkalis, and metal ions are very stable. The poloxamers are readily soluble in aqueous, polar and non-polar organic solvents and due to this fact they have established themselves as a preferred molecule in the formulation techniques. (Tejal et al., 2007; Yadav and Tanwar et.al., 2015).

Surfactants can also be used as plasticizers when they are incorporated into a polymeric material, a plasticizer improves the workability and flexibility of the polymer by increasing the intermolecular separation of the polymer molecules (Saritha and Shastri., 2010).

1.2.5. Solvent Selection for Solid Dispersion Systems

In order to prepare solid dispersion, solvents should be selected on the basis of following:

(a) Dissolve both drug and carrier
(b) Toxic solvents to be avoided due to the risk of residual levels after preparation e.g. chloroform and dichloromethane
(c) Ethanol is a less toxic alternative
(d) Water based systems preferable
(e) Use of surfactants to create carrier drug solutions but care should be taken as they can reduce the glass transition point (Priyanka et al., 2013).

Table 1.1: Class of solvent

Class of Solvent	Solvent	Remark
Class I	Benzene	Solvents in this class should not be employed in the manufacture of drug substances, excipients and drug product because of their deleterious environmental effect
	Carbon tetrachloride	
	1,2-dichloroethane	
	1,1-dichloroethene	
	1,1,1- trichloroethane	
Class II	Chlorobenzene	Solvent in class II should be limited in pharmaceutical product due to their inherent toxicity
	Chloroform	
	Cyclohexane	
	Methanol	
	Pyridine	
	Toluene	
Class III	Ethylene glycol	Class III solvents are regarded as less toxic and of lower risk to human health
	Acetic acid	
	Acetone	
	1-Butanol, 2-Butanol	
	Butyl acetate	
	Ethanol	
	Formic acid	
	Heptane Methyl	
	acetate Isopropyl	
	acetate	

Class IV Solvents (Solvents for which no adequate toxicological data was found)

Some solvents may also be of interest to manufacturers of excipients, drug substances, or drug products. However, no adequate toxicological data on which to base PDE (Permitted Daily Exposure) was found (Tiwari et al., 2009).

1.2.6. Methods of Solid Dispersion Preparation

The various methods used for preparation of solid dispersion are summarized under this section.

i) Fusion/Melting Method

The melting or fusion method was first employed by Sekiguchi and Obi to prepare fast-release solid dispersion dosage forms. A physical mixture of a drug and a water-soluble carrier was heated directly until it melted and the melted mixture was then cooled and solidified rapidly in an

ice bath under rigorous stirring. The final solid mass was crushed, pulverized, and sieved (Bhowmik, et al., 2012). The solidified masses were often found to require storage of one or more days in a desiccator at ambient temperature for hardening and ease of powdering (Chiou and Riegelman., 1971). Some systems, such as griseofulvin and citric acid, were found to harden more rapidly if kept at 37º C or higher temperatures (Daisy et al., 2009).

ii) Solvent Evaporation Method

In the solvent evaporation method, the drug and carrier are first solubilized in a volatile organic solvent. The next step in this method is evaporation of the solvent resulting in manufacturing of a solid dispersion. The major merit of this method compared to the melting method is that thermal degradability of the drug and carrier can be inhibited because volatile organic solvent is easily evaporated at relatively low temperatures. Nevertheless, the difficulty in complete evaporation of the volatile solvents remains the major disadvantage of this method. The residual solvent presented in solid dispersion after drying may cause toxicity. Moreover, selecting a suitable volatile solvent is difficult since phase separation, especially crystallization, may occur during evaporation of the solvent (Kim et al., 2011).

iii) Melting Solvent Method (melt evaporation)

Here the solid dispersions are organized by dissolving the drug in appropriate liquid solvent and then including the solution directly into a melt of polyethylene glycol, which is then evaporated until a clear, solvent free film is left. The film is dried to constant weight. The 5 to 10% (w/w) of liquid compounds can be combined into polymer without significant loss of its solid property. It is possible that the particular solvent or dissolved drug may not be miscible with the melt of polymer. Liquid solvent are also used and affect the polymorphic form of the drug, which precipitates as a solid dispersion (Dhillon et al., 2014).

iv) Hot Melt Extrusion Methods

Melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. When compared to melting in a vessel, the product stability and dissolution are similar, but melt extrusion offers the potential to shape the heated drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms. Just like in the traditional fusion process, miscibility of drug and matrix can be a problem. Solubility parameters are investigated to predict the solid state miscibility and to select matrices suitable for melt extrusion.

High shear forces resulting in high local temperatures in the extruder are a problem for heat sensitive materials. However, compared to the traditional fusion method, this technique offers the possibility of continuous production, which makes it suitable for large-scale production. Furthermore, the product is easier to handle because at the outlet of the extruder the shape can be adapted to the next processing step without grinding (Arunachalam et al., 2010).

v) Lyophilization Technique

Freeze-drying involves transfer of heat and mass to and from the product under preparation. Lyophilization has been thought of a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion. Betageri et al., and Topalogh et al., have successfully investigated the potential applications of lyophilization in manufacturing of SD(s) (Jatinder et al., 2012).

vi) Melt Agglomeration Process

This technique has been used to prepare solid dispersion, wherein the binder acts as a carrier. In addition, solid dispersions are prepared either by heating binder, drug and excipients to a temperature above the melting point of the binder or by spraying a dispersion of drug in molten binder on the heated excipients by using high shear mixer (Ingle et al., 2011).

vii) The Use of Surfactant

The utility of surfactant in solubilization is very important. Adsorption of surfactant on solid surface can modify their hydrophobicity, surface charge, and other key properties that govern interfacial processes such as flocculation/dispersion, floating, wetting, solubilization, detergency, and enhanced oil recovery and corrosion inhibition. Surfactants have also been reported to cause solvation/plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, glass transition temperature and the combined glass transition temperature of solid dispersions. Because of these unique properties, surfactants have attracted the attention of investigators for preparation of solid dispersions (Iswarya et al., 2013).

viii) Electrospinning

This technology is used in polymer industry which combines solid solution/dispersion technology with nanotechnology. In this process, a potential between 5 and 30 kV is applied on the liquid stream of a drug/polymer solution. And as when the electrical forces overcome the surface ten-

sion of the drug/polymer solution at the air interface, fibers of submicron diameter are formed. After evaporating the solvent, the formed fibers can be collected on a screen (Aggarwal et al., 2010).

ix) Super Critical Fluid (SCF) Technology

The SAS process involves the spraying of the solution composed of the solute and of the organic solvent into a continuous supercritical phase flowing concurrently. Use of supercritical carbon dioxide is advantageous as it is much easier to remove from the polymeric materials when the process is complete, even though a small amount of carbon dioxide remains trapped inside the polymer; it poses no danger to the patient. In addition the ability of carbon dioxide to plasticize and swell polymers can also be exploited and the process can be carried out near room temperature. Moreover, supercritical fluids are used to lower the temperature of melt dispersion process by reducing the melting temperature of dispersed active agent. The reason for this depression is the solubility of the lighter component (dense gas) in the forming phase (heavier component) (Argade et.al., 2013).

The other possibility is to use supercritical fluid as a non-solvent. The Advantages of this method is that supercritical anti-solvent rapidly penetrates into the droplets, in which drug and matrix become supersaturated, crystallize and form particles. The general term for this process is precipitation with compressed anti- oven. Anti solvent like CO_2 or aerosol solvent extraction system are used inorder to enhance dispersion by supercritical fluid. However, as with the other solvent techniques, the critical step in these precipitation techniques might be the dissolution of drug and matrix in one solution. The use of water is limited, because the water solubility in compressed CO_2 is limited (Patidar et al., 2011).

x) Dropping Method

The dropping method, developed by Bülau and Ulrich (1977) to facilitate the crystallization of different chemicals, is a new procedure for producing round particles from melted solid dispersions. A solid dispersion of a melted drug–carrier mixture is dropped onto a cooling plate, where it solidifies into round particles. The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. As viscosity is highly temperature dependent, it is very important to adjust the temperature so that, when the melt is dropped onto the plate, it solidifies into a spherical shape.

The dropping method does not use organic solvents and therefore has none of the problems associated with solvent evaporation. The method also avoids the pulverization, sifting, and compressibility difficulties encountered with other melt methods. The disadvantage is that only thermostable drugs can be used, and the physical instability of solid dispersions is a further challenge (Shahroodi et al., 2008).

1.2.7. Mechanisms for Drug Release from Solid Dispersions

Different factors influence the enhancement of dissolution rate of solid dispersions. The use of increased amount of carrier enhances the dissolution rate of drug due to the reduction in particle size. However, it was later found that the dissolution rate could be improved without any change in the particle size. Non surface active carrier can enhance the wettability of a drug by reducing the contact angle and thus causing an increase in the surface area available for dissolution. A drug can be retained in the solution by inhibiting its precipitation with the addition of a polymer. The drug dissolves back into the solution, after precipitating out as metastable polymorph as this form is more soluble than the original polymorph of the drug (Khan., 2010).

Carrier-controlled or drug-controlled dissolution mechanisms were first proposed by Craig in which the drug release depends either on the carrier or the drug itself. The dissolution surface is non-disintegrating and the dissolution of both parts is diffusion controlled (Khan., 2010). Corrigan (1986) provided a very valuable contribution by not only measuring the dissolution rate of the incorporated drug but also assessing that of the polymer itself, in this case PEG. He found that the dissolution rate of the drug in the polymer and the polymer alone were in fact equivalent, leading to the suggestion of carrier-controlled dissolution where by the dissolution rate of the drug is controlled by that of the inert carrier. This finding was supported by the work of Dubois and Ford (1985) who noted that the dissolution rates of a range of drugs in a single carrier, prepared under comparable conditions, were identical in most cases. In this instance the particles dissolve into the polymer-rich diffusion layer at a sufficiently rapid rate that there is insufficient time for the particles to be released intact into the medium. Consequently, the drug is molecularly dispersed within this concentrated layer (Argade et.al., 2013).

1.2.8. Characterization of Solid Dispersion

i) Determination of Saturation Solubility

An excess amount of the physical mixture and solid dispersion is taken in a conical flask and 10 ml of distilled water is added and shaken on rotator shaker for 48 hour at 37°C. Remove the flask and filter it. Suitable amount of aliquot is withdrawn from the filtered solution and the drug content was analyzed after appropriate dilution with distilled water and was compared with pure drug solubility(Akiladevi et al., 2011).

ii) Fourier Transform Infrared Spectroscopic Analysis

The interaction between the drug and the carrier in solid dispersion is assessed by FTIR. In the solid dispersion preparation the peak band shows shift in the absorption spectrum for the drug molecule. However, careful interpretation of the spectrum is required for some of the delicate changes (Rakesh et al., 2008). Infrared spectroscopy (IR) can be used to detect the variation in the energy distribution of interactions between drug and matrix. Sharp vibrational bands indicate crystallinity [58]. Fourier Transformed Infrared spectroscopy (FTIR) was used to accurately detect crystallinity ranging from 1 to 99% in pure material (Mehta et.al., 2014)

iii) Differential Scanning Calorimetry (DSC)

DSC measures the heat loss or gain resulting from physical or chemical changes within a sample as a function of temperature. DSC enables the quantitative detection of all processes in which energy is required or produced (i.e. endothermic and exothermic phase transformations). The usual method of measurement is to heat the reference and test samples in such a way that the temperature of the two is kept identical (Shinde S et al., 2010). Exothermic transitions, such as conversion of one polymorph to a more stable polymorph, can also be detected. For characterizing crystal forms, the heat of fusion, ΔHf, can be obtained from area under the DSC curve for the melting endotherm. Lack of a melting peak in the DSC of a Solid dispersion indicates that the drug is present in an amorphous rather than a crystalline form. Since the method is quantitative in nature, the degree of crystallinity can also be calculated for systems in which the drug is partly amorphous and partly crystalline (Yadav and Tanwar et.al., 2015).

iv) Hyper Differential Scanning Calorimetry (HDSC)

This method employs excess heating rate starting from 100 to 500° C/min. However, in DSC the heating rate ranges from about 1 to 20 °C/min. Hyper differential scanning calorimetry have a number of advantages, which involves its use to prevent recrystalisation during the heating step. Besides, HDSC can be used to enhance thermal signals. It also has advantage of minimizing and preventing the changes in morphology and interaction during the heating process (Muhammad., 2010).

v) X Ray Powder Diffraction (XRPD)

The diffraction method is very important and efficient tool in studying the physical nature of Solid dispersion which has been used in crystal structure studies in two different ways. Sharper diffraction peaks indicate more crystalline material. Random orientation of a crystal lattice in a powder sample causes the x-rays to scatter in a reproducible pattern of peak intensities at distinct angles (θ) relative to the incident beam. Each diffraction pattern is characteristic of a specific crystalline lattice for a given compound. An amorphous form does not produce a pattern. The relationship between wavelength, of the x-ray, the angle of diffraction, θ, and the distance between each set of atomic planes of crystal lattice, d, is given by equation: M $\lambda=2d \sin \theta$, where M represent the order of diffraction (Dalwadi et al., 2010).

vi) Scanning Electron Microscopy

Scanning electron microscopy can be used to investigate the morphology of both the pure drug and the solid dispersion (Vishalkumar et al., 2011).

vii) In Vitro Release Studies

The dissolution of actives from solid dispersion as well as from the final product can be determined using a US Pharmacopeia type II dissolution test apparatus (USP30-NF25, 2007).

viii) Isothermal Titration Calorimetry (ITC)

It is an important method for understanding biological processes at molecular level. In this method a small change of heat during the reaction can be detected. This method is also useful in determining thermodynamic parameters like Gibbs free energy, enthalpy, entropy, binding constant, heat capacity and effective numbers of binding site in the biological reaction. This method

has advantages like it is the only technique that can establish all binding site in the biological reaction. It also allows the measurement of heat signals (Muhammad., 2010).

1.2.9. Marketed Formulations of Solid Dispersion

These are some marketed solid dispersion of which some are summarized in Table 1.2.

Table 1.2: Marketed products using solid dispersion

Brand name	Manufacturer	Modal drug	Carrier	Dosage form
Gris-PEG	Pedinol Pharmacal Inc.	Griseofulvin	PEG 6000	Tablet
Cesamet	Valeant Pharmaceuticals	Nabilone	PVP	Tablet
Kaletra	Abbott	Lopinavir, ritonavir	PVPVA	Tablet
Sporanox	Janseen Phamaceutica	Itraconazole	HPMC	Capsule
Intelence	Tibotec	Etravirin	HPMC	Tablet
Certican	Novartis	Everolimus	HPMC	Tablet
Isoptin SR-E	Abbott	Verapamil	HPC/HPMC	Tablet
Nivadil	Fujisawa Pharamceuticals Co.Ltd	Nivaldipine	HPMC	Tablet
Prograf	Fujisawa Pharamceuticals Co.Ltd	Tacrolimus	HPMC	Capsule
Rezulin	Developed by Sankyo, Manufactured by Parke-Davis	Troglitazone	PVP	Tablet

Adopted from (Saharan et al., 2009) (Jin Lee. B, et.al., 2013) (Chau Le-Ngoc Vo, 2013)

1.2.10. Pharmaceutical Applications of Solid dispersion

The application of solid dispersions for increasing drug bioavailability is by no means a new field of pharmaceutical research. Apart from absorption enhancement, the solid dispersion technique may have numerous pharmaceutical applications, which should be further explored. The pharmaceutical applications of solid dispersion techniques include:

1. To increase the solubility of poorly soluble drugs thereby enhance the dissolution rate, absorption and bioavailability.
2. To obtain a homogeneous distribution of a small amount of drug in solid state.

3. To stabilize unstable drugs and protect against decomposition by processes such as hydrolysis, oxidation, racemization, photo oxidation etc.

   To dispense liquid or gaseous compounds:- liquid drugs can be manufactured as solid drug formulations such as powders, capsules or tablets e.g. unsaturated fatty acids, essential oils, nitroglycerin, benzaldehyde, prostaglandin, clofibrate etc.
4. To formulate a fast release priming dose in a sustained release dosage form.
5. To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers. To reduce pre systemic inactivation of drugs like morphine and progesterone. Polymorphs in a given system can be converted into its amorphous, solid solution, eutectic or molecular addition compound (Vemula et al., 2010).
6. To minimize unpleasant taste and smell and avoid undesirable incompatibilities of drugs.
7. To reduce pre systemic inactivation of drugs like morphine and progesterone (Iswarya et al., 2013).

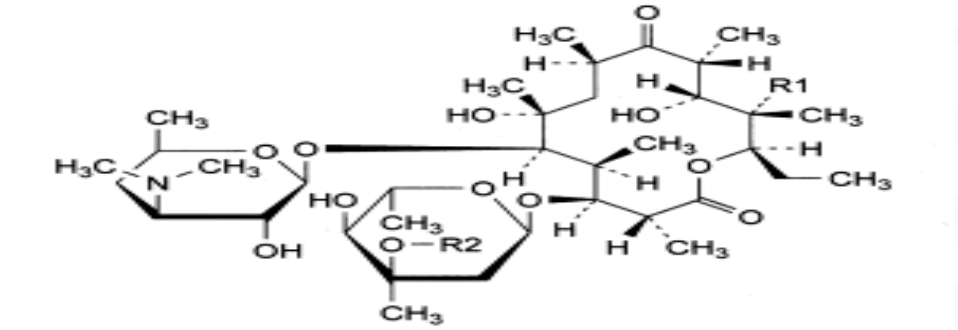
1.2.11. Challenging Future for Solid Dispersion Technique

Since solid dispersions were introduced in 1961, an immense amount of research has been done in this area. However, very few solid dispersion systems have been marketed due to the inability to scale bench top formulations to manufacturing- sized batches, and difficulty to control physicochemical properties.

1.3. Erythromycin Stearate

Erythromycin is a broad-spectrum macrolide antibiotic, which is often used for the treatment of upper and lower respiratory tract infection primarily caused by gram-positive micro-organisms (Birhanu et.al., 2013) and certain susceptible gram-negative and anaerobic bacteria (Sayed et al., 2012). It has some use for certain sexually transmitted diseases such as gonorrhea, which is caused by mixed infections involving cell wall free organisms like *chalimidia trachomitis* (Birhanu et.al., 2013). Macrolides are a group of drugs that belong to the polypeptide class of natural products by Saccharopolyspora erythreas and whose activity stems from the presence of a macrolide ring, a large macrocyclic lactone ring to which one or more deoxy sugars, usually cladinose or desosamine, may be attached. The lactone rings are usually 14, 15, or 16-membered.

