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FORMULATION AND EVALUATION OF TABLETS OF BCS CLASS IV DRUG BY ENHANCING SOLUBILITY USING SOLID DISPERSION TECHNIQUE

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ABSTRACT

The poor dissolution characteristics of water insoluble drugs are a major challenge for pharmaceutical science. The objective of this study was to improve solubility, release and comparability of dissolution of a poor soluble drug using solid dispersion two methods. The phenomenon of dissolution of solid phase in liquid phase to obtain a homogenous system is known as solubility. Many drugs, in particular, have poor solubility in water but we also know that water is the chief solvent of choice to be used for liquid pharmaceutical formulations. And thus, this poorly solubility ultimately affects the therapeutic plasma concentrations and also the bioavailability of the drugs. To ameliorate the dissolution of poorly water-soluble drugs as well ultimately ameliorating their bioavailability, the dispersion of one or more active pharmaceutical ingredients in a carrier that too at solid-state is used. This phenomenon is known as Solid dispersion. There are two method use in solubility enhancement Solvent evaporation method and Fusion method with different polymer PEG4000 HPMC with different ratio Solid dispersion of Sulfamethoxazole by solvent evaporation method using HPMC polymer show that increase in solubility and good dissolution as compared to PEG4000. The optimum dissolution was shown by the F5, F10, S5, S9, S10 batches. S10 batch of (solvent evaporation method) 1:5 ratio using HPMC polymer enhance the dissolution rate showing dissolution efficiency comparable to that obtained with F5, F10 batches of fusion method. The study thus presented a system capable of increasing the dissolution rate of Sulfamethoxazole, immediate release formulation is a solution to overcome the variable bioavailability problem of Sulfamethoxazole.

KEYWORD: Solubility; Solid dispersion; dissolution; solubility enhancement.

INTRODUCTION

The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion. From a patient's perspective, swallowing a dosage form is a comfortable and a familiar means of taking medication.[1,2] Although the oral route of administration is preferred, for many drugs it can be a problematic and inefficient mode of delivery for a number of reasons. Limited drug absorption resulting in poor bioavailability is paramount amongst the potential problems that can be encountered when delivering an active agent via the oral route.[3-5] Drug absorption from the gastrointestinal (GI) tract can be limited by a variety of factors with the most significant contributors being poor aqueous solubility and/or poor membrane permeability of the drug molecule. When delivering an active agent orally, it must first dissolve in gastric and/or intestinal fluids before it can then permeate the membranes of the GI tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include.

(i) Enhancing solubility and dissolution rate of poorly water-soluble drugs
(ii) Enhancing permeability of poorly permeable drugs.

So, solid dispersion technologies is used to improve the dissolution characteristics of poorly water-soluble drugs and in turn their oral bioavailability.[6]

Solubility is the property of a solid, liquid, or gaseous chemical substance called a solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent.[1] The solubility of a substance fundamentally depends on the solvent used as well as on temperature and pressure. The extent of solubility of a substance in a specific solvent is measured as the saturation concentration where adding more solute does not increase its concentration in the solution.[1] The extent of solubility ranges widely, from infinitely soluble

(fully miscible) such as ethanol in water, to poorly soluble, such as silver chloride in water. The term insoluble is often applied to poorly or very poorly soluble compounds.[2]

Solubility is defined in quantitative terms as the concentration of the solute in a saturated solution at a certain temperature. In qualitative terms, solubility may be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion.[3] A saturated solution is one in which the solute is in equilibrium with the solvent. The solubility of a drug may be expressed as parts, percentage, molality, and volume fraction and mole fraction.[3] Solubility occurs under dynamic equilibrium, which means that solubility results from the simultaneous and opposing processes of dissolution and phase joining (e.g., precipitation of solids). Solubility equilibrium occurs when the two processes proceed at a constant rate.[4] Under certain conditions equilibrium solubility may be exceeded to give a so-called supersaturated solution, which is metastable.[4] Solubility is not to be confused with the ability to dissolve or liquefy a substance, since these processes may occur not only because of dissolution but also because of a chemical reaction. For example, zinc is insoluble in hydrochloric acid, but does dissolve in it by chemically reacting into zinc chloride and hydrogen, where zinc chloride is soluble in hydrochloric acid.[4] Solubilization may be defined as the preparation of a thermodynamically stable solution of a substance that is normally insoluble or very slightly soluble in a given solvent, by the introduction of one or more amphiphilic components.[5] The United States Pharmacopoeia (USP) and British Pharmacopoeia (BP) classify the solubility regardless of the solvent used, only in terms of quantification and have defined the criteria as given below in Table: 1.