Erythromycin is produced by a strain of *Streptomyces erythreus*. Structurally, erythromycin is a 14-membered lactone ring with ten asymmetric centers and two sugar molecules (L-cladinose and D-desoamine). Fig 1.1 It seems very difficult to synthesis erythromycin (Ali M et al., 2012). An amino sugar, desosamine, is attached through a -glycosidic linkage to the C-5 position of the lactone ring. The tertiary amine of desosamine confers a basic character to erythromycin (pKa 8.8). Through this group, a number of acid salts of the antibiotic have been prepared. A second sugar, cladinose, which is unique to erythromycin, is attached via a -glycosidic linkage to the C-3 position of the lactone ring (Sayed, et al., 2012).



Erythromycin	Mol. Formula	R1	R2
A	$C_{55}H_{103}NO_{15}$	OH	CH_3
B	$C_{55}H_{103}NO_{14}$	H	CH_3
C	$C_{54}H_{101}NO_{15}$	OH	H

Figure1.1: Chemical structure of erythromycin

It has an antimicrobial spectrum similar to or slightly wider than that of penicillin, and is often prescribed for people who have an allergy to penicillin's. This medicament is essentially bacteriostatic, (Taveechai et al., 2007) but in high concentrations erythromycin is bactericidal against very susceptible organisms. It is most often administered orally or intravenously (Grujicic et al., 2009).

The physicochemical properties are summarized in Table 1.3. According to BCS, Erythromycin belong to class IV drugs that is low solubility and low permeability and is not eligible for a biowaiver (Sultana et al., 2013).

Table 1.3: Physicochemical properties of Erythromycin Stearate

Category	Macrolide Antibiotic
Appearance	White to off White powder
BCS Class	Class II
Solubility	Practically insoluble in water, freely soluble in methanol, alcohol, chloroform, ether and acetone.
Bioavailability	25%
Tmax	3-4 hours
Plasma $t_{1/2}$	1-1.5 hours
Melting Point	100-104°C
Daily Dose	1 – 2 gm for adult ; 30 – 50 mg/kg per day for children
pKa	8.8

The oral bioavailability of Erythromycin Stearate is limited by factors such as the membrane permeability, the solubility, the dissolution rate of the drug. Specially, the solubility and the dissolution rate of a practically water insoluble drug is a critical factor for its oral bioavailability(Salam and Lupuleasea., 2009).

Erythromycin easily degrades in acidic conditions giving inactive compounds (Sultana et al., 2013). To increase its acid stability and bioavailability, erythromycin is available in several forms including estolate, ethysuccinate and stearate (Taveechai et al., 2007). Modifications of the drug and its product formulations have attempted to improve absorption and subsequent serum levels by two methods. One involves providing a protective enteric coating to shield erythromycin base from acid degradation in the upper-gastro-intestinal tract. The other involves altering the chemical structure of erythromycin molecule itself to decrease acid inactivation (Ogwal and Xide., 2011).

Pharmacokinetics of erythromycin stearate

Erythromycin base is destroyed by gastric acid, except if administered with a protective enteric coating. Acidic media degrades erythromycin rapidly to form derivates with little antimicrobial activity. Erythromycin stearate is more stable, however in vitro studies have demonstrated that

erythromycin stearate dissolves in gastric acid, retains only 2% antibiotic activity and is rapidly destroyed (DiSanto and Chodos., 1981; Periti et al., 1989; Martindale., 1989). The major site of absorption in rat, dogs and humans is the small intestine. Erythromycin is only slightly absorbed from the stomach. In man, absorption occurs mainly in the duodenum (Anderson., 1959; Huber., 1977). It is very rapidly absorbed and diffuses into most tissues and phagocytes. It is metabolized by de-methylation in the liver. Its main elimination route is in the bile, and a small portion in the urine (Bekele and Gebeyehu., 2012).

1.4. OBJECTIVES

1.4.1. General Objectives

- To formulate and evaluate erythromycin stearate capsules with enhanced dissolution by using Solid Dispersion technique.

1.4.2. Specific Objectives

- To formulate solid dispersions and physical mixtures of erythromycin stearate using different polymers in different ratios.
- To carry out drug polymer interaction study using FTIR and DSC
- To compare the *In-vitro* dissolution profile of pure erythromycin stearate with the physical mixtures, solid dispersions and a marketed product of erythromycin stearate.
- To study surface morphology of pure erythromycin stearate and SDs
- To study the crystallinity if the SDs using XRD
- To carry out short term stability study for selected formulations showing promising results.

2. Materials and Methods

2.1. Materials

Erythromycin Stearate (Mehta API Pvt. Ltd. Ahmedabad, India), PVP K30 (Koje polymer, USA), PEG 6000 were kindly donated by Cadila Pharmaceuticals PLC (Ethiopia).PEG 4000 (Laffans petrochem. Ltd, Mumbai, India), Eudragit® E100 (Röhm GmbH, Darmstadt, Germany), Erysin 250 (Maiden Pharmaceuticals Ltd., New Delhi, India)Ethanol (National Alcohol and Liquor Factory, Addis Ababa, Ethiopia), Methanol HPLC grade (Bhagat Aromatics Ltd., Uttar Pradesh, India), Glacial acetic acid (G.A.A), and Hydrochloric acid (HCL) (Unichem Corporation, Nagpur, India), sodium acetate (Loba Chemical Pvt.Ltd., Mumbai, India) and 4-dimethylaminobenzaldehyade (Jilin Zhongxin Chemical group Co. Ltd). All other chemicals and reagents used were of analytical grade and were used as procured.

2.2. Methods

2.2.1. Polymer Screening

Polymers like PEG 4000, PEG 6000, PVP K30, HPMC 5cps and eduragit ® E100 at different ratio of drug to polymer like 2:1, 1:1, and 1:2 were weighed accurately and prepared. The weighed amount was dissolved in ethanol. The solution prepared was poured into the petri dish to form a thin film. The petri dishes were kept at room temperature until solvent was completely evaporated. The polymers which formed clean film in each ratio were selected for further analysis (Enose et.al., 2014)

2.2.2. Construction of calibration curve of Erythromycin Stearate

From a 100 µg/ml stock solution of ES in methanol different equivalent amount of ES samples were taken (10 µg/ml, 12 µg/ml, 14 µg/ml, 16 µg/ml, 18 µg/ml, 20 µg/ml, 22 µg/ml, 24 µg/ml and 26 µg/ml) and diluted using 40ml G.A.A and 10ml 0.5%w/v solution of 4-dimethyl aminobenzaldehyde in G.A.A was added and the volume was made up to the mark using a mixture of G.A.A and concentrated HCL (35.4% w/w) (35ml G.A.A + 70ml HCL). The absorbance of the samples was measured at 485nm using UV/Vis spectrophotometer (Perkin Elmer, Model-Lambda 25 UV/Vis spectrophotometers, USA) and a graph was plotted between absorbance and concentration (British Pharmacopoeia 2009).

2.2.3. Preparation of Solid Dispersion

Solid dispersion containing ES and selected hydrophilic polymer, was prepared by fusion, solvent evaporation and/or kneading method as shown in Table 2.1.

i. Fusion Method

The drug and the hydrophilic carriers were melted in porcelain dish by heating it on a hot plate with continuous stirring until a homogenous mixture was obtained. The heating temperature was controlled between 75°C to 80°C and after melting the melted mass was rapidly cooled over an ice bath.

ii. Solvent Evaporation Method

Accurately weighed amount of ES and a hydrophilic polymer was dissolved in 98% ethanol and the solvent was evaporated in an oven at 50°C over 72 h.

iii. Kneading Method

Accurately weighed amount of ES and a hydrophilic polymer was placed in a mortar and the mixture was kneaded with 20ml of ethanol for 20 min to give a homogenous dispersion. Once the homogenous slurry was obtained samples were dried in an oven at 50°C until dryness. In all the three cases the dried dispersion was pulverized, sifted through a 244µm sieve and were stored in a desiccator for 48 h (Venkatesh., 2008**).**

iv. Physical Mixture: Physical mixture of ES and the selected polymer was prepared by lightly triturating accurately weighed amount of the drug and polymer mixture for 5 min using mortar and pestle.

Table 2.1: Compositions and codes of various formulations of solid dispersions investigated

Drug : Carrier	Method	Drug : carrier Ratio	Formulation Code
ES : PEG 4000	Fusion	2:1, 1:1, 1:2	PEG4-f21, PEG4-f11, PEG4-f12
ES : PEG 4000	Solvent evaporation	2:1, 1:1, 1:2	PEG4-s21, PEG4-s11, PEG4-s12
ES : PEG 4000	Kneading	2:1, 1:1, 1:2	PEG4-k21, PEG4-k11, PEG4-k12
ES : PEG 6000	Fusion	2:1, 1:1, 1:2	PEG6-f21, PEG6-f11, PEG6-f12
ES : PEG 6000	Solvent evaporation	2:1, 1:1, 1:2	PEG6-s21, PEG6-s11, PEG6-s12
ES : PEG 6000	Kneading	2:1, 1:1, 1:2	PEG6-k21, PEG6-k11, PEG6-k12
ES : PVP K30	Solvent evaporation	2:1, 1:1, 1:2	PVP-s21, PVP-s11, PVP-s12
ES : PVP K30	Kneading	2:1, 1:1, 1:2	PVP-k21, PVP-k11, PVP-k12

2.2.4. Fourier Transform Infrared Spectroscopy

Drug-excipient interaction study was carried out by FTIR spectroscopic method. Thus, the FTIR spectra of the pure ES and the solid dispersions (1:1, 1:2) prepared were acquired at room temperature using an FTIR spectrophotometer (Perkin Elmer Spectrum 1000 FT-IR spectrometer, California, USA) in transmittance mode. Before measurement, the samples were ground with KBr in a mortar to reduce the average particle size and were compressed. The spectra were obtained by scanning the sample in the range of 4000 – 400 cm^{-1} at a resolution of $1cm^{-1}$.

2.2.5. Differential Scanning Colorimeter

DSC (NETZSCH DSC 200F3 240-20-427-L, Germany) studies were performed on the pure drug and carrier as well as the physical mixtures (1:1) and solid dispersions in order to study the interaction between pure drug and the carrier. Accurately weighed samples (4-5 mg) were hermetically sealed in an aluminum pan and the scanning was carried out at a temperature ranging from 30^0C to 450 ^{0}C at a rate of 15 K/min under nitrogen gas flow.

2.2.6. Determination of Flow and Related Properties of the Solid Dispersions

A. Determination of Angle of Repose

To determine the angle of repose, 30gm of the solid dispersion was allowed to flow through a funnel from a fixed height of 10cm. Then, the height and radius of the heap of powder was noted and the angle of repose was calculated using Eq.2 (Shrivastava, et al., 2009).

$$Angle of\ repose\ (\theta) = \tan^{-1}\left(\frac{H}{R}\right) \qquad \text{Eq.1}$$

B. Determination of Bulk and Tapped Density

The pre-sieved bulk powder blend was weighed, placed in a graduated cylinder and the bulk volume was read. Subsequently, the powder was tapped 100 times on tapped densitometer and the tapped volume was read. Finally the bulk and tapped densities were calculated using Eqs. 3 and 4 (Shrivastava, et.al., 2009).

$$D_b = \frac{M}{V_b} \qquad \text{Eq.2}$$

Where, D_b is bulk density (g/cm^3), M is weight of sample (g), and V_b is volume of microspheres (cm^3).

$$D_t = \frac{M}{V_t} \qquad \text{Eq.3}$$

Where D_t is tapped density (g/cm^3), M is weight of sample (g), and V_t is final tapped volume of powder (cm^3).

C. Carr's Index (Compressibility index)

It is an important parameter to study compressibility behavior of composites. Carr's index was calculated using Eq. 5 (Chowdary K. P. R and Veeraiah Enturi., 2011).

$$Carr's\ index\ (\%) = \frac{(D_t - D_b)}{D_t} \times 100 \qquad \text{Eq. 4}$$

Where, D_b is bulk density (g/cm^3), and D_t is tapped density (g/cm^3).

D. Hausner Ratio

It is used to measure the flow properties of powders. Hausner ratio was calculated by average of three determinations using Eq. 6

$$Hausner\ ratio = \frac{(D_t)}{(D_b)} \qquad \text{Eq.5}$$

2.2.7. Determination of Percent Practical Yield

The percentage practical yield of each method was calculated using Eq.1

$$Yield(\%) = \frac{\text{Practical mass (SD)}}{Theoretical\ mass(polymer + drug)} \times 100 \qquad \text{Eq. 6}$$

2.2.8. Drug Content Analysis

The content of ES in the solid dispersion and the physical mixture was determined by using UV-visible spectrophotometric method. Accordingly, accurately weighed amount of the Solid dispersion equivalent to 10mg of ES was transferred to 100ml volumetric flask and was dissolved in 5ml of methanol. Then, to the sample 40ml of glacial acetic acid, 10ml of 0.5%w/v solution of 4-dimethyl aminobenzaldehyde in glacial acetic acid was added and the volume was made up to the mark using a mixture of glacial acetic acid and HCL (35ml G.A.A + 70ml HCL). The absorbance of these samples was measured at 485nm and the percentage drug content was calculated using Eq.7

$$\%\ Drug\ content = \frac{Actual\ ES\ content\ in\ weighed\ quantity\ of\ solid\ dispersion}{Theoretical\ amount\ of\ ES\ in\ solid\ dispersion} \times 100 \qquad Eq.\ 7$$

2.2.9. Determination of Solubility

Solubility determination was carried out by using a shake flask method for the drug and the SD. Accordingly, an excess amount of the sample was put in a round bottom flask containing 10 ml of distilled water and the flask was agitated for 24 hours at room temperature. Then the supernatant was filtered through a Whatman filter paper 0.45µm and to 5ml of the filtrate 40ml of G.A.A, 10ml of 0.5%w/v solution of 4-dimethyl aminobenzaldehyde in G.A.A was added and the volume was adjusted to 100ml using a mixture of G.A.A and HCL (35ml G.A.A + 70ml HCL). Finally, the absorbance of the solution was measured spectrophotometrically and the amount and hence the solubility of ES in the sample was calculated (Vijaya et al., 2006).

2.2.10. Preparation and Evaluation of Capsules

The PM and SDs equivalent to 250 mg of erythromycin stearate was filled into hard gelatin capsules.

Disintegration Study: Disintegration time of the capsules was determined as per B.P. procedure in which six capsules were placed in the disintegration apparatus, add a disc. Fill it with 900ml distilled water maintained at 37±2°C. The time of disintegration with no palpable mass remaining on the apparatus was recorded as the disintegration time (B.P 2009).

Mass Uniformity: 20 capsules were randomly selected. Each capsules were weight and the capsules were opened to remove the content, and the empty capsules were weighed again. Then the weight content was determined (B.P.2009).

2.2.11. *In-vitro* Dissolution Study

In-vitro dissolution studies of pure drug, physical mixture and solid dispersions were performed according to BP 2009 using USP Dissolution Apparatus II (paddle type) at 50 rpm using acetate buffer (pH 5) maintained at 37°C ± 5°C as a dissolution media. During the study 10ml of the dissolution media was withdrawn at specified time intervals (5, 10, 15, 20, 30, 45 and 60minutes) and filtered. Equivalent volume of the solvent withdrawn was replaced by a fresh dissolution medium to maintain the sink condition. The filtered samples were then analyzed spectrophotometrically at 485 nm.

For the dissolution study the physical mixture and solid dispersion equivalent to 250 mg of ES was filled in a capsule (size 1).

2.2.12. Scanning Electron Microscopy

The morphology of selected ES solid dispersion was observed under a scanning electron microscope (model JEOL 5400, Japan). The samples were coated with a layer of gold using a gold sputter technique to improve the conductivity of the surface of the sample to obtain good images. Scanning electron photomicrograph of gold-coated sample was taken at appropriate magnification applying voltage of 20KV. SEM was carried out to study the surface morphology and shape of solid dispersion.

2.2.13. X-Ray Diffraction

Systems giving the best dissolution profiles were further evaluated with X-ray diffraction. The samples were exposed to Cu Ka radiation (40 × kV 30 mA) at a scan rate of 8 deg:min. A fixed slit system was employed with the following slit parameters: divergence, 1°; scatter, 1°; receiving, 0.3 mm. The output is given as intensity versus 2Ɵ. For comparative purposes, the Hanawalt method (Cullity, 1990) was adopted, where the three highest values for relative intensity and their corresponding spacing's were compared for the drug, carrier and the corresponding systems. XRD was carried out for qualitative and semi-quantitative detection of materials and study the amorphous transitions.

2.2.14. Comparison of Prepared Solid Dispersion with Commercial ES Product

A mathematical approach for calculating similarity factor (*f2*), Eq.13 and dissimilarity factor (*f1*) Eq.14 were used for comparison among the dissolution profiles. Following the preparation of solid dispersion, the release of ES from selected formulations was also compared with a commercialized ES product (Erysin 250mg).

The difference factor (*f1*) as defined by FDA calculates the % difference between 2 curves at each time point and is a measurement of the relative error between 2 curves (Dalwadi et.al., 2010). Whereas the similarity factor (*f2*) as defined by FDA is logarithmic reciprocal square root transformation of sum of squared error and is a measurement of the similarity in the percentage (%) dissolution between two curves.

$$f_1 = \left\{ \frac{\left\{ \sum_{t=1}^{n} |Rt - Tt| \right\}}{\sum_{t=1}^{n} Rt} \right\} \times 100$$

Eq. 8

Where, n = number of time points

Rt = % dissolved at time t of reference product (pre change),[i]

Tt = % dissolved at time t of test product (post change)

$$f2 = 50 \times \log\left[\left\{ 1 + \frac{1}{n} \sum_{t=1}^{n} wt(Rt - Tt) \right\}^{-0.5} \times 100 \right]$$

Eq. 9

Here idea of weight Wt is to provide more weighting to some dissolution time point than others. If it is not appropriate to weight time profile Wt may be set to one at each time point. If, *f1* close to zero and *f2* close to 100 are considered as similar profiles. Generally values of *f1* lies between 0 - 15 and values of *f*2 lies between 50 -100 ensures equivalence (Dalwadi et al., 2010).

2.2.15. Determination of Release Kinetics from the Various Formulations

Determination of the release kinetics and the release mechanism from variosus formulations was made by fitting the dissolution data into various drug release kinetic models shown in Eq. 8-12.

a) Zero order release kinetics

$$Q = Q_O - K_O t \qquad \text{Eq.10}$$

Where Q is the amount of drug remaining at time t, Q_o is the quantity of drug present initially in the dosage form and K_o is the zero order release constant.

b) First order release kinetics

$$\ln Q = \ln Q_0 - K_1 t \qquad \text{Eq.11}$$

Where Q is the amount of drug remaining at time t, Q_o is the quantity of drug present initially in the dosage form and K_1 is the first order release constant.

c) Higuchi's equation

$$M_t/M_o = K_H t^{1/2} \qquad \text{Eq.12}$$

Where M_t is the amount of drug released at time t, M_o is the amount of total drug in the capsule and K_H is Higuchi's constant.

d) Hixson Crowell cube root law equation

$$Q_t^{1/3} = Q_o - K_{HC} t \quad \text{Eq. 13}$$

Where Q_t is the amount of Drug release at time t, Q_o is the quantity of drug present initially in the dosage form and K_{HC} is the rate constant for Hixson Crowell equation (Demirtürk and Öner., 2005).

2.2.16. Accelerated Stability Study

Stability study was conducted on those capsules of ES with best dissolution profile and for the study the capsules were packed in an air tight container and stored in stability chamber at 40 ± 2°C and 75 ± 5% RH for a period of 3 months. The samples were then withdrawn at interval of 30, 60 and 90 days and were evaluated for the physical appearance, drug content and *In-vitro* dissolution studies (Dalwadi et.al., 2010).

3. Results and Discussions

3.1. Selection of Dispersing Hydrophilic Polymer

A number of hydrophilic polymers can be used for the preparation of solid dispersion hence, formulation of a solid dispersion should begin with selection of appropriate hydrophilic polymers that can better dissolve the drug of choice. Accordingly, for this study the potential uses of five polymers including HPMC 5cps, PEG 4000, PEG 6000, Eudragit ® E100, and PVP K30 as a dispersing hydrophilic polymer were assessed by forming polymeric films containing different drug to polymer ratio (2:1, 1:1, and 1:2) in alcohol. The results of the study showed that ES: HPMC (1:1) gave a hazy film and ES: HPMC (1:2) and ES: Eudragit (1:1, 1:2) gave opaque films indicating that HPMC and Eudragit are not polymers of choices. However, clear films of drug to polymer were obtained with PEG 4000, PEG 6000 and PVP K30 at all proportions and hence these polymers were chosen for further investigations.

3.2. Construction of Calibration Curve

The calibration curve of ES was constructed at 485nm and the results are shown in Fig.3.1. The equation describing the relationship absorbance (A) and concentration (C) is given by A = 0.0135C – 0.0058 with an acceptable correlation coefficient of R^2 of 0.9997, $p < 0.0001$.

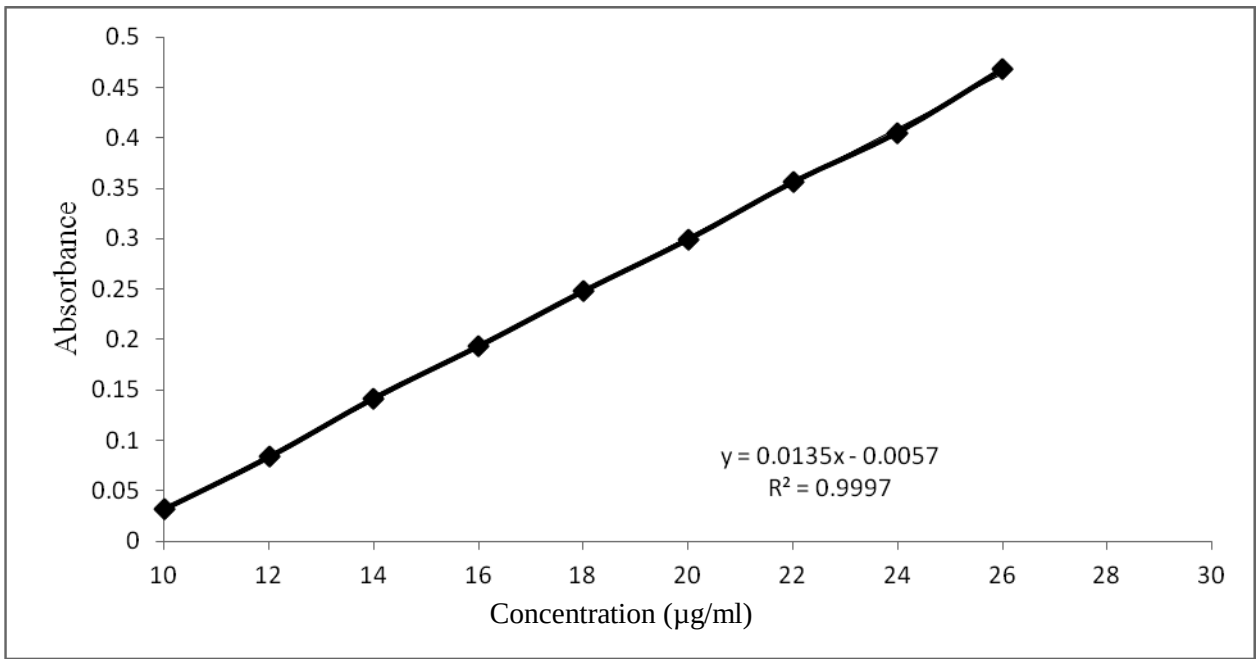


Figure 3.1: Calibration Curve of Erythromycin Stearate

3.3. Investigation of Drug Polymer Interaction

3.3.1. Fourier Transform Infrared Spectroscopy

FTIR spectroscopy is another quick and simple technique for identifying any chemical changes or interaction between the drug and the excipients and to ascertain the presence of different functional group(Rajpurohit et al., 2011). Thus, it was also used a technique to investigate the interaction between ES and the different polymers used (Gangurde et al., 2013).

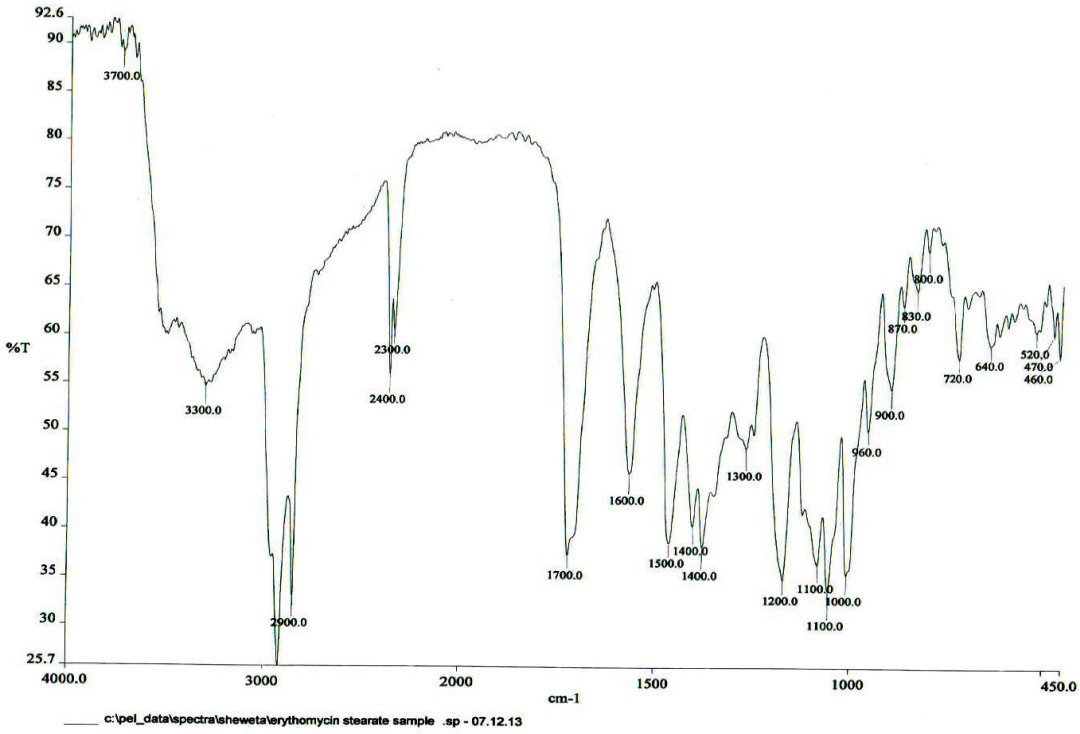
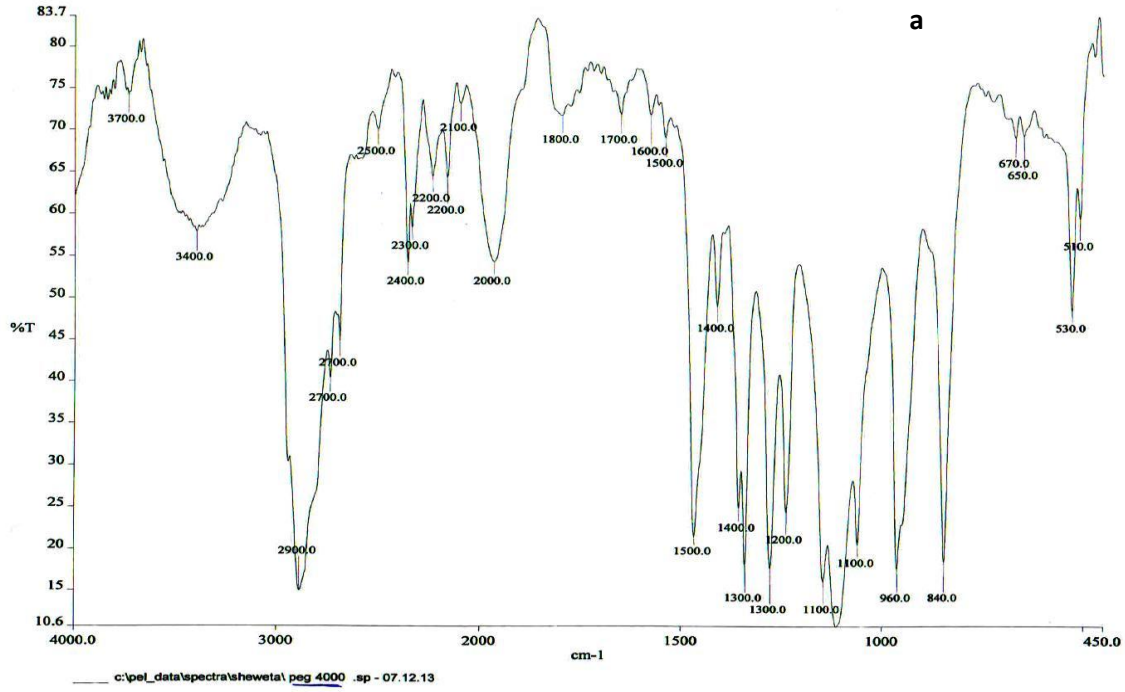


Figure 3.2: FTIR Spectra of ES

As can be seen in the Figure 3.2, the FT-IR spectrum of ES showed characteristic peaks at 3300 cm^{-1} for O-H stretching, 2900cm^{-1} for C-H stretching, 1700cm^{-1} for C=O Stretching, 1500cm^{-1} for C-C stretching, 1400cm^{-1} for $N(CH_3)_2$ Stretching, 1300 cm^{-1} for OH Stretching, 1200cm^{-1} and 1100 $cm^{-1}$for C-O stretching.

Figure 3.3 a, b and c shows the FTIR spectra of the carrier PEG 4000, physical mixture containing ES: PEG 4000 at 1:1 ratio and the solid dispersion prepared by fusion method at a ratio of 1:2. FTIR peaks are summarized in Table 3.1.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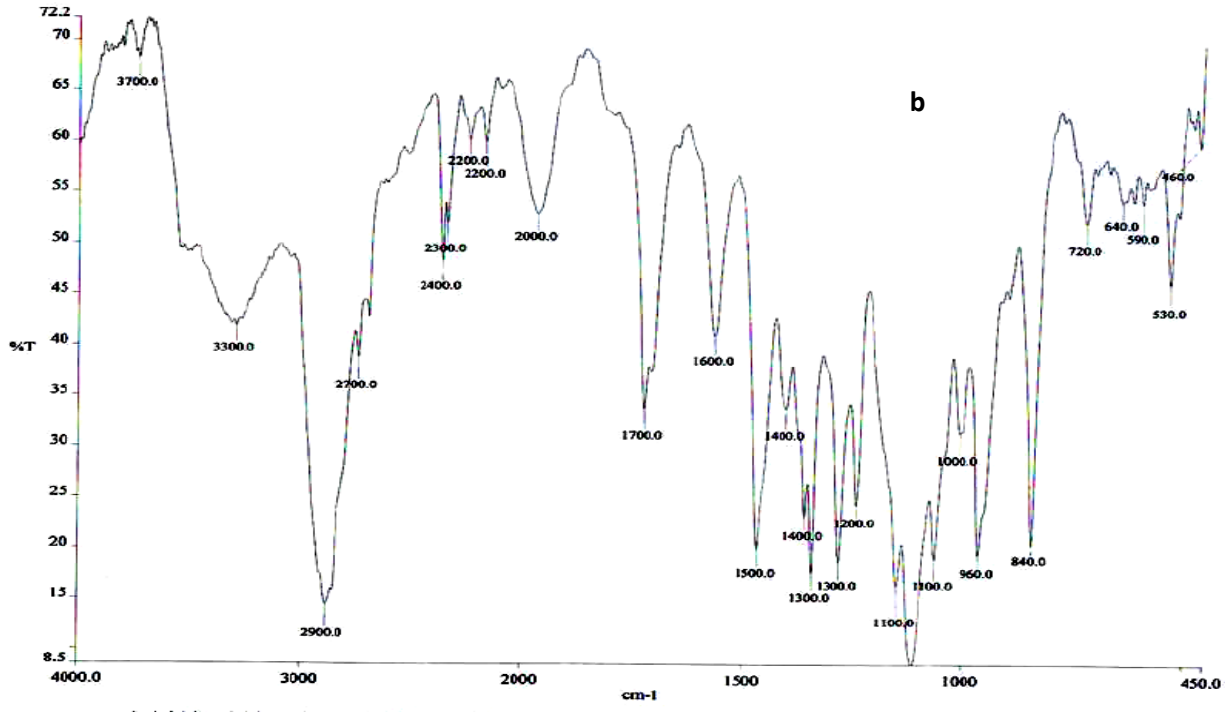
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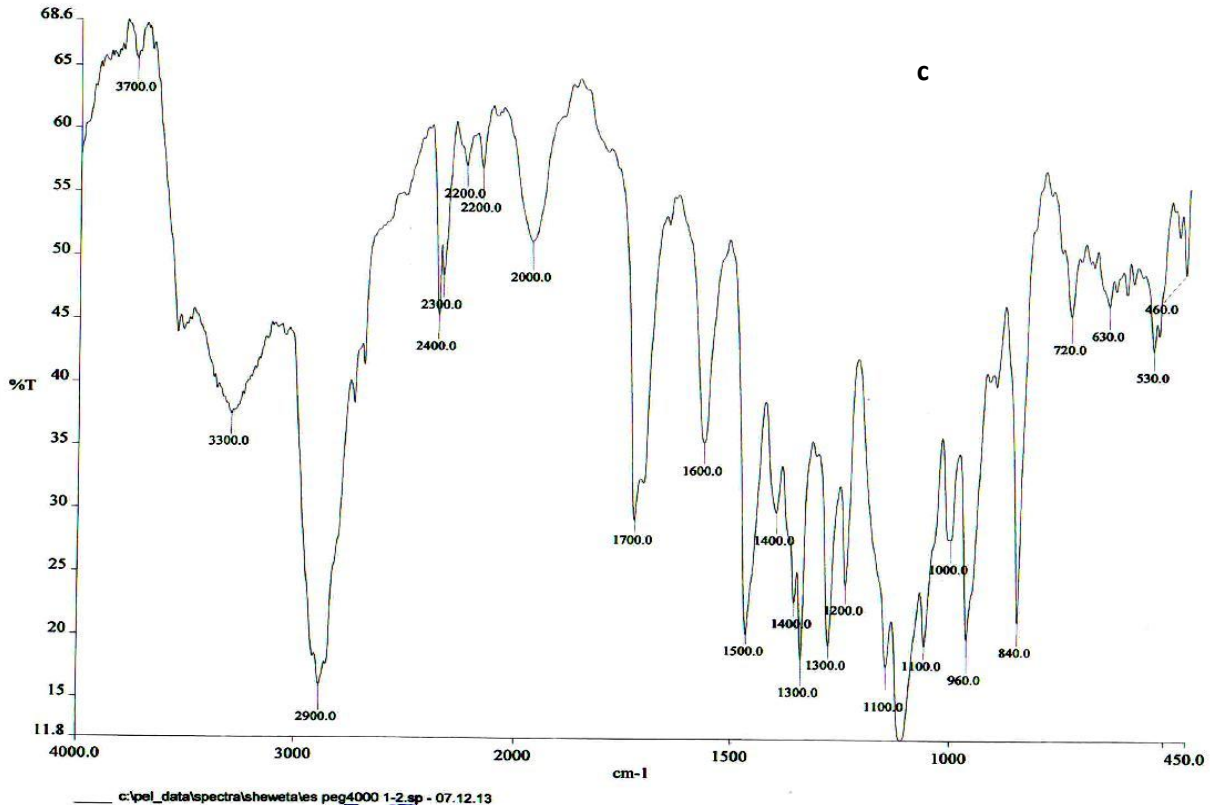
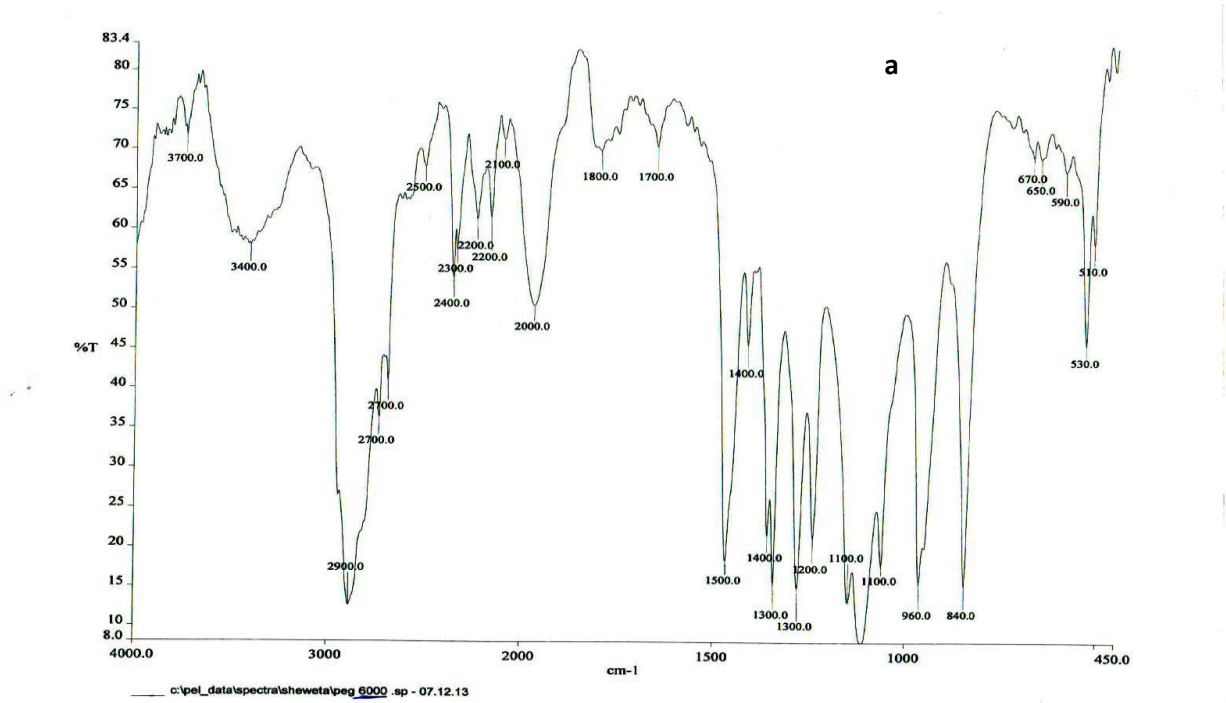