Table 1: Descriptive terms of Solubility[6]

Descriptive Term	Parts of Solvent Required for 1 Part of Solute
Very soluble	Less than 1
Freely soluble	Soluble From 1 to 10
Soluble	Soluble From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble or Insoluble	10,000 and over

The International Union of Pure and Applied Chemistry (IUPAC) defines solubility as the analytical composition of a saturated solution expressed as a proportion of a designated solute in a designated solvent.[5] Solubility is an important determinant in drug liberation and absorption and hence plays a key role in its bioavailability.[5] For a drug to be absorbed, it must be present in the form of an aqueous solution at the site of absorption. Aqueous solubility of the drug can be regarded as a key factor responsible for low oral bioavailability of poor water-soluble drugs thereby limiting their therapeutic potential. Other issues related to low oral bioavailability for a sparingly soluble drug are lack of dose proportionality, substantial food effect, and high intra & inter subject variability, gastric irritancy and slow onset of action.[5] Unfortunately many chemical compounds including NCE (New Chemical Entities) possess very low aqueous solubility at physiological pH. This could be attributed to their high inherent lipophilicity incorporated by drug design in order to ensure good absorption.[5] Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost effectiveness, least sterility constraints, and flexibility in the design of a dosage form. However, the major challenge with the design of oral dosage forms lies with their poor bioavailability. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, pre-systemic metabolism, and susceptibility to efflux mechanisms.[7] Water is the solvent of choice for liquid pharmaceutical formulations. Most of the drugs are either weakly acidic or weakly basic having poor aqueous solubility.[7]

The Biopharmaceutics Classification System (BCS) is a scientific framework for classifying a drug substance based on solubility, permeability, and dissolution criteria.[3,8]

According to the BCS, drug substances are classified as follows.

Table 2: Biopharmaceutics Classification System (BCS)

Class I	High solubility	High permeability
Class II	Low solubility	High permeability
Class III	High solubility	Low permeability
Class IV	Low solubility	Low permeability

General view on the solubility problem of various BCS Class II drugs can be summarized as-• The bioavailability of Class I compounds is determined only by delivery of the drug solution to the intestine (Formulation independent).[7,8,9]

- The bioavailability of Class II compounds is limited by drug solubility/dissolution (Formulation dependent).[7,8,9]

- The bioavailability of Class III compounds is limited by intestinal permeability (Dependent on barrier properties).[7,8,9]
- The bioavailability of Class IV compounds is limited both by solubility/dissolution and intestinal permeability (Formulation and barrier properties dependent).[7,8,9]

For BCS Class II and IV compounds, the bioavailability of these products is limited by their solvation rate and dissolution is the rate limiting step for drug absorption. Various approaches have been investigated extensively to improve the aqueous solubility and poor dissolution rate of BCS Class II and IV drugs.[10,11] The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability. This is especially true for Class II (low solubility and high permeability) substances according to the BCS. The bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids. As for BCS Class II drugs the rate limiting step is drug release from the dosage form and solubility in the gastric fluid and not the absorption, so increasing the solubility in turn increases the bioavailability for BCS Class II drugs.

1.1 Techniques for Solubility Enhancement

Solubility improvement techniques can be categorized into physical modification chemical modifications of the drug substance, and other techniques.

- **Physical Modifications** — These methods include particle size reduction such as micronizatin and nanosuspensions, modification of the crystal habit such as polymorphs, amorphous form and cocrystallization, drug dispersion in carriers such as eutectic mixtures, solid dispersions, solid solutions and cryogenic techniques.
- **Chemical Modifications** — These include a change in pH, the use of buffers, derivatization, complexation, and salt formation.
- **Miscellaneous Methods** — These include supercritical fluid processes, use of an adjuvant such as surfactants, solubilizers, cosolvency, hydrotrophy, and novel excipients.Among the commonly utilized methods, one of the most efficacious is the use of solid dispersions (SDs).

1.2 Solid Dispersion

The concept of solid dispersions was originally proposed by Sekiguchi and Obi[13], who investigated the generation and dissolution performance of eutectic melts of a sulfonamide drug and a water-soluble carrier in the early 1960s. Solid dispersions represent a useful pharmaceutical technique for increasing the dissolution, absorption, and therapeutic efficacy of drugs in dosage forms.[14] The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, as an amorphous particle (clusters) or as crystalline particles.[14, 15] When dissolving the solid dispersions, it is believed that the drug substance is released as small discrete units owing to a fast dissolution of the easily soluble carrier. If the drug solubility in the carrier is high enough, a so-called solid solution can be obtained.[16] Such a preparation will then give a system similar to a molecular solution after the carrier has been dissolved. For such systems it has been claimed that the dissolution of the carrier is the rate limiting step. The formation of the solid solution is therefore normally restricted to relatively low concentrations of drugs. Coprecipitates and melts are solid dispersions that provide a means of reducing particle size to the molecular level. Sekiguchi and Obi[13] first introduced the concept of using solid dispersions to improve bioavailability of poorly water-soluble drugs in 1961. They demonstrated that the eutectic of sulfathiazole and the physiologically inert water-soluble carrier urea exhibited higher absorption and excretion after oral administration than sulfathiazole alone. Chiou and Riegelman[18] defined the term solid dispersion as "a dispersion of one or more active ingredients in an inert carrier or matrix in solid state prepared by the melting (fusion), solvent, or melting-solvent method." Dispersions obtained through the fusion process are often called melts, and those obtained by the solvent method are frequently referred to as coprecipitates or coevaporates.