Figure 3.3: FTIR Spectra of a) PEG 4000, b) physical micture of Erythromycin Stearate - PEG 4000 (1:1) and c) Solid Dispersion of Erythromycin Stearate - PEG 4000 (1:1)

As can be referred from the Table and Figure 3.3 a, b and c shows the FTIR spectra of PEG 4000, PM and SD respectively. The FTIR spectra of the solid dispersion showed the characteristic peaks at 3300 $^{cm-1}$ O-H stretching, 2900 cm^{-1} for C-H stretching, 1700 cm^{-1} for C=O stretching, 1500 cm^{-1} for C-C stretching, 1400 cm^{-1} for $N(CH_3)_2$ stretching, 1300 cm^{-1} for OH stretching, 1200 cm^{-1} and 1100 cm^{-1} for C-O stretching.

Figure 3.4 a, b and c shows the FTIR spectra of the carrier PEG 6000, physical mixture containing ES: PEG 6000 at 1:1 ratio and the solid dispersion prepared by fusion method at a ratio of 1:1 respectively. Similar to PEG 4000 it also showed all the characteristic peaks.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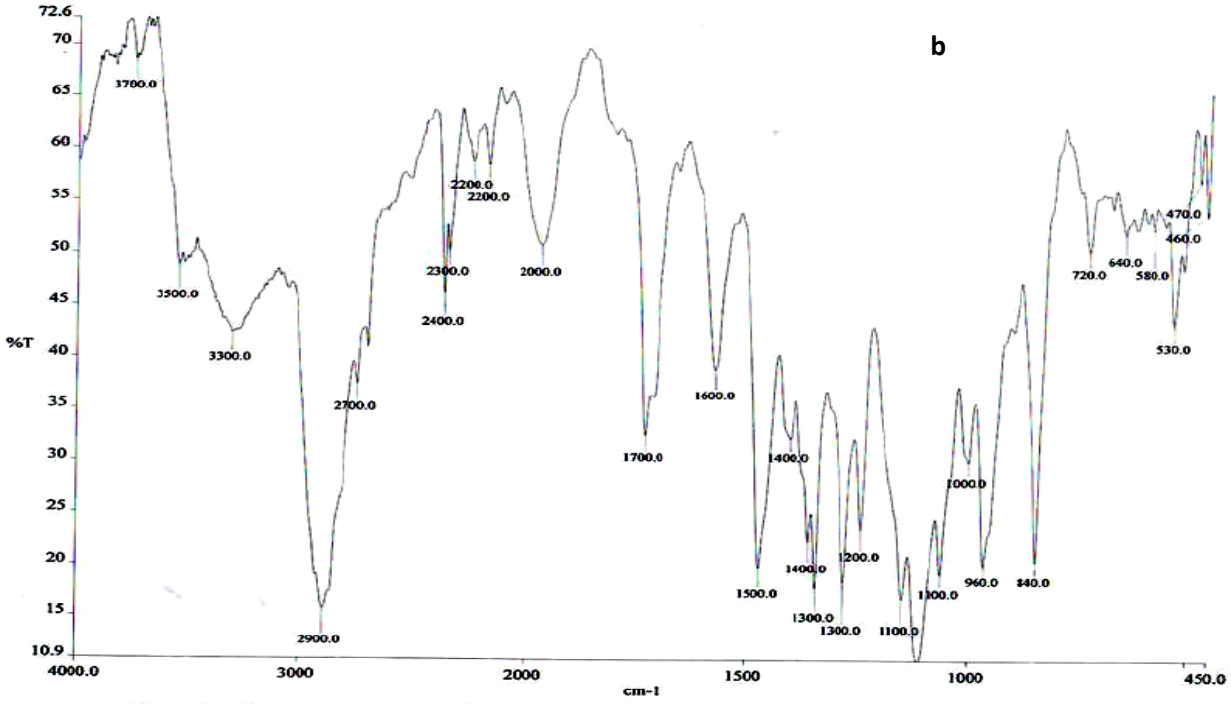
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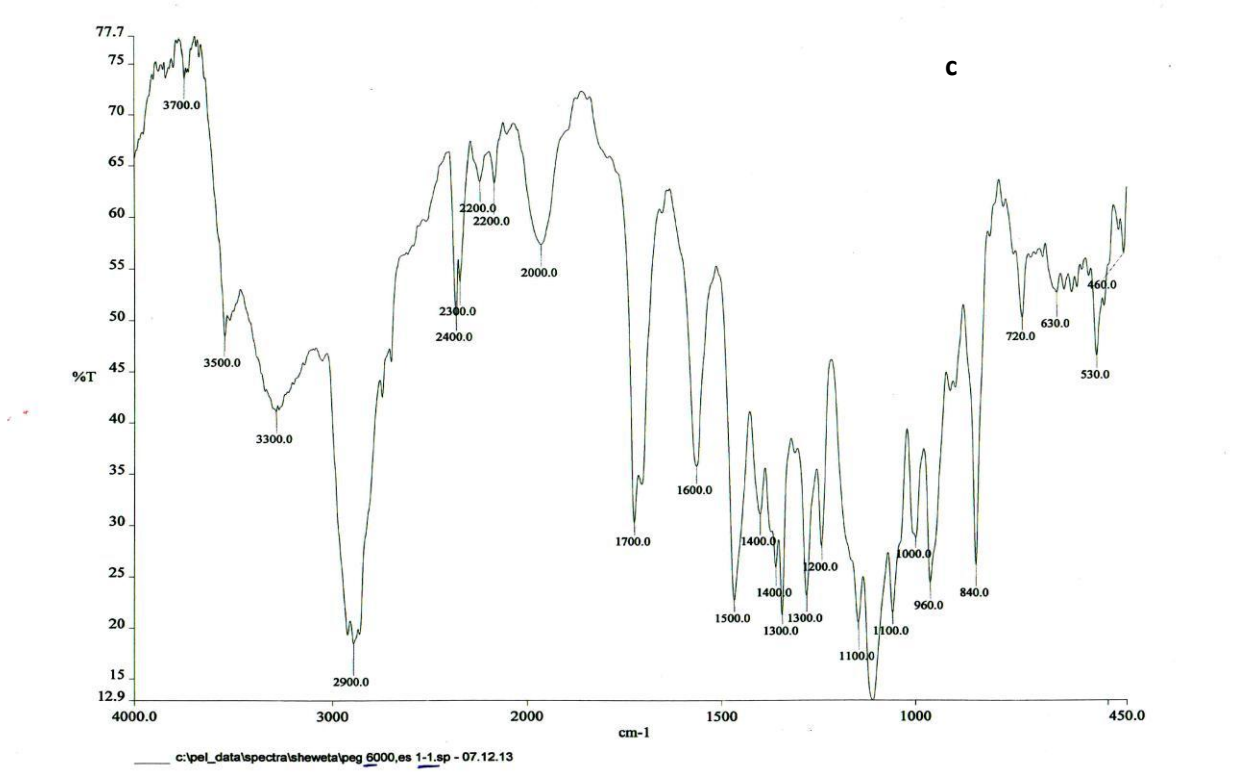
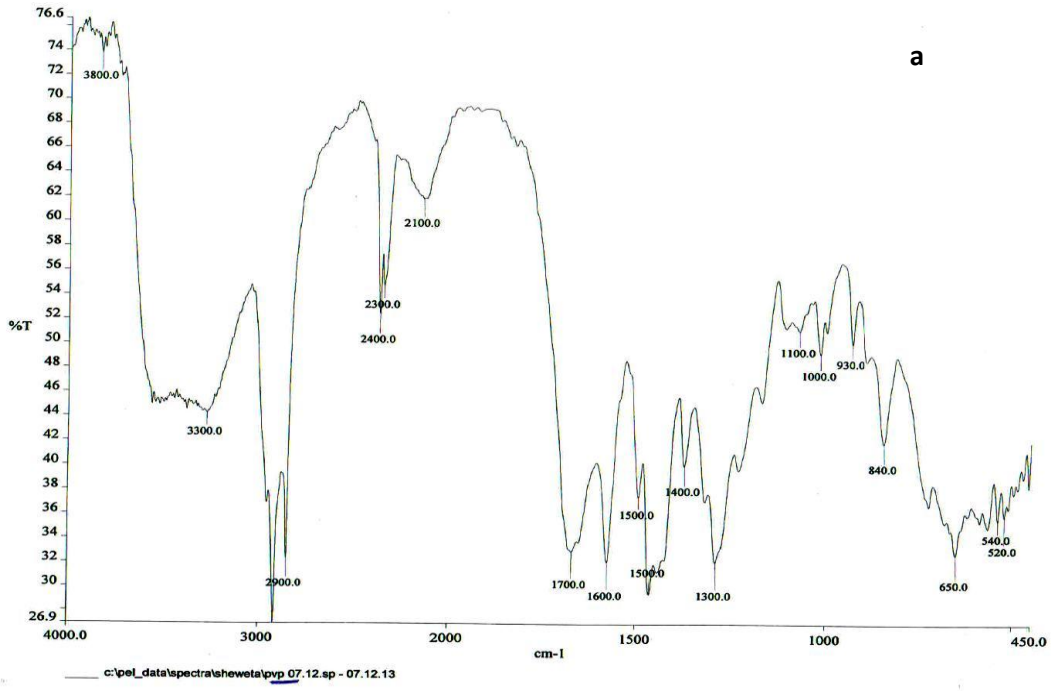


Figure 3.4: FTIR Spectra of a) PEG 6000, b) physical micture of Erythromycin Stearate - PEG 6000 (1:1) and c) Solid Dispersion of Erythromycin Stearate - PEG 6000 (1:1)

Figure 3.5 a, b and c shows the FTIR spectra of the carrier PVP K30, physical mixture containing ES: PVP K30 at 1:1 ratio and the solid dispersion prepared by solvent evaporation method at a ratio of 1:2 respectively. Similar to PEG 4000 and PEG 6000, solid dispersion of PVP K30 also showed all the characteristic peaks.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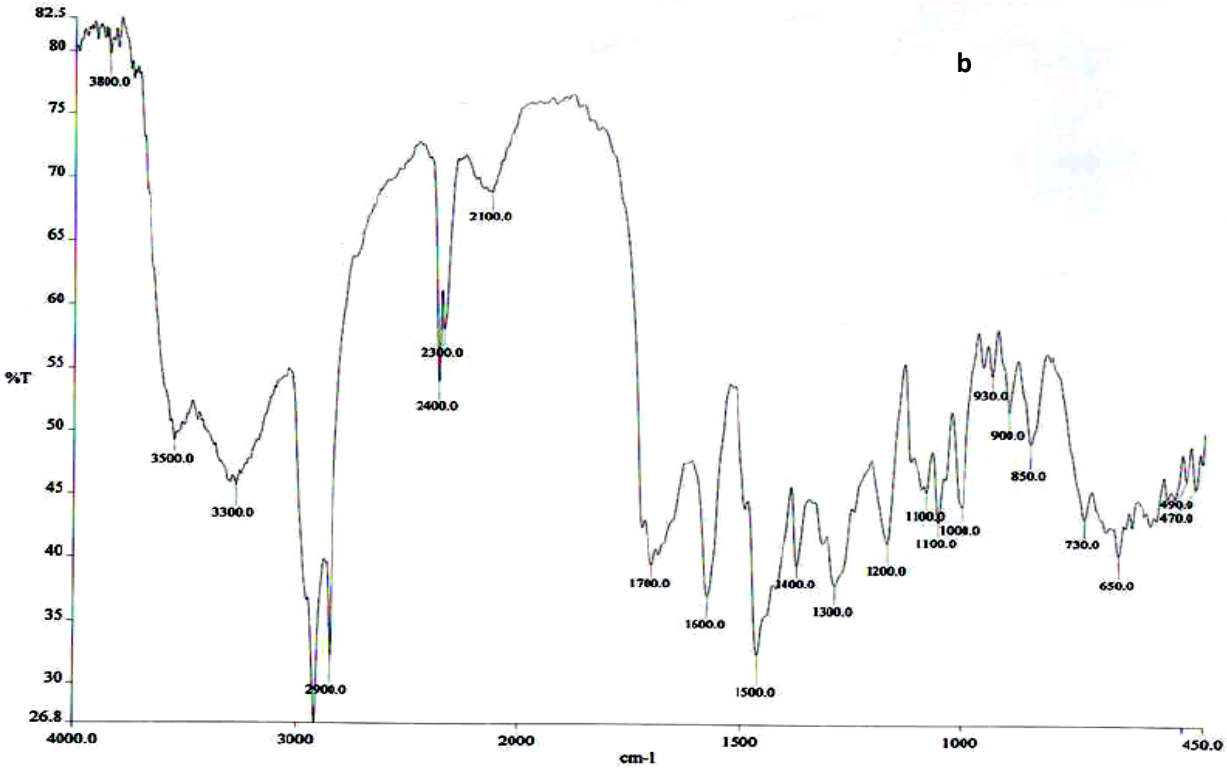
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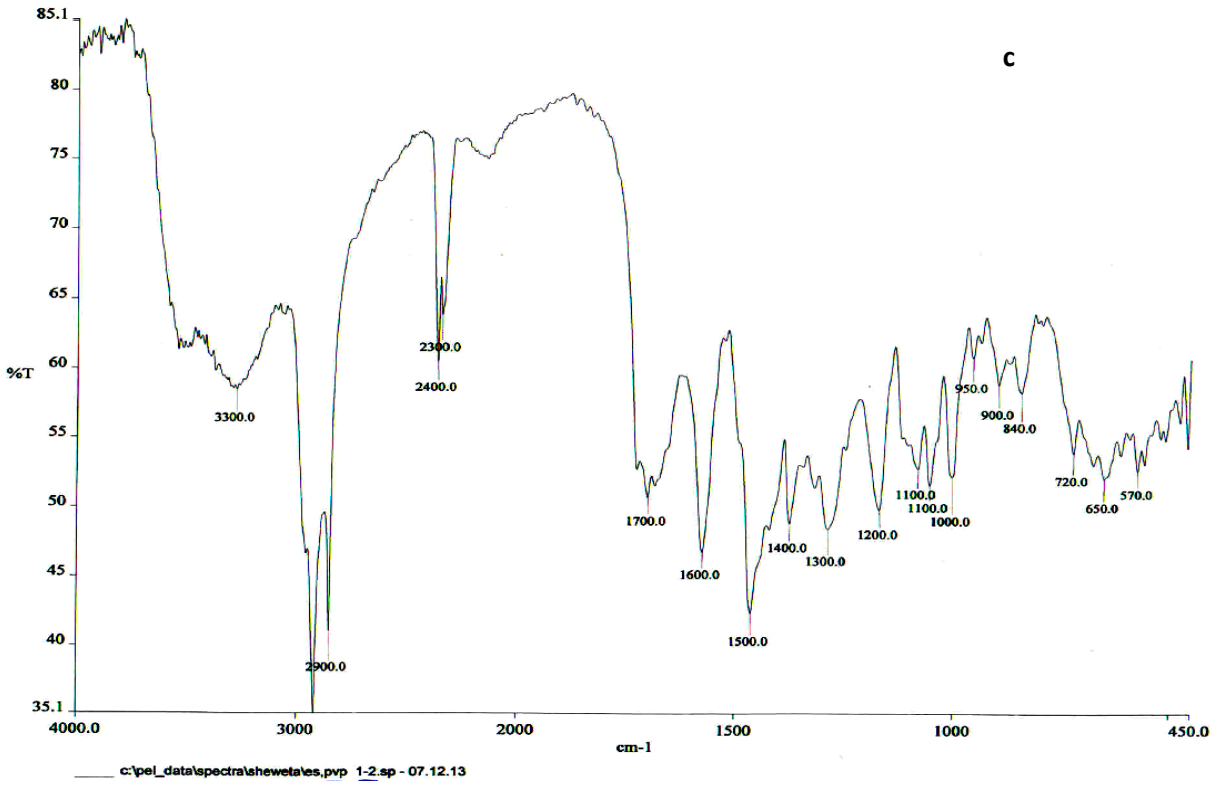


Figure 3.5: FTIR Spectra of a) PVP K30, b) physical micture of Erythromycin Stearate - PVP K30 (1:1) and c) Solid Dispersion of Erythromycin Stearate - PVP (1:2)

The FT-IR spectrum of the SD and the physical mixtures showed the characteristic peaks of ES without any shift. The FT-IR spectrum of the SD also showed most of the characteristic peaks of the corresponding polymer. Apart from these no additional peaks were observed and any characteristic peaks of solid dispersion were not changed when those were compared with pure drug. Hence, from the FTIR spectra and Table 3.1 it can be concluded that no chemical interaction occurred between the drug and the polymers. However, the results of the FTIR were confirmed using DSC thermogram.

Table 3.1: FTIR study of Erythromycin stearate and solid dispersion at a ratio of 1:2

ES	PEG 6000 + ES (1:2)	PEG 4000 + ES (1:2)	PVP K30 + ES (1:2)	Vibrations
3300	3300	3300	3300	O-H Stretching
2900	2900	2900	2900	CH_3, CH_2 Stretching
1700	1700	1700	1700	C=O Stretching
1500	1500	1500	1500	C-C Stretching
1400	1400	1400	1400	$N(CH_3)_2$ Stretching
1300	1300	1300	1300	O-H Stretching
1200	1200	1200	-	C-O Stretching
1000	1000	1000	1000	C-N Stretching

3.3.2. Differential Scanning Calorimeter

When a material is heated or cooled, there is a change in its structure (e.g. melting or crystallization), or its composition (e.g. oxidation). These changes are connected with heat exchange. Some of these changes are endothermic (i.e. heat consuming process such as melting), and others are exothermic (i.e. heat producing process such as crystallization). DSC is used extensively in pharmaceutical industry to determine the melting points, purity, and glass transition temperatures of materials. In the solid dispersion area, DSC is a powerful tool in evaluating the drug-carrier interactions, determining the solubility of a drug in a polymeric carrier, detecting polymorphic modifications and examining age-induced changes. The absence of the drug melting peak in the DSC thermal profile of a solid dispersion indicates that the drug is dispersed molecularly, or it exists in the amorphous form (Dhalli., 2007). The thermal behavior of Erythromycin stearate alone, the physical mixtures and solid dispersion are shown in Figure 3.6.

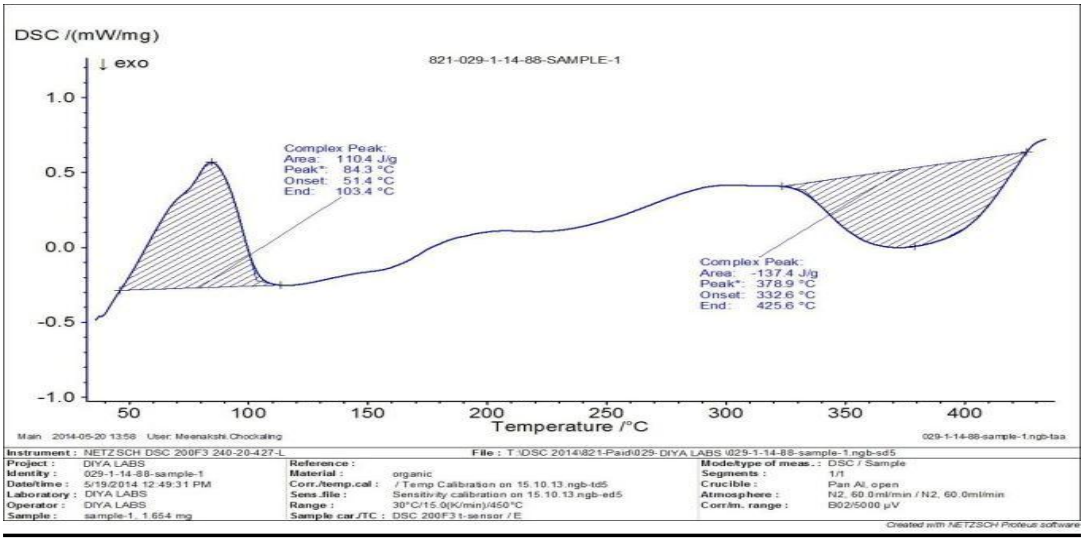
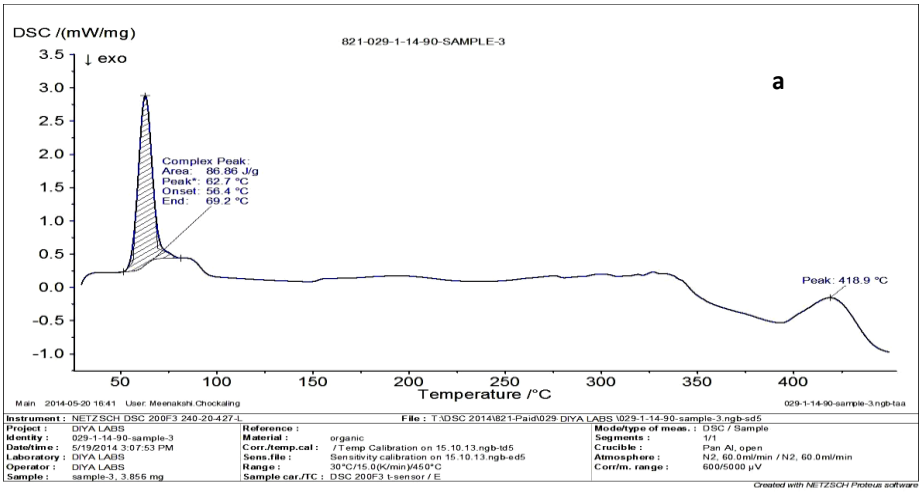


Figure 3.6: DSC thermogram of pure erythromycin stearate

The thermal curve of erythromycin stearate showed an endothermic peak at 84.3°C, corresponding to the melting point of the drug, followed by an exothermic peak at 378.9°C attributable to its thermal decomposition.

Figure 3.7 a, b and c shows the DSC thermogram of the carrier, physical mixture and solid dispersion respectively of the ES and PEG 4000 at 1:1 ratio. The carrier showed endothermic peak at 62.7 °C. In case of physical mixture the endothermic peak was observed at 62.9°C, corresponding to the peak of the carrier. However another small peak was also observed near about at 80°C corresponding to the peak of ES. However, in case of SD it shows sharp peak at 65.2°C corresponding to the peak of the carrier showing the solid dispersion is converted completely into amorphous form.



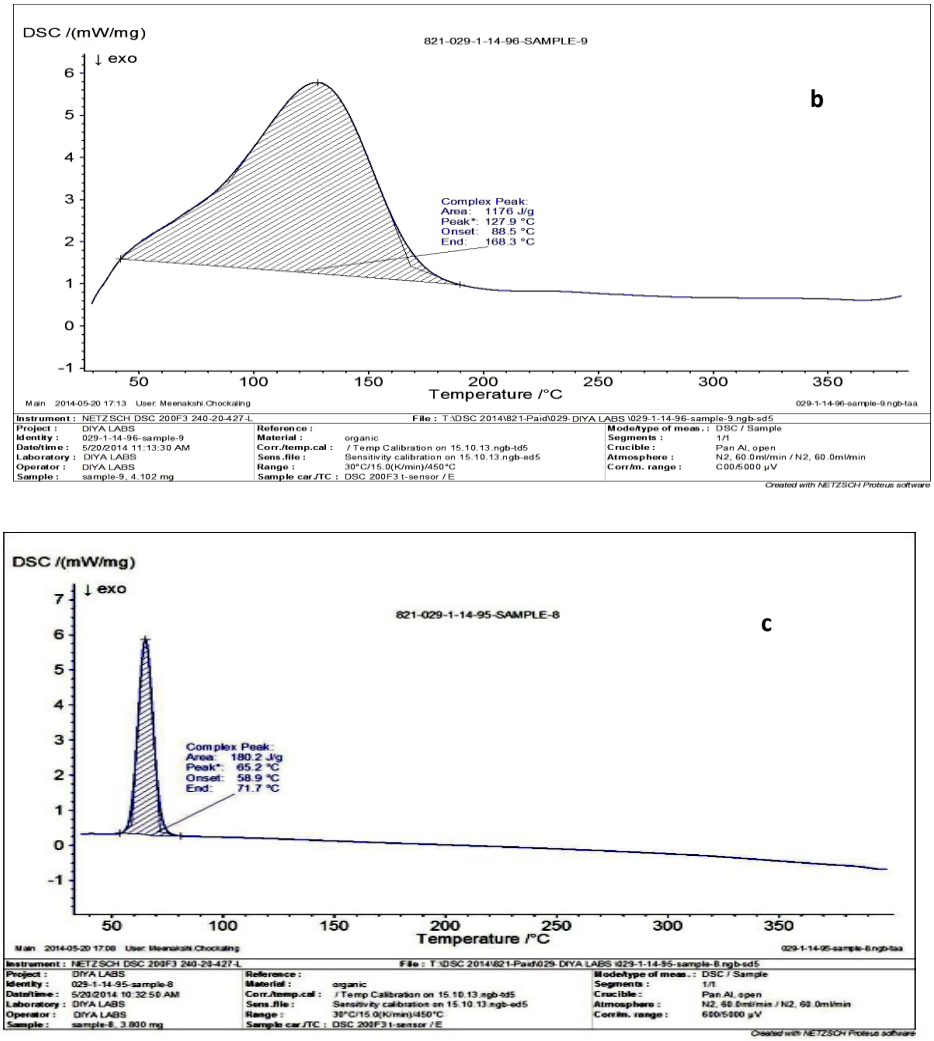


Figure 3.7: a) PEG 4000, b) physical mixture of ES:PEG 4000 (1:1) c) DSC thermogram of 1:1 SD of ES:PEG 4000

Figure 3.8 a, b and c shows the DSC thermogram of carrier, physical mixture and solid dispersion respectively of ES and PEG 6000 at 1:1 ratio. The carrier showed endothermic peak at 63.6 °C. The physical mixture showed peak at 69.2°C however, broadening of peak is observed indicating the drug is in crystalline form. However a sharp peak was observed in the SD of ES and PEG 6000 at 64.3°C corresponding to the peak of the carrier showing the solid dispersion is converted into amorphous form.

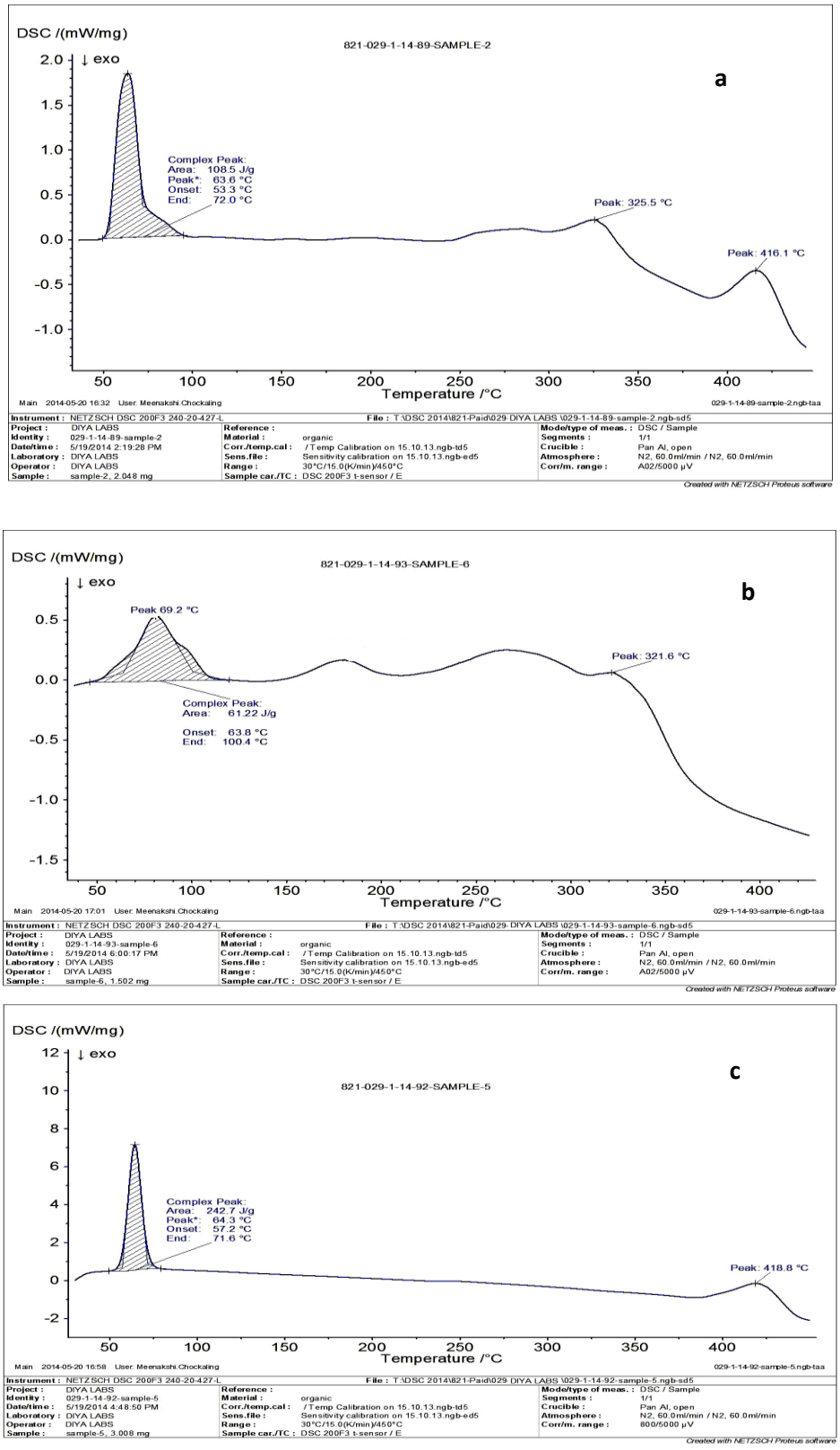
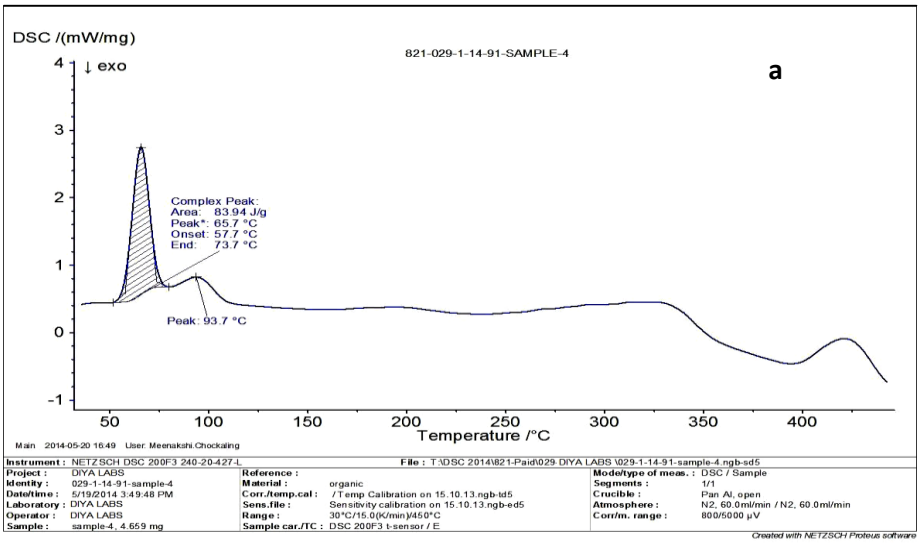
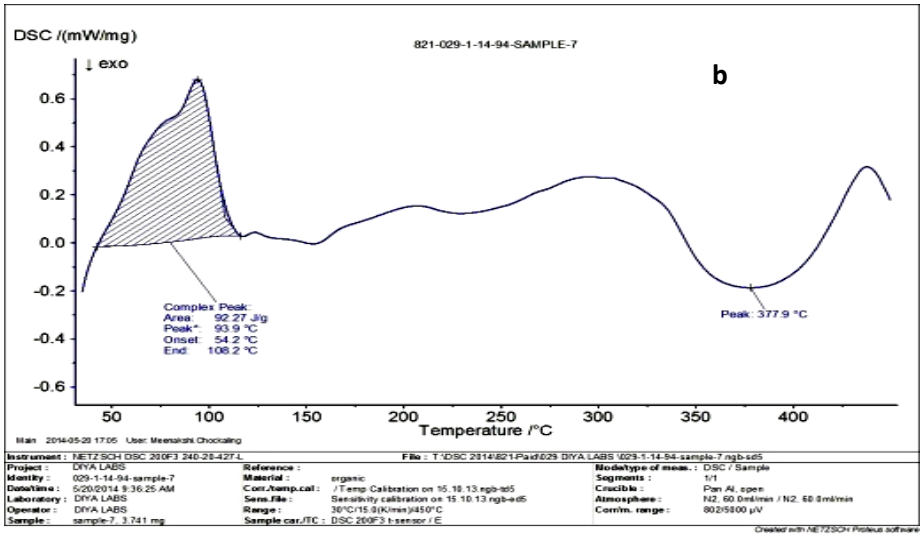


Figure 3.8: DSC thermogram of a) PEG 6000, b) physical mixture of ES:PEG 6000 (1:1) c) DSC thermogram of 1:1 SD of ES:PEG 6000

Figure 3.9 a, b and c shows the DSC thermogram of carrier, physical mixture and solid dispersion respectively of ES and PVP K30 at 1:1 ratio. The DSC thermogram of the carrier showed peaks at 65.7°C and 93.7°C. The physical mixture showed broadening of the peak indicating the crystallinity of the drug. However a sharp peak was observed in the SD of ES and PVP K30 at 65.7°C corresponding to the peak of the carrier showing the solid dispersion is converted completely into amorphous form.