1.3 Classification of Solid Dispersions

Chiou and Riegelman[18] classified solid dispersions into the following six representative types.

1) Simple eutectic mixtures
2) Solid solutions
3) Glass solutions and glass suspensions
4) Amorphous precipitations in a crystalline carrier
5) Compound or complex formation
6) Combinations of the previous five types

1. Simple Eutectic Mixtures

These are prepared by rapid solidification of the fused melt of two components that show complete liquid miscibility but negligible solid-solid solubility. Thermodynamically, such a system is an intimately blended physical mixture of its two crystalline components.[19] Thus, the x-ray diffraction pattern of a eutectic constitutes an additive composite of the two components. A phase diagram representing a two-component system is given in Fig. 1. Examples of this type include phenacetin-phenobarbital, chloramphenicol-urea, griseofulvin-succinic acid[19], paracetamol-urea, and the dispersions of griseofulvin and tolbutamide in polyethylene glycol-(PEG-2000;[20]).

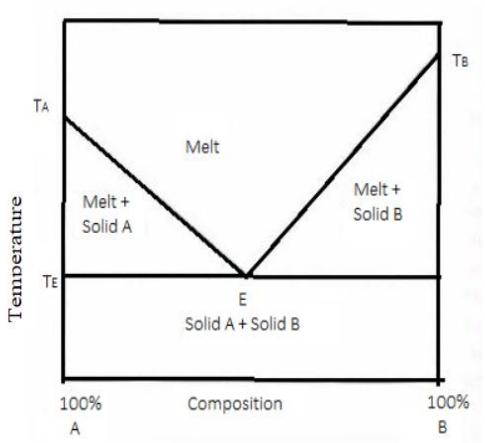


Fig 1: Phase Diagram of Eutectic Mixtures.

Fig.1 Representation of a simple binary-phase diagram with eutectic formation. TA is the melting point of pure A; TB is the melting point of pure B; and E is the eutectic point.

2. Solid Solutions

In a solid solution, the two components crystallize together in a homogeneous one-phase system. The particle size of the drug in the solid solution is reduced to its molecular size.[21] Thus, a solid solution can achieve a faster dissolution rate than its corresponding eutectic mixture. According to the extent of miscibility of the two components, they may be classified as continuous or discontinuous. In continuous solid solutions, the two components are miscible in the solid state in all proportions. Typical phase diagrams for continuous and discontinuous solid solutions are given in Figs. 2 and 3, respectively. Discontinuous solid solutions exist at extremes of composition. In general, some solid-state solubility can be expected for all two-component systems.

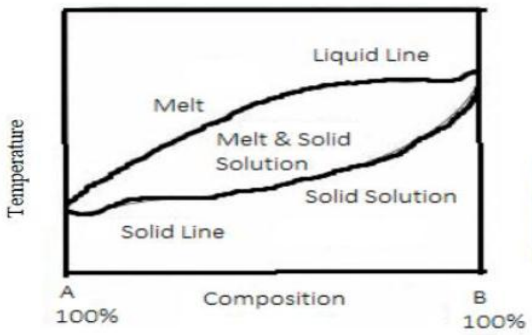


Fig. 2: Phase Diagram of Continuous Solid Solution.

Fig. 2 Representation of aphase diagram of a continuous solid solution for a binary system A and B.

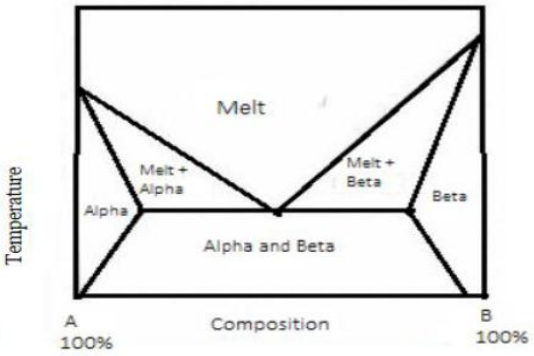


Fig.3: Phase Diagram ofDiscontinuous Solid Solution.

Fig.3 Representation of atypical phase diagram of a discontinuous solid solution for a binary system A and B; α and β are regions of solid solution formation.