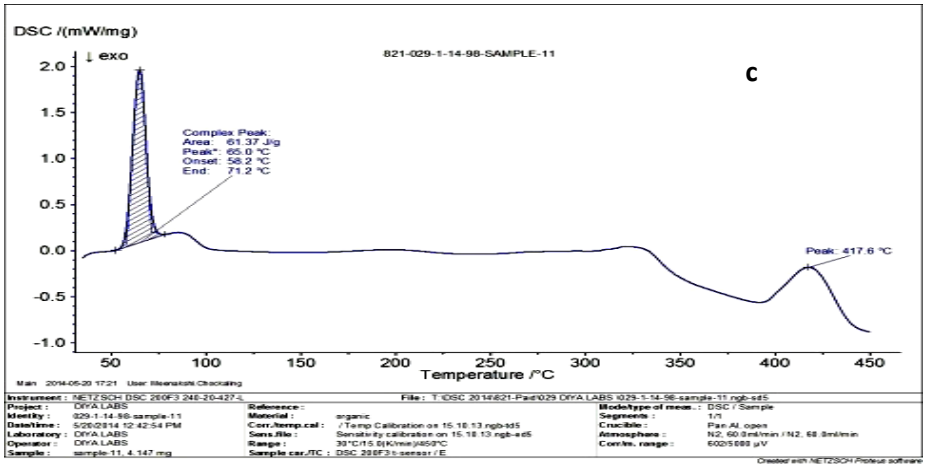


Figure 3.9: DSC thermogram of a) PVP K30, b) physical mixture of ES:PVP K30 (1:1) c) DSC thermogram of 1:1 SD of ES:PVP K30

The DSC thermograms of SDs showed no peak related to ES. Thus, all the prepared solid dispersion changed in the crystallinity of the drug and the drug was dispersed at the molecular level within the polymer and the extent of conversion to the amorphous form varies, and XRD studies were carried out to confirm the result. These indicate that ES may have been converted into amorphous form. XRD studies will help in confirming the results suggested by the DSC studies.

3.4. Physicochemical Characterization of Solid Dispersion

3.4.1. Flow and Flow Related Properties

The flow and flow related properties of prepared SDs are shown in Table 3.1. As can be seen in the table 3.2 the bulk density of the prepared SDs lie within the range of 0.40 ± 0.012 to 0.53 ± 0.020 g/cm^3 and the tapped density was between 0.50 ± 0.011 to 0.66 ± 0.022 g/cm^3. Besides all the solid dispersion formulations had Hausner's ratio is less than 1.25 indicating good flow. The compressibility index was in an acceptable range of 10 ± 0.023 to 16.67 ± 0.016. The results for angle of repose were found in the range of 21.31° to 30.55°, p-value <0.05 indicating good flowability. However, in the physical mixture the angle of repose was in the range of 29.09 ± 1.10 to 32.35 ± 0.63, the carr's index was in range of 15.15 ± 0.011 to 24.64 and hausner ratio was in range of 1.16 ± 0.13 to 1.33 ± 0.14. Thus, indicating some of the formulations of physical mixture showed good flow however, other showed poor flowability.

Table 3.2: Flow properties of erythromycin stearate solid dispersions and physical mixtures in different ratios

Formulation	Angle of Repose (in degree) ± SD	Bulk Density g/cm^3± SD	Tapped Density g/cm^3± SD	Carr's Index (%) ± SD	Hausner Ratio ± SD
PEG6-f21	30.45 ± 4.64	0.52 ± 0.019	0.61 ± 0.022	14.75 ± 0.010	1.17 ± 0.021
PEG6-f11	27.15 ± 2.04	0.45 ± 0.021	0.50 ± 0.010	10.00 ± 0.023	1.11 ± 0.013
PEG6-f12	23.25 ± 2.12	0.42 ± 0.009	0.49 ± 0.013	14.29 ± 0.020	1.17 ± 0.015
PEG6-s21	29.68 ± 0.43	0.46 ± 0.015	0.52 ± 0.009	11.54 ± 0.012	1.13 ± 0.024
PEG6-s11	26.09 ± 1.66	0.44 ± 0.016	0.51 ± 0.017	13.73 ± 0.013	1.16 ± 0.019
PEG6-s12	24.37 ± 1.51	0.47 ± 0.015	0.53 ± 0.005	11.32 ± 0.017	1.13 ± 0.022
PEG4-f21	30.28 ± 4.44	0.42 ± 0.013	0.51 ± 0.015	15.65 ± 0.021	1.21 ± 0.010
PEG4-f11	24.84 ±1.80	0.45 ± 0.020	0.53 ± 0.006	15.09 ± 0.02	1.18 ± 0.017
PEG4-f12	22.94 ± 1.22	0.44 ± 0.020	0.52 ± 0.018	15.38 ± 0.019	1.18 ± 0.012
PEG4-s21	28.81 ± 0.76	0.49 ± 0.016	0.58 ± 0.013	15.52 ± 0.011	1.18 ± 0.026
PEG4-s11	24.52 ± 2.22	0.44 ± 0.024	0.52 ± 0.011	15.38 ± 0.022	1.18± 0.011
PEG4-s21	21.59 ± 3.05	0.47 ± 0.015	0.54 ± 0.010	12.96 ± 0.016	1.15 ± 0.023
PVP-s21	30.55 ±4.41	0.50 ± 0.022	0.58 ± 0.012	13.79 ± 0.021	1.16 ± 0.014
PVP-s11	29.20 ± 2.79	0.45 ± 0.023	0.51 ± 0.015	11.76± 0.014	1.13± 0.021
PVP-s12	26.41 ± 0.53	0.42 ± 0.021	0.48 ± 0.024	12.50 ± 0.011	1.14± 0.017
PVP-k21	29.65 ± 1.99	0.53 ± 0.020	0.60 ± 0.020	11.67± 0.018	1.13± 0.029
PVP-k11	29.02 ± 3.57	0.46 ± 0.018	0.55 ± 0.016	16.36± 0.020	1.20± 0.021
PVP-k12	25.16 ±1.61	0.40 ± 0.012	0.48 ± 0.018	16.67± 0.016	1.20± 0.018
PM4-21	31.38 ± 0.73	0.54 ± 0.025	0.67 ± 0.047	19.46 ± 0.014	1.24 ± 0.011
PM411	29.68 ± 0.87	0.54 ± 0.029	0.64 ± 0.003	17.19 ± 0.018	1.21 ± 0.17
PM412	30.72 ± 2.71	0.56 ± 0.030	0.66 ± 0.034	15.15 ± 0.011	1.18 ± 0.10
PM6-21	28.20 ± 1.70	0.53 ± 0.011	0.66 ± 0.043	19.70 ± 0.016	1.25 ± 0.18
PM611	32.35 ± 0.63	0.55 ± 0.013	0.67 ± 0.031	17.91 ± 0.013	1.22 ± 0.20
PM612	29.09 ± 1.10	0.52 ± 0.012	0.69 ± 0.016	24.64 ± 0.021	1.33 ± 0.14
PMpvp-21	30.65 ± 2.33	0.55 ± 0.015	0.68 ± 0.031	19.12 ± 0.014	1.24 ± 0.19
PMpvp-11	31.92 ± 1.58	0.57 ± 0.028	0.66 ± 0.010	13.63 ± 0.020	1.16 ± 0.13
PMpvp-12	31.90 ± 1.86	0.51 ± 0.26	0.63 ± 0.045	19.05 ± 0.012	1.24 ± 0.15

3.5. Practical Yield and Drug Content Analysis

The practical yield and drug content of the SDs is given in Table 3.3. The practical yield for all the SDs was found to be between 84.69 to 98.44%. The results showed that solid dispersion prepared by fusion method gave better practical yield. Likewise, the drug content in various ES solid dispersions ranged from 86.93% to 100.69%. The solid dispersion prepared by kneading method gave low drug content. The drug content of SDs prepared by fusion method and solvent evaporation method was above 90%.

Table 3.3: Practical yield and drug content analysis of solid dispersion formulations

Sr. No.	Formulation	Practical Yield (%)	% Drug Content
1.	PEG6-f21	96.65 ± 0.82	96.46
2.	PEG6-f11	96.75 ± 1.49	97.52
3.	PEG6-f12	96.42 ± 1.88	100.69
4.	PEG6-s21	91.00 ± 1.25	92.75
5.	PEG6-s11	90.94 ± 1.70	96.99
6.	PEG6-s12	90.06 ± 1.69	99.64
7.	PEG4-f21	96.92 ± 1.76	93.69
8.	PEG4-f11	96.46 ± 1.31	94.28
9.	PEG4-f12	96.21 ± 0.79	97.93
10.	PEG4-s21	90.63 ± 1.21	90.11
11.	PEG4-s11	90.10 ± 1.17	91.16
12.	PEG4-s21	90.15 ± 1.71	98.58
13.	PVP-s21	89.85 ± 1.79	89.05
14.	PVP-s11	90.81 ± 1.86	91.69
15.	PVP-s12	89.90 ± 1.17	99.11
16.	PVP-k21	85.17 ± 2.06	86.93
17.	PVP-k11	84.69 ± 1.22	88.52
18.	PVP-k12	89.10 ± 1.69	96.46

3.6. Investigation of the Solubility of ES from SDs and Physical mixtures

The results of the solubility of ES from various selected SDs and a physical mixture is shown in Table 3.4. As can be seen, although formation of physical mixture increases solubility, the solubility of ES from SDs was by far better than its solubility from physical mixtures. The increase in solubility can be attributed to the hydrophilic nature of the polymers, decreased agglomeration and aggregation of ES particles and particle size reduction of ES particles. Moreover, in line with dissolution study, among various ES SDs prepared and investigated SDs prepared by fusion method showed better solubility than the solid dispersion prepared by solvent evaporation and kneading methods.

Table 3.4: solubility of ES, physical mixtures and SDs in distilled water

Sr.No.	Media	(Solubility ± SD) (mg/ml)
1.	Pure ES	0.085 ± 0.025
2.	PM ES:PEG 4000 (1:2)	0.460 ± 0.040
3.	PM ES: PEG 6000 (1:2)	0.394 ± 0.047
4.	PM ES: PVP K30 (1:2)	0.490 ± 0.030
5.	PEG6-f12	2.614 ± 0.025
6.	PEG4-f12	2.048 ± 0.015
7.	PEG6-s12	1.680 ± 0.037
8.	PEG4-s12	1.653 ± 0.025
9.	PVP-s12	1.759 ± 0.019

3.7. Preparation and Evaluation of Capsules

The SD formulation equivalent to 250mg of erythromycin stearate was filled into hard gelatin capsule. The mass uniformity of formulation was found to be in between 599.7 ± 0.09 mg to 606.6 ± 0.06 mg, the disintegration time of gelatin capsules prepared with different SDs was in the range of 4.41 to 4.80 minutes.

3.8. *In-vitro* Dissolution Study

3.8.1. Dissolution Profile of SDs Prepared by Fusion Method

The dissolution profile of SDs prepared by fusion method is shown in Figure 3.10 and 3.11. As can be seen in the figures, the dissolution of ES from the solid dispersion was significantly great-

er than that of pure ES. The increase in the dissolution kinetics of erythromycin stearate from polyethylene glycol solid dispersion may be due to the reduction of particle size, absence of aggregation of drug crystals, conversion of the drug from crystalline to amorphous state and improvement in the wettability of the ES thus reducing the hydrophobicity of their surfaces. This explains the improvement in the dissolution of solid dispersion. Solid dispersion with PEG 6000 showed greater dissolution rate than PEG 4000. These might be due to increase in molecular weight there by increasing in the viscosity and hindering the precipitation of the drug and dissolution of the drug (Shahroodi et.al., 2007).

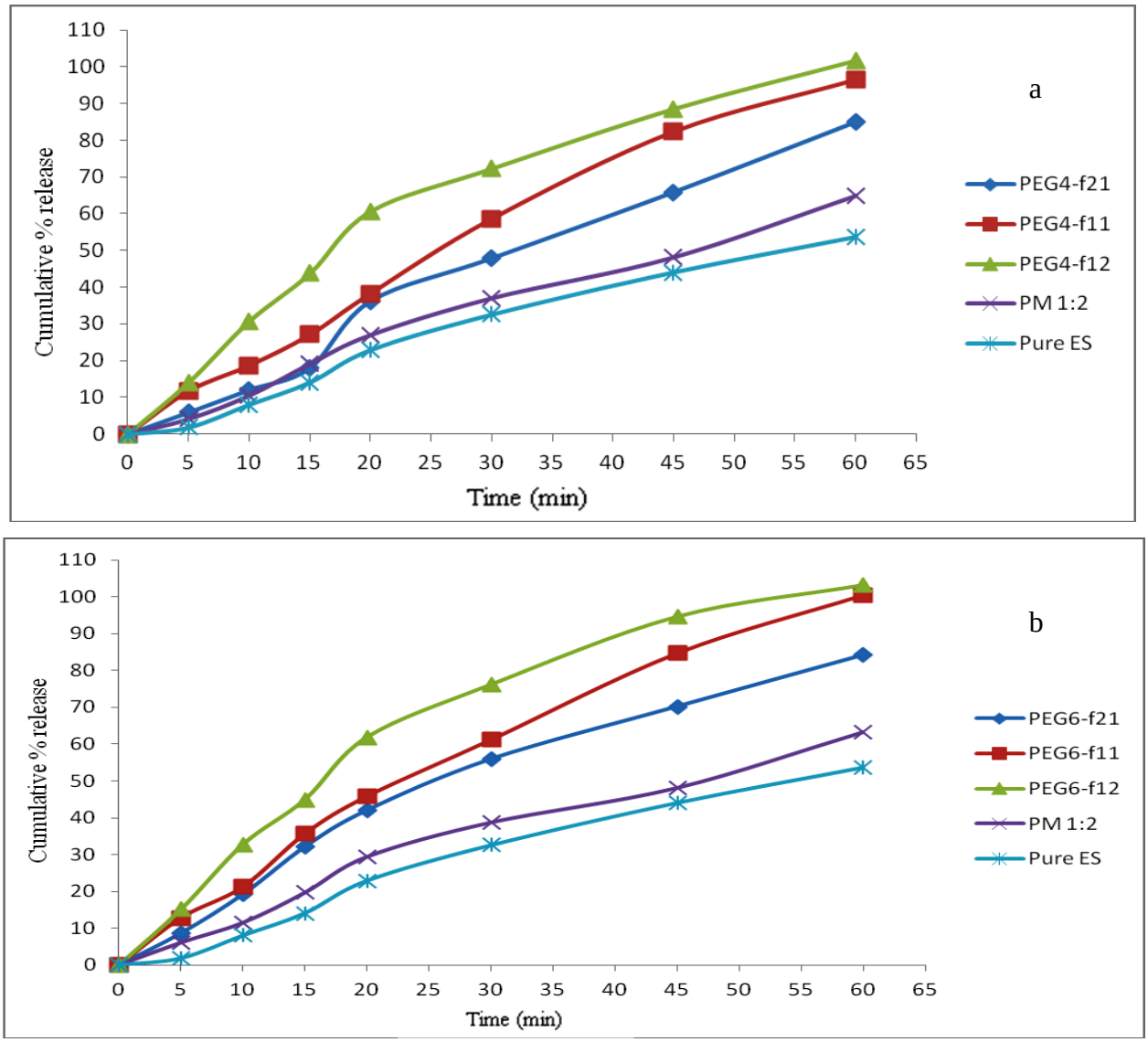
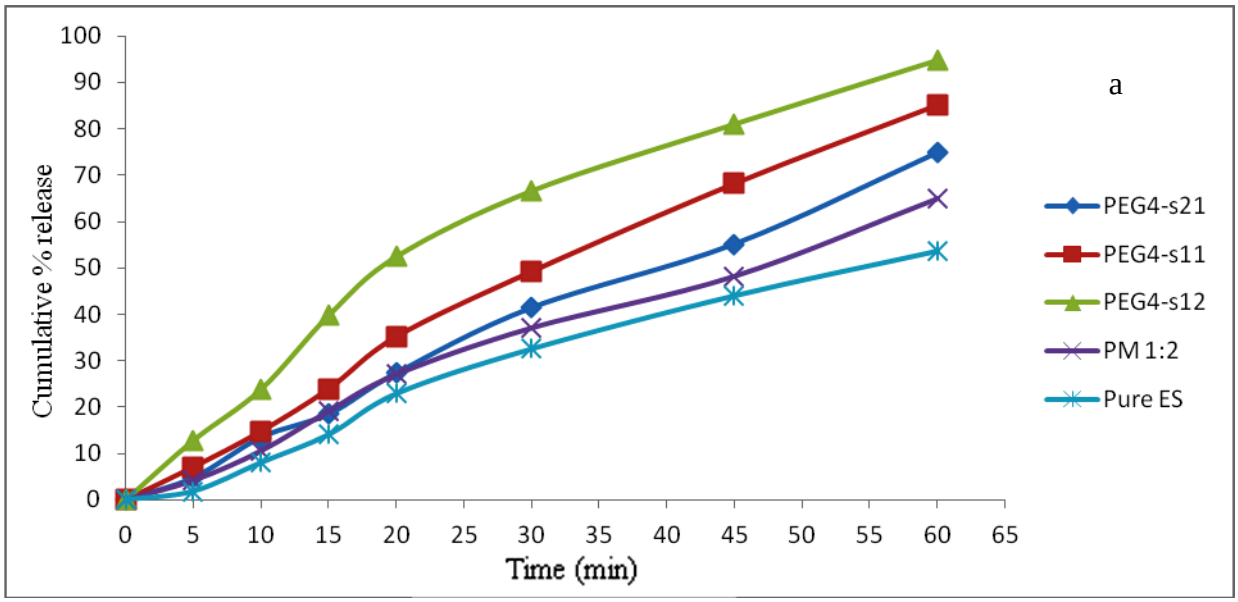
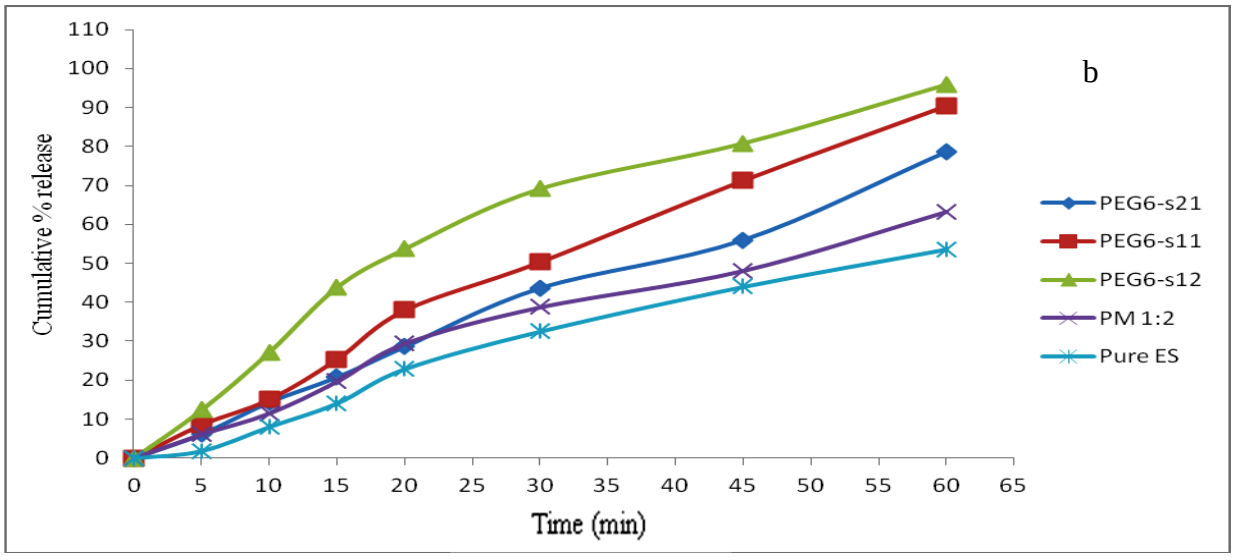


Figure 3.10: Comparative dissolution profile of SDs of ES prepared by fusion method using in acetate buffer at pH 5.0 a) PEG4000 b) PEG 6000

3.8.2. Dissolution Profiles of SDs Prepared by Solvent Evaporation Method

The dissolution profile of the SDs prepared by solvent evaporation method is shown in Figs.3.12 to 3.14. Like the case of the fusion method, SDs prepared by solvent evaporation method showed significantly enhanced dissolution rate. Besides, dissolution rate increased with an increase in polymer concentration. Better results for dissolution profile were seen with PVP K30 than PEG 4000 or PEG 6000. These might be due to increased wettability, and as the Tg temperature of PVP K30 is high (156°C), thereby increases the stability of the drug (Khatry, et al., 2013; Nikghalb, et al., 2012).





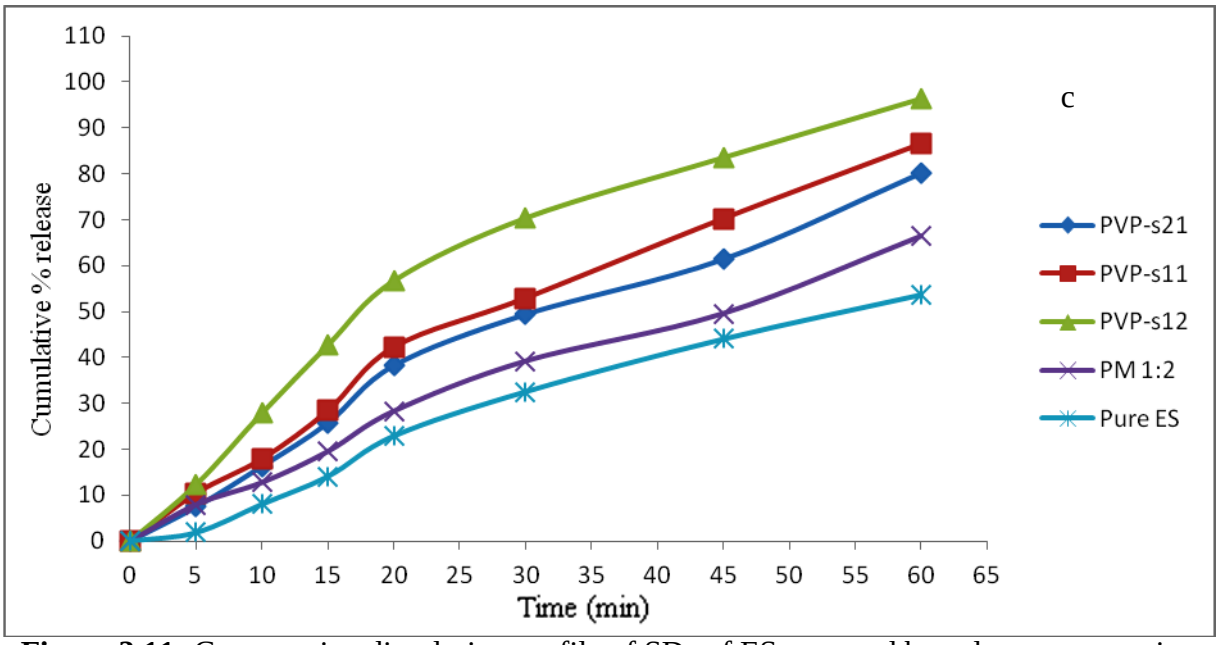
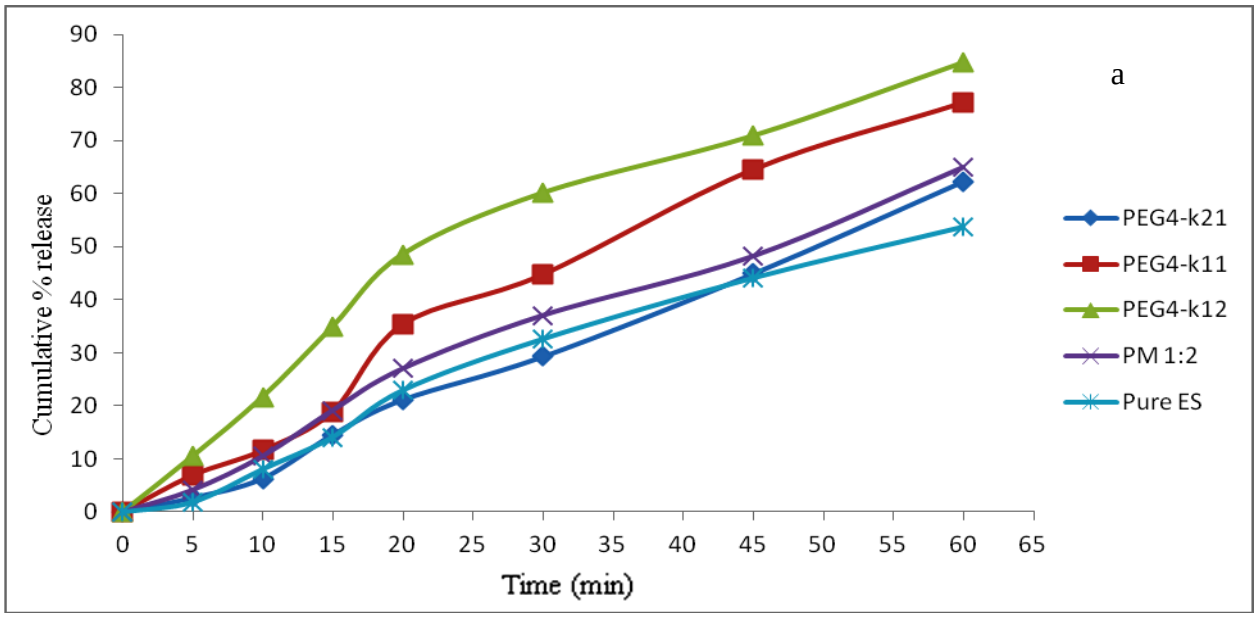
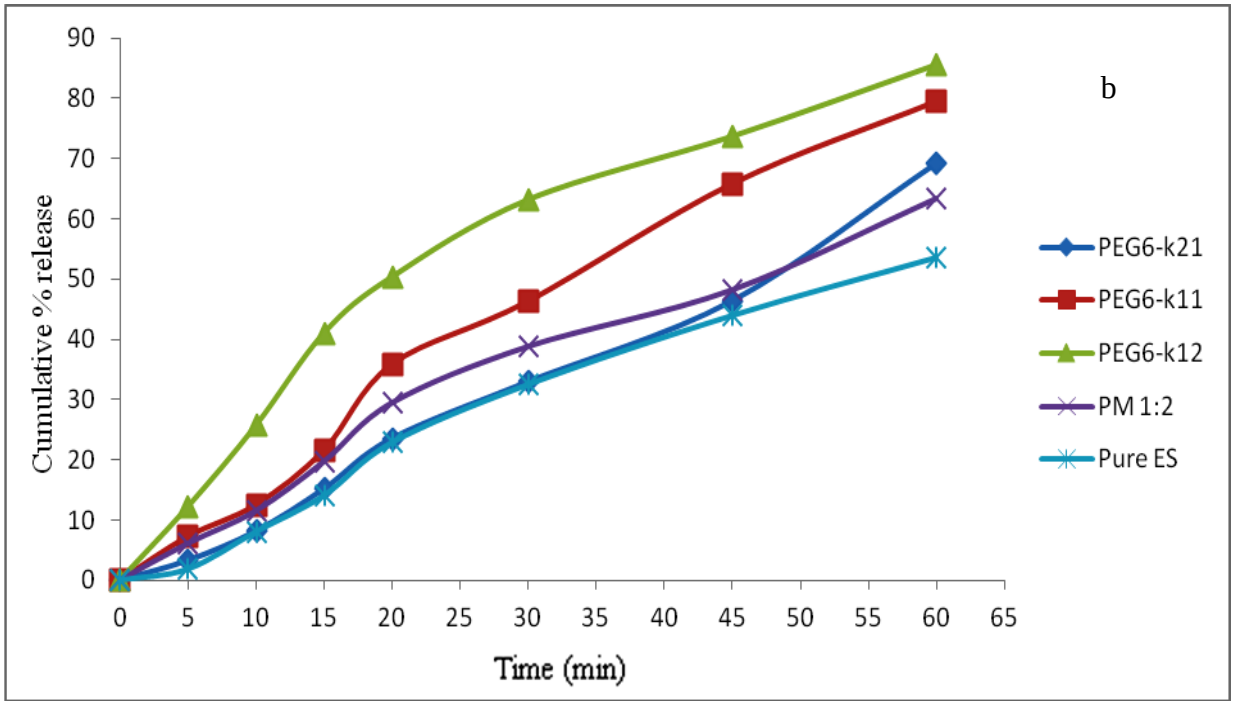


Figure 3.11: Comparative dissolution profile of SDs of ES prepared by solvent evaporation method acetate buffer at pH 5.0 using a) PEG 4000 b) PEG 6000 and c) PVP K30

3.8.3. Dissolution Profiles of SDs Prepared by Kneading Method

The dissolution profile of SDs prepared by kneading method is given in Figure 3.15 to 3.17. As can be seen from the figures, at higher concentration of the polymers, like the case of the fusion and solvent evaporation methods formation of solid dispersion enhanced dissolution of ES and, hence better dissolution rate was obtained at higher concentration of the polymer. However, at drug to polymer ratio of 2:1 no significant improvement of dissolution was observed. Unlike the fusion and solvent evaporation method solid dispersions prepared by kneading method showed the release of the drug was less than 80% within 45 minutes which showed no promising result in accordance to BP (British Pharmacopeia, 2009).


a
Cumulative % release
Time (min)
PEG4-k21
PEG4-k11
PEG4-k12
PM 1:2
Pure ES


b
Cumulative % release
Time (min)
PEG6-k21
PEG6-k11
PEG6-k12
PM 1:2
Pure ES

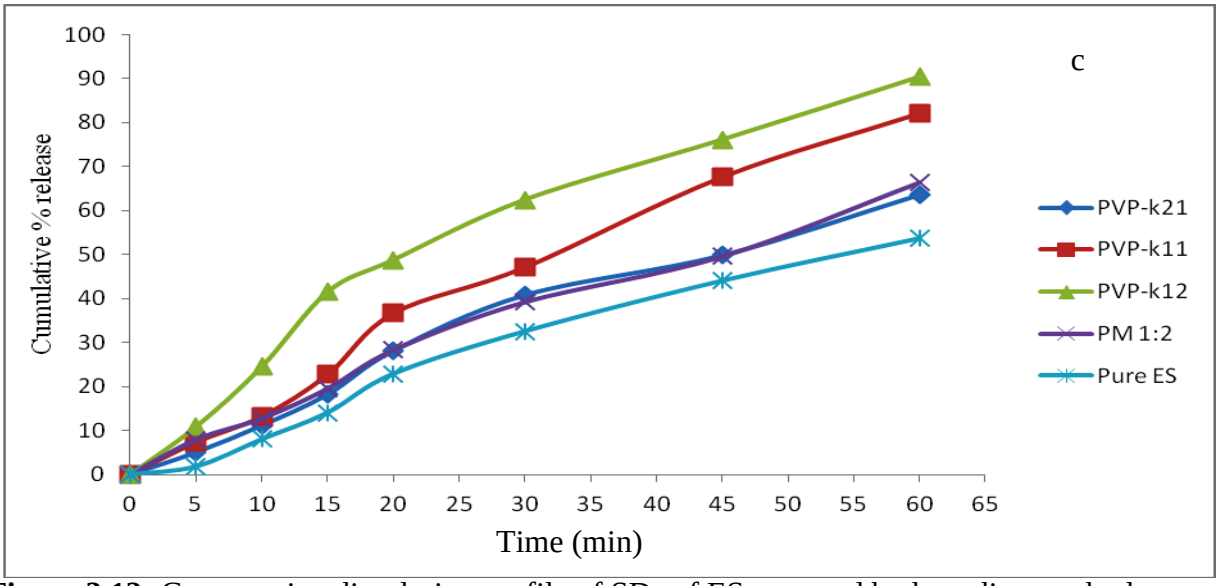


Figure 3.12: Comparative dissolution profile of SDs of ES prepared by kneading method acetate buffer at pH 5.0 using a) PEG 4000, b) PEG 6000 and c PVP K30

Generally observing, SDs prepared by fusion method showed better results than SDs prepared by solvent evaporation method and kneading method. The highest improvement in solubility and *in vitro* drug release was observed in SDs prepared with PEG 6000 by fusion method these maybe because as the molecular weight increases the dissolution rate also increased. From the study it the higher dissolution was observed using fusion method > solvent evaporation method > kneading method. From the studies fusion method was preferred over solvent evaporation because the chance of residual solvent may lead to faster crystallization (Calahan., 2011). The solubility and *in vitro* drug release from the physical mixture, when compared to that of solid dispersion, was improved to a lesser degree (Rakesh et al., 2008).

Studies have also shown the drug to carrier ratio in SDs is one of the main factors on the performance of a SD. If the percentage of drug is too high, it forms small crystal within the solid dispersion rather than remaining molecularly dispersed. On the other hand, if the percentage is too low, this can lead to complete absence of crystallinity of the drug thereby enormous increase in the solubility and the release rate(Shahroodi., 2007).

3.8.4. Comparison of the Dissolution Profile of the Formulated SDs with Marketed Product

The dissolution profile of ES from Erysin 250, an ES containing marketed product, and three selected SDs i.e. PEG4-f12, PEG6-f12, PVP-s12, which showed superior dissolution profiles, along with the release of pure ES is shown in Figure 3.18. As can be seen in the figure, two of the formulated products exhibited better dissolution than the marketed product while PVP-s12 showed comparable dissolution profile.

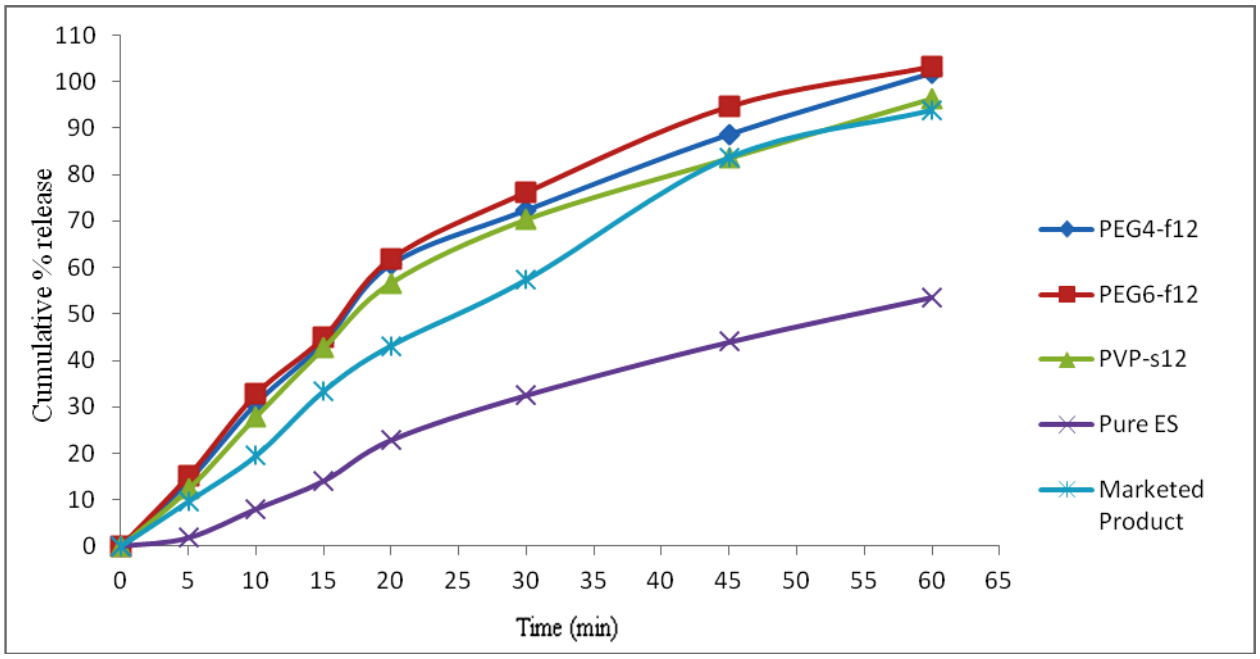


Figure 3.13: Comparison of the dissolution profile of Erysin 250 with the dissolution profiles of the formulated SDs in acetate buffer at pH 5.0

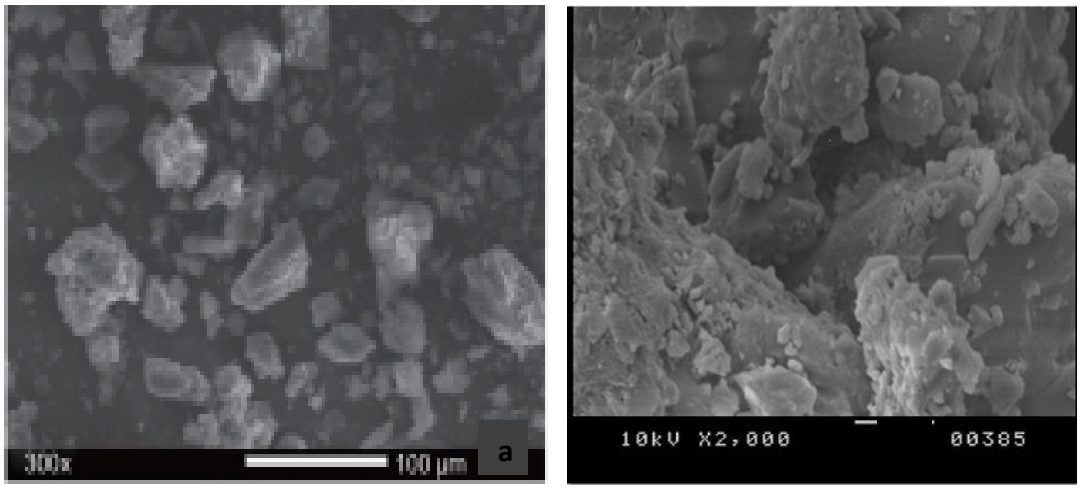
Further quantitative comparison of the dissolution profiles of the above formulations, along with other SDs, was also made to demonstrate comparison of release with the marketed product, using Food and Drug Administration (FDA) recommended dissimilarity factor (*f1*) Eq. 8 and similarity factor (*f2*) Eq. 9. Accordingly, the *f1* and *f2* factors of selected SDs were calculated. Table 3.5 results showed that the selected formulations, although showing better release profiles, can be considered equivalent to the marketed capsule Erysin 250 mg.