According
to the criterion for molecular size of the two components, solid solutions are classified as substitutional or interstitial. In the substitutional type, the solute molecule substitutes for the solvent molecule in the crystal lattice (Fig. 4). The molecular size of the two components should not differ by more than 15%. This class is represented by solid solutions of p-dibromobenzene p-chlorobromobenzene, anthracene-acenaphthene, and ammonium and potassium thiocyanate.[21] An interstitial solid solution is obtained when the solute (guest) molecule occupies the interstitial space (Fig. 4) in the solvent (host) lattice. For this to occur the solute molecule diameter should be less than 0.59 times that of the solvent molecule; therefore, the volume of the solute molecule should be less than 20% of the solvent molecule. Owing to their large molecular size, polymers favor the formation of interstitial solid solutions.[21] They all exhibit a fast rate of dissolution.

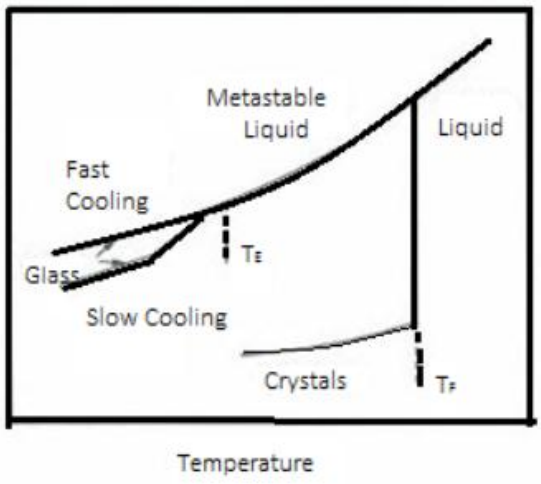


Fig 4: A Substitution and Interstitial Solid Solutions.

Fig. 4 A schematic representation of substitution and interstitial solid solutions. The dark symbols represent solute atoms or molecules; open symbols indicate solvent atoms or molecules.

3. Glass Solutions and Suspensions

A glass solution is a homogeneous glassy system in which a solute dissolves in the glassy carrier.[21] A glass suspension refers to a mixture in which precipitated particles are suspended in a glassy solvent. The glassy state is characterized by transparency and brittleness below the glass transition temperature. Glasses do not have sharp melting points. Instead, they soften progressively on heating. The lattice energy, which represents a barrier to rapid dissolution, is much lower in glass solutions than in solid solutions. Fig. 5 shows the volume changes associated with glass formation when a melt is cooled down. Examples of carriers that form glass solutions and suspensions include citric acid, sugars such as dextrose, sucrose, and galactose; PVP; urea; and PEG.[22,23,24]

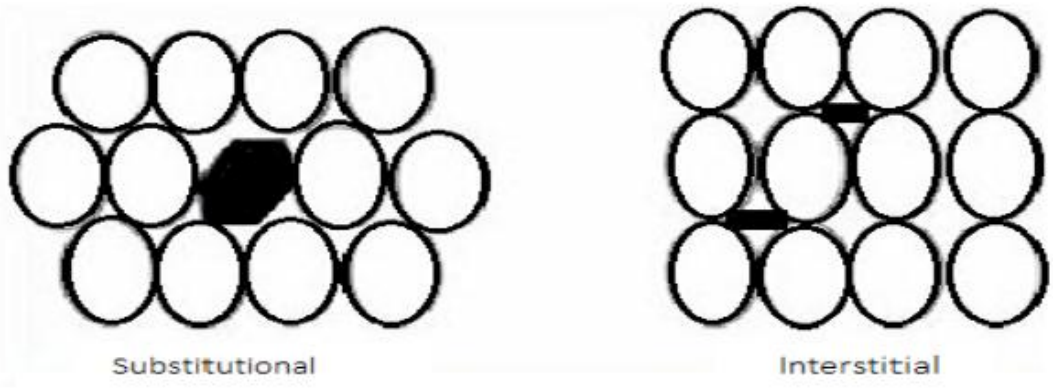


Fig. 5: The Volume Changes Associated with The Cooling ofa Melt.

Fig. 5 Representation of the volume changes associated with the cooling of a melt: The Tg is the glass transition temperature and Tf is the melting point of the material.

4. Amorphous Precipitations in a Crystalline Carrier

This type of solid dispersion is distinguished from a simple eutectic mixture by the fact that the drug is precipitated out in an amorphous form.[21] In a simple eutectic mixture, the drug is precipitated out in a crystalline form. It is postulated that a drug with a propensity to super cooling has more tendency to solidify as an amorphous form in the presence of a carrier.[21]

5. Compound and Complex Formation

When two substances form a molecular compound, it usually gives rise to a maximum in the phase diagram. It is difficult to generalize the influence that complex formation has on dissolution. A complex between digoxin and hydroquinone exhibited a high dissolution rate.[22,21], whereas the insoluble complex between phenobarbital and PEG was shown to reduce both the rates of dissolution and the permeation of phenobarbital through rat gut.[19,21]

5.a Complexation and Cyclodextrins

Complexation is one of several ways to favorably enhance the physicochemical properties of pharmaceutical compounds. It may loosely be defined as the reversible association of a substrate and ligand to form a new species.[21] Although the classification of complexes is somewhat arbitrary, the differentiation is usually based on the types of interactions and species involved, e.g., metal complexes, molecular complexes, inclusion complexes, and ion-exchange compounds. Cyclodextrins (CDs) are classic examples of compounds that form inclusion complexes. These complexes are formed when a "guest" molecule is partially or fully included inside a "host" molecule e.g. CD with no covalent bonding. When inclusion complexes are formed, the physicochemical parameters of the guest molecule are disguised or altered and improvements in the molecule's solubility, stability, taste, safety, bioavailability, etc., are commonly seen.[22] Limitations in the pharmaceutical utility of the CDs were becoming known and derivatives were prepared with the goal of improving characteristics such as complexing ability, solubility, and safety. Scientific articles have established the research applications for CDs, however it is the patents that have shown an increasing interest in the commercial protection of CDs in pharmaceutical products. Increasing numbers of pharmaceutical products are reaching the market place as CD formulations and research studies exploring their applications are growing exponentially. Nevertheless, the routine use of CDs in formulations is still questioned. The reluctance to develop a CD formulation is mainly due to the uncertain regulatory acceptance of a formulation containing a "nonstandard" inactive ingredient.[22]

Inclusion Complexation and CD

CDs are cyclic oligosaccharides containing 6, 7, or 8 glucopyranose units, referred to as α, β, or γ-CD, respectively. Each glucose unit contains two secondary alcohols at C-2 and C-3 and a primary alcohol at the C-6

position, providing 18-24 sites for chemical modification and derivatization.[22]

5.a.i Factors Affecting Complexation

• **Steric effects:** Cyclodextrins are capable of forming inclusion complexes with compounds having a size compatible with the dimensions of the cavity. Complex formation with molecules significantly larger than the cavity may also be possible in such a way that only certain groups or side chains penetrate into the carbohydrate channel. The three natural CDsnamelyα, β, and γ have different internal diameters and are able to accommodate molecules of different size. The presence of bulky groups can sterically block entrance to the CD cavity. Some groups, depending on their number, flexibility, and position of attachment, may actually act to extend the cavity and provide for better complexation.[22, 24, 25, 26]

•**Electronic effects:** Electronic effects seem to be more of a factor than steric effects. The ionic substituents too close to the CD cavity adversely disrupt the thermodynamics driving the inclusion complexation.[26, 27, 28]

•**Micellaneous:** The effect of proximity of charge to CD cavity: Moving the charge away from the cavity re-establishes the complexation characteristics but this is dependent on the charge density in the structure. The effect of charge density and the effect of charge state of the CD and drug are important considerations.[28]

5.a.ii Release from the Complex

Complexation of drugs by CDs improves their delivery characteristics and does not interfere with their activity because complexation is a rapidly reversible process. In aqueous solution, drug:CD complexes are continually forming and dissociating.[29] Although slower kinetics of dissociation are seen with stronger binding, the rates are still fast and essentially instantaneous. After administration, the drug is released from the complex upon dilution, and in some cases with contributions from competitive displacement with endogenous lipophiles, as well as binding to plasma and tissue components. Drug uptake into tissues is not available to the complex, and rapid elimination of the CD occurs.[30, 31]

4.5.b. Complexation and Non-Cyclodextrins.[32]

Complexation processes, also known simply as complexation, are based on the ability of many well-known drugs to interact and to form new complex drugs with altered properties in comparison with a drug alone.[32] The pharmaceutical technology and the pharmaceutical industry have long considered research and development in the area of complexation a priority.[32] The complexation process offers new possibilities for the improvement of existing drugs (side effects, therapeutical activity, and solubility).[32] Such drug complexes with optimized characteristics can be prepared by complexation as a result of various interactions such as drug-metal ion, drug-drug, drug-excipient(s), etc.

The non-cyclodextrins complexes can be broadly categorized as.

- Complexes formed by interactions with metal ions.
- Complexes formed by interactions with excipients.
- Complexes formed by drug-drug interactions.

1.5 Methods of Preparation for Solid Dispersion

The fusion and solvent process are the most common methods used to prepare solid dispersions. General methods employed to prepare the solid dispersion are as follows.