Table 3.5: Dissimilarity (f1) and Similarity (f2) factors values of selected SD formulation compared with Marketed Capsule

S.No.	Comparison	f_1	f_2	Dissolution Profile
1.	PEG4-S21	29.33	40.77	Dissimilar
2.	PEG4-S21	11.39	60.47	Similar
3.	PEG6-F11	8.66	65.18	Similar
4.	PEG6-K21	43.90	32.02	Dissimilar
5.	PVP-S12	14.75	54.44	Similar
6.	PVP-K21	34.92	36.46	Dissimilar
7.	PEG4-F12	12.62	59.46	Similar
8	PEG6-F12	11.73	62.77	Similar

3.9. Scanning Electron Microscopy

The Scanning Electron Microscopy (SEM) images of ES and SDs are shown in Figure 3.19. As can be seen in figure pure ES particles appeared as dense particles which are irregular in shape. The SDs showed the drug is homogenously dispersed in the carriers. Nonetheless the SDs prepared by fusion method and solvent evaporation methods, appeared to be fluffy, which might be associated with the formation of an amorphous solid dispersion state.



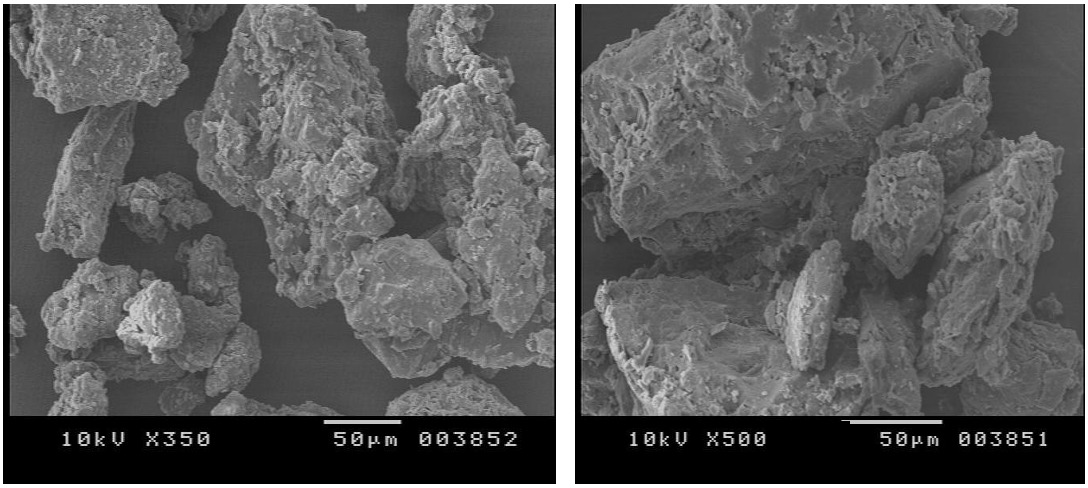


Figure 3.14: a) SEM image of ES, b) SEM image of PEG4-f12, c) SEM image of PEG6-f12, d) SEM image of PVP-s12

3.10. X-Ray Diffraction

The XRD pattern of ES alone and the solid dispersions prepared using fusion method and solvent evaporation method at 1:2 drug to polymer ratio is shown in Figure 3.20. In the diffractrogram for some characteristic peak in 2θ (angle of diffraction) such as 12.39; 16.93; 18.23; 19.87; 21.42; 26.85; 29.37; 33.90; 37.86;44.08; 64.43; 77.54 are present revealing the crystalline nature of erythromycin stearate. The diffraction peak at 2θ =19.87 was used as a point of reference to determine the (degree of relative Crystallinity) DRC.

In SD of PEG4-f12 and PEG6-f12 the diffractrogram showed characteristic peak at 2θ such as 18.02; 23.13 and 18.54; 23.21 respectively this revealed that the solid dispersion did not recrystallize during the preparation of solid dispersion. In case of SDs, particularly in the case of PEG 4000 and PEG 6000, the intensities of the characteristic crystalline peak decreased considerably indicating that high proportion of the drug was dissolved in the solid state carrier matrix in an amorphous structure.

In SD of PVP-s12 the diffractrogram characteristic peak in 2θ such as 18.24; 23.72; 37.85; 42.58 which revealed that the solid dispersions was partially converted into amorphous form in case of solid dispersion subsequent to the evaporation of the solvent (Hitendra S. Mahajan, Ghanashyam A. Girnar et al. 2012).

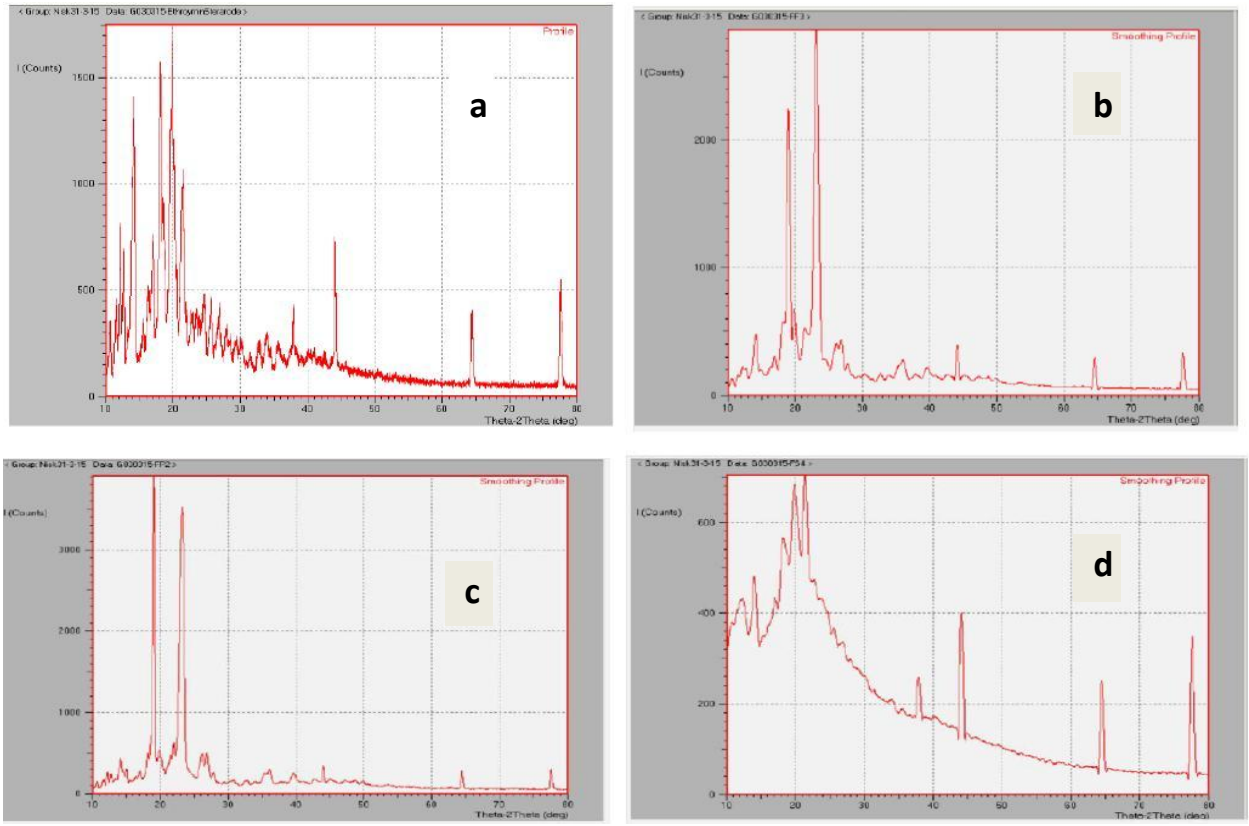


Figure 3.15 (a) XRD of ES; (b) XRD of ES: PEG 4000; (c) XRD of ES: PEG 6000 and (d) XRD of ES: PVP K30

Hence this study confirmed that ES was converted in amorphous state in the solid dispersion prepared by PEG 4000 and PEG 6000. However, solid dispersion with PVP K30 showed the reduction in the number and intensities of the peak which confirms partial conversion of crystalline form to amorphous form.

3.11. Release Kinetics

The *in vitro* drug release data from the capsules of different formulation were evaluated for their release kinetics by fitting them into four mathematical models like zero order, first order, Higuchi, and Hixson-Crowell for understanding their release kinetics from the formulated solid dispersion. The drug release pattern of all the formulation did not fit satisfactorily to zero order, first order, and Hixson-Crowell models but showed good fit to the Higuchi with r^2 values between 0.9778 – 0.9994.

Table 3.6: The correlation coefficients and rate constants of the ES release data from the SDs fitted into various kinetic models.

S. No	Formula-tion	Zero order		First order		Hickson Crow-ell		Higuchi	
		(R^2)	K_0	(R^2)	K_1	(R^2)	K	(R^2)	K
1.	PEG6-F21	0.9546	1.4079	0.8863	0.0397	0.6762	5.6394	0.9952	13.8588
2.	PEG6-F11	0.9763	1.6793	0.9187	0.0563	0.6875	5.9257	0.9948	16.4902
3.	PEG6-F12	0.9062	1.8111	0.9429	0.0663	0.6039	5.7359	0.9919	17.4186
4.	PEG6-S21	0.9911	1.2761	0.8926	0.0308	0.7493	5.6312	0.9778	12.9228
5.	PEG6-S11	0.9890	1.4984	0.7980	0.0852	0.7400	5.9295	0.9872	15.2503
6.	PEG6-S12	0.9125	1.4297	0.7909	0.0461	0.6215	5.6651	0.9914	15.0042
7.	PEG4-F21	0.9827	1.4609	0.9478	0.0776	0.7727	6.0354	0.9974	14.1940
8.	PEG4-F11	0.9871	1.6555	0.9364	0.0392	0.7254	6.9993	0.9815	16.4726
9.	PEG4-F12	0.9121	1.6634	0.7392	0.0514	0.6124	5.7244	0.9812	15.9426
10.	PEG4-S21	0.9952	1.2466	0.9694	0.0231	0.7637	5.6653	0.9830	12.6441
11.	PEG4-S11	0.9869	1.4285	0.8716	0.0325	0.7438	5.8775	0.9920	14.5798
12.	PEG4-S21	0.9285	1.4519	0.9610	0.0484	0.6396	5.7050	0.9964	15.1604
13.	PVP-S21	0.9663	1.2747	0.9719	0.0402	0.7020	5.5841	0.9904	13.1156
14.	PVP-S11	0.9716	1.3758	0.8541	0.0473	0.6904	5.6558	0.9917	14.1303
15.	PVP-S12	0.9029	1.4511	0.8730	0.0679	0.6213	5.7056	0.9928	15.2694

3.12. Accelerated Stability Study

Formulation of SDs (PEG6-F12, PEG4-F12, PVP-S12) which showed promising results, were further subjected to accelerated stability study at 40°C and 75% RH for 3 months. Observation of the capsules over the three month period showed no change like discoloration or brittleness. The drug content analysis results shown in Table 3.7 revealed that the drug was stable in the SDs. Moreover, the dissolution of ES from SDs over the three month periods was determined, from figures 3.21 to 3.23, no significant change in the release was observed.

Table 3.7: Percent Drug Remaining in the selected SDs analyzed over three months of storage at accelerated stability study conditions of 40°C and 75% RH

Tests		Initial ± SD	After 30 days ± SD	After 60 days ± SD	After 90 days ± SD
Drug Content	PEG6-f12	99.06% ± 0.006	96.44% ± 0.014	96.57% ± 0.014	94.51 ± 0.015
	PEG4-f12	95.44% ± 0.008	95.51% ± 0.015	94.78% ± 0.018	91.97 ± 0.017
	PVP-s12	98.04% ± 0.010	93.92% ± 0.014	93.43% ± 0.012	92.11 ± 0.011

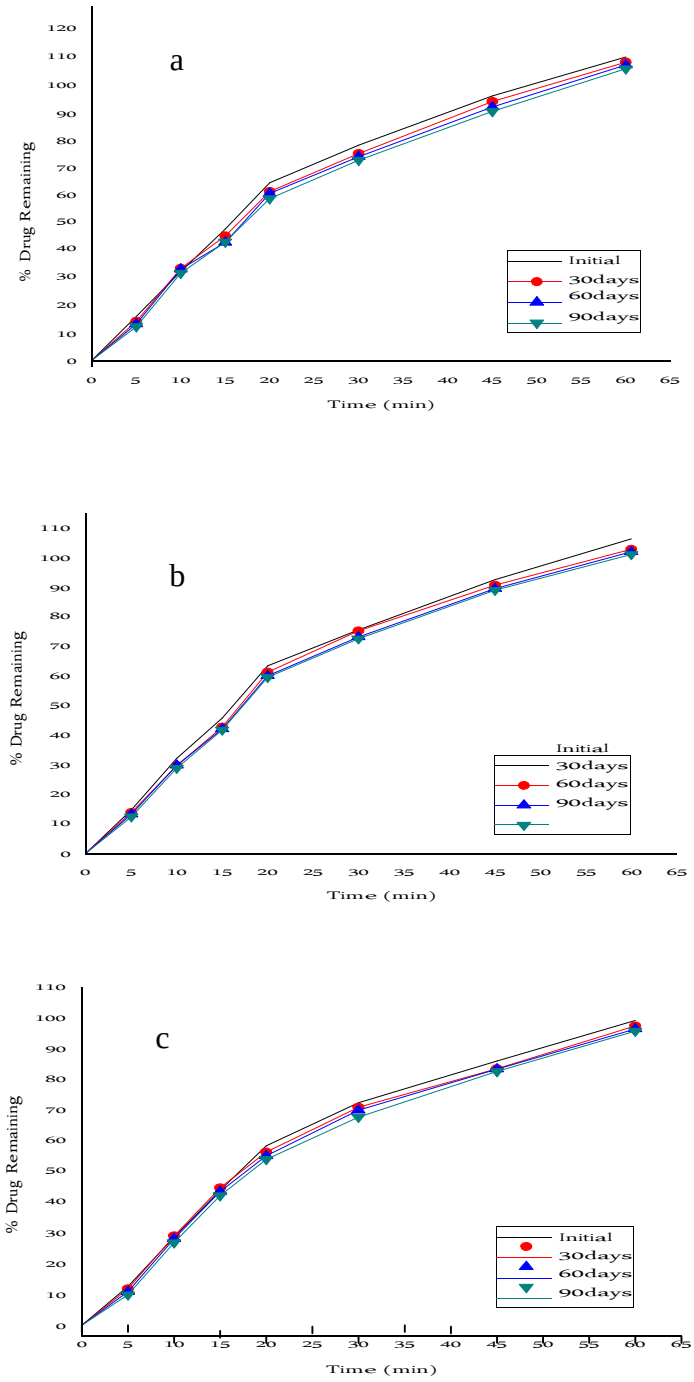


Figure 3.16: Dissolution profile for stability study products a) PEG6-f12, b) PEG4-f12 and c) PVP-s12 kept in stability chamber at temperature 40°C and RH 75%

4. CONCLUSION

Polymer drug interaction studies were conducted using FTIR and DSC techniques and the results showed that solid dispersion of ES with the carriers revealed no difference in the absorption bands, hence showing compatibility which was further confirmed with the DSC. The results of XRD study showed decrease in the crystallinity of erythromycin stearate.

Physicochemical characterization of the formed SDs showed that the formulations are fine, free flowing and easy to prepare. The drug content estimation revealed that the percentage of erythromycin stearate in all the solid dispersion formulations was between 84.69 ± 1.22 and 98.44 ± 0.88.

Dissolution studies were performed for pure drug, physical mixture and solid dispersion. The results of the study showed that as compared to the pure ES, formation of SDs significantly improved the dissolution and release of the drug. This increase in dissolution rate of solid dispersion was attributed to molecular dispersion of the drug. Generally formulations prepared at higher concentration of the polymer exhibited better dissolution profiles. The method of preparation also affected solubility and drug release with the following order Fusion method > Solvent Evaporation method > Kneading method> Physical mixture and > drug.

It was also observed that in case of all the SDs, prepared by fusion method, solvent evaporation method and kneading method containing polymers PEG 4000, PEG 6000 and PVP K30 showed as the polymer ratio increased the dissolution rate also increased. It was also observed PEG 6000 showed better result than PEG 4000 which might be due to increase in the molecular weight in case of PEG 6000.

The release pattern of all the formulations followed Higuchi model which showed r^2 value greater than 0.991.

Three formulations (PEG6-f12, PEG4-f12, PVP-s12) were chosen and were compared with a marketed product, Erysin 250, of which the two (PEG4-f12 and PEG6-f12) showed better release profile and one was comparable.

The results of stability study showed no change in the physical appearance of the capsule or significant change in drug content. Besides, the *in vitro* dissolution profile of ES within the SD remained unchanged over the 3 months, indicating that the formulations are stable over 3 month.

In conclusion, the studies showed that PEG 4000, PEG 6000 and PVP K30 could be used as potential carriers in the dissolution rate enhancement of erythromycin stearate out of which SD prepared with PEG 6000 showed the best results. The solid dispersion with PEG 6000 showed better result than the Erysin 250.

5. Suggestions for Future Work

i) Long term stability study

ii) Scalability

iii) In vivo evaluation of the formulation.

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