1.5.1 Fusion Process

In the fusion method of preparation, the carrier is heated to a temperature just above its melting point and the drug is incorporated into the matrix. The mixture is cooled with constant stirring to homogeneously disperse the drug throughout the matrix. Several mechanisms could operate during the process of dispersion. If the drug has a high degree of solubility in the carrier, the drug could remain "dissolved" in the solid state, yielding what is known as a solid solution. Particle size reduction under these conditions proceeds to the ultimate level leading to molecular dispersion of the drug in the carrier matrix. These systems show very high drug dissolution rates compared to control samples. If, on the other hand, the solubility of the drug in solid state is not so high, crystallites of the drug become dispersed in the matrix. Such systems show only moderate increases in dissolution rates. A third mechanism is the conversion of a drug to an amorphous form in the presence of the matrix, again exhibiting different dissolution rates and solubility. Other factors that may play a role include solubilizing effect conferred by the carrier itself, improved wetting or decreased surface hydrophobicity, complexation, and crystallization of the drug in a metastable polymorphic form of altered thermodynamic properties. An important limitation of the fusion method of preparation is the exposure of drugs to elevated temperatures, particularly if the carrier is a high-melting solid and the drug is heat-sensitive.[36]

Advantages: This method is very suitable for drugs and carrier that are miscible in the molten state, making melting of the ingredients very easy to accomplish. Preparing solid dispersion by the melt method is not time consuming. Hence, many batches of the product can be prepared in a very short period of time. The method is also advantageous for compounds, which do not undergo significant thermal degradation.

Disadvantages: The main disadvantages of the melt method include thermal degradation, sublimation, and polymeric transformation. These can affect the physicochemical properties of the drug including its rate of dissolution. The decomposition or thermal degradation

is often composition dependent and affected by melting time and the rate of cooling.

In order to reduce decomposition to acceptable levels, melting may be carried out at a temperature just above the highest melting component of the dispersion, which completely melts both drug and the carrier.[37,38] The temperature at which the dispersion solidifies affects crystallization rates and may alter both the size of the crystals and the hardness of the dispersion. This may result in tacky or glassy and unmanageable dispersions, which will require storage at elevated temperature to facilitate hardening. Upon communution of such dispersions, crystallization may be induced resulting in the modification of dissolution characteristics.[36]

1.5.2 Solvent Evaporation Method

In the solvent method of preparation, the carrier and the active ingredient are dissolved in a suitable organic solvent. This solvent is evaporated at an elevated temperature or under vacuum. As the solvent is being removed, supersaturation occurs followed by simultaneous precipitation of the constituents resulting in a solid residue. The coprecipitate is then dried under vacuum to drive out any solvent freely adhering to the particle surface. However, there is a possibility of the formation of a solvate within the crystal lattice. This presents a problem in terms of pharmaceutical acceptance since most of the solvents used are non-aqueous (organic) and toxic. Today there is a trend to move away for organic solvents to hydrophilic solvents if possible. Hence, removal of even trace amounts of the solvent is implied. Highly sensitive techniques such as differential scanning calorimetry (DSC), differential thermal analysis (DTA), thermogravimetric analysis (TGA), and less sensitive procedures such as gravimetry and spectroscopy can be used to demonstrate complete solvent removal.[39]

Selection of Solvent

The choice of solvent and its removal rate are critical to the quality of the dispersion. Since the chosen carriers are generally hydrophilic and the drugs are hydrophobic, the selection of a common solvent is difficult and its complete removal, necessitated by its potential toxic nature, is imperative. Certain solvents may plasticize polymeric carriers, e.g., Polyvinylpyrrolidone (PVP), making their complete removal even more difficult. Careful control of the temperature and rate of evaporation of solvents is essential in controlling the particle size of the drug, and although low temperature cannot always be avoided. The Tolbutamide- PVP dispersion showed an instability that varied with the evaporatingtemperature.[36]

Advantages: The procedure is suitable for drugs that are thermolabile; reduced pressure and lower temperatures can be used to evaporate solvent. For aqueous systems, frozen temperatures can be used to evaporate the solvent, which can enhance the integrity of the drug.[39, 40]

Disadvantages: Finding a suitable solvent that will dissolve both the drug and the carrier is very difficult and sometimes impossible. This is due to the fact of that most of the carriers are hydrophilic, whereas most of the drugs are hydrophobic organic substances. This may be further complicated by the fact that different polymorphic forms of the same drug may be obtained if different solvents are used.

Spironolactone dispersions in polyvinyl pyrollidone were evaporated from solutions of ethanol, acetonitrile, and chloroform, respectively.[41] The highest dissolution rate was provided by ethanolic dispersions, whereas the chloroform dispersion provided the lowest dissolution rate. After a suitable solvent has been found, the rate of its removal is very critical in some solid dispersion, and complete removal of the solvent is even more difficult to accomplish. Plasticization of some polymers such as polyvinyl pyrrolidone has occurred with the use of some solvents.[42] This made removal of the solvent extremely difficult. The volume of organic solvent needed to dissolve a suitable amount of drug and carrier may be very large in some cases, and the recovery of the solvent may be economically prohibitive.

1.5.3. Fusion – Solvent Method

In the fusion method a carrier(s) is/are melted and the drug(s) is/are incorporated in the form of a solution. If the carrier is capable of holding a certain proportion of liquid yet maintaining its solid properties, and if the liquid is innocuous, the need for solvent removal may be eliminated. Otherwise, this method faces the same criticism of solvent retention described before. This method is particularly useful for drugs that have high melting points or that are thermolabile. The feasibility of the method has been demonstrated for spironolactone and griseofulvin dispersions in polyethylene glycol 6000.[39]

1.5.4. Spray Drying

In this type of preparation, the carrier and the active ingredient are dissolved or suspended in a suitable solvent. This solvent is evaporated by drying by applying a stream of heated air to remove the solvent [43.] Due to the large surface area of the droplets, the solvent rapidly evaporates and the solid dispersion is formed quickly.

1.6.5 Lyophilization (Spray Freeze Drying Method)

This method is used to avoid heating during the preparation of thermosensitive drugs; Spray freeze drying (SFD) has been successfully developed to prepare solid dispersions at ambient temperature. The SFD technology involves the atomization of a feed liquid containing poorly water-soluble or insoluble active pharmaceutical ingredients (APIs) and excipients directly into a cryogenic liquid at ambient temperature to produce a frozen micronized powder that is subsequently dried. This process offers a variety of advantages compared to traditional technologies for solid dispersions, including amorphous structure and high surface area.[44, 45, 46]

1.5.6. Hot-melt Extrusion

It is a very common method used in the polymer industry. However Speiser.][47, 48] and Huttenrach[49] were the first persons who used this technology for pharmaceutical purposes. A melt extrusion consists of the following required processing equipment.

• An opening to feed raw materials
• A heated barrel that consists of extruder screws to convey and mix the fed materials
• And an exit port, which consists of an optional die to shape the extruding mass. The active ingredients and the carrier are fed into the heated barrel of the extruder at a constant rate. When the mixture of active ingredient and the carrier is conveyed through the heated screws, it is transformed into its "fluid like state". This state allows intimate and homogeneous mixing by the high shear of the extruder screws. An exit port, which consists of an optional die, shapes the melt in the required form such as granules, pellets, films, or powder. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about one minute, which enables drugs that are somewhat thermo labile to be processed.

1.5.7. Electrostatic Spinning Method

The electrostatic spinning method is a straight-forward process for generating nanofibers. The popularity of this system is due to its ease of implementation, capability of being used with a variety of materials, convenience in obtaining composites of multiple components, and with secondary microstructures (such as core-sheath, side-by-side, and island-in-sea). The applications for electro spun products are expanding, especially in areas relating to tissue engineering and drug delivery.[50-54] The fast-drying electrospinning process is able to "freeze" drug molecules randomly in the solid polymer fiber matrix into a state comparable with that in a liquid form. This is very useful for preventing phase separation, eg, recrystallization of either drug or matrix during removal of solvents.[5-60]

1.5.8. Supercritical Fluid Technology

Supercritical fluid technology (SCFT) is a new method to produce fine drug particles and is valuable for product quality. In the pharmaceutical field, the supercritical fluid technology was industrially applied in the early 1980's.[60] In this technique the active ingredient and the carrier are dissolved in a common solvent that is introduced into a particle formation vessel through a nozzle, simultaneously with CO2. When the solution is sprayed, the solvent is rapidly extracted by the supercritical fluid, resulting in the precipitation of solid dispersion particles on the walls and bottom of the vessel.[61] A supercritical fluid exists as a single phase above its critical temperature and pressure.[62] The most commonly used supercritical fluids include supercritical fluid carbon dioxide (SC-CO2), nitrous oxide, water, methanol, ethanol, ethane, propane, n-hexane and ammonia-18. SC-CO2 is a popular solvent or anti-solvent since it is safe, inexpensive, readily available, and an ideal substitute for many hazardous and toxic solvents. The SC-CO2 exist when both the temperature and pressure equals or exceeds the critical point of 31°C and atm and has both gas-like and liquid-like qualities. It is this dual characteristic of supercritical fluids that provides the ideal conditions for extracting compounds with a high degree of recovery in a short period of time. By controlling the level of pressure/temperature /modifier, SC-CO2 can dissolve a broad range of compounds, both polar and non-polar. At present, carbon dioxide technology is one of the fastest growing new process technologies being adopted by the pharmaceutical industry.[63] Supercritical water is a unique medium for safe destruction of dangerous waste by total oxidation due to its special physicochemical properties.

Various supercritical fluid technologies used in pharmaceutical processing include.

- Rapid expansion of supercritical solutions (RESS),
- Supercritical antisolvent (SAS) precipitation technique
- Particles from Gas Saturated Solutions (PGSS),
- Gas antisolvent system (GAS),
- Precipitation using compressed antisolvent (PCA),
- Aerosol solvent extraction system (ASES),
- Solution enhanced dispersion by supercritical fluids (SEDS),
- Supercritical antisolvent system with enhanced mass transfer (SAS-EM).

1.5.9. Coating on Sugar Beads Using Fluidized Bed-Coating System

In this method a fluidized bed-coating concept is involved. The drug and the active ingredient solution are sprayed onto the granular surface of excipients or sugar spheres to produce either granule ready for tableting or drug-coated pellets for encapsulation in one step. The method can be applied for both controlled- and immediate-release solid dispersion.

1.6 Mechanism of increased Solubility and dissolution rate

The enhancement in dissolution rate as a result of solid dispersion formation, relative to pure drug, varies from as high as 400-fold33 to less than twofold. Corrigan34 reviewed the current understanding of the mechanism of release from solid dispersions. The increase in dissolution rate for solid dispersions can be attributed to a number of factors. It is very difficult to show experimentally that anyone particular factor is more important than another. The main reasons postulated for the observed improvements in dissolution of these systems are as follows.

1. Reduction of particle size

In the case of glass, solid solutions, and amorphous dispersions, particle size is reduced to a minimum level. This can result in an enhanced dissolution rate due to an increase in both the surface area and solubilization.

2. Solubilization effect
The carrier material, as it dissolves, may have a solubilization effect on the drug. This was shown to be the case for acetaminophen and chlorpropamide in urea, as well as for numerous other drugs.[63]

3.Wetability and dispersibility
The carrier material may also have an enhancing effect on the wetability and dispersibility of the drug in the dissolution media. This should retard any agglomeration or aggregation of the particles, which can slow the dissolution process.

4.Metastable forms
Formation of metastable dispersions with reduced lattice energy would result in faster dissolution rates.

1.7 Characterization of Solid Dispersions
Many methods are available that can contribute information regarding the physical nature of solid dispersion system. A combination of two or more methods is required to study its complete picture and may include the following.
•Thermal analysis (Modulated temperature differential scanning calorimetry).
•Spectroscopic method.
•X-ray diffraction method.
•Dissolution rate method and Dissolution testing
•Microscopic method. (Scanning Electron Microscopy and Transmission Electron Microscopy)
•Thermodynamic method.

1.8 Applications of Solid Dispersion
A part from absorption enhancement, the solid dispersion technique may have numerous pharmaceutical applications, which should be further explored. It is possible that such a technique can be used[63]

1. To obtain a homogeneous distribution of a small amount of drug in solid state.
2. To stabilize the unstable drug.
3. To dispense liquid (up to 10%) or gaseous compounds in a solid dosage form.
4. To formulation a fast release primary dose in a sustained released dosage form.
5. To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
6. Polymorphous in a given system can be converted into isomorphous, solid solution, eutectic or molecular addition compounds.

1.9 The Limitations
The limitation of this technology has been a drawback for the commercialization of solid dispersion. The limitation include.[63]

1. Laborious and expensive method of preparation.
2. Lack of reproductivity of physicochemical characteristics.
3. Scale-up of manufacturing process.
4. Stability of the drug and vehicle.

7.1 Preformulation Studies
Preformulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance are characterized with the goal of designing optimum drug delivery system.

7.1.1 Physical properties
7.1.1.1 Organoleptic Properties
Sulfamethoxazole was tested for organoleptic properties such as appearance, colour, odor, etc.

7.1.1.2 Melting point determination
Melting point of Sulfamethoxazole was determined by capillary method. Drug filled capillary was placed in the melting point apparatus containing silicon oil as a heating medium and the melting point was noted. Average of triplicate reading was taken.

7.1.1.3 Solubility determination
The approximate solubility of pharmacopial substance is indicated by descriptive terms in accompanying table.

Table 5: Descriptive terms of solubility.

Descriptive Term	Parts of solvent Required for 1 Part of Solute
Very soluble	Less than 1
Freely soluble	Soluble from 1 to 10
Soluble	Soluble from 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10000
Practically insoluble or insoluble	10000 and over

The solubility of the selected drug was determined in distilled water, ethanol, dichloromethanol and methanol by the following method.

METHOD
Excess amount of drug was taken and dissolved in a measured amount of each solvent in a glass beaker to get a saturated solution. The solution was shaken intermittently to assist the attainment of equilibrium with the undissolved drug particles. Then measured quantity of the filtered drug solution was withdrawn after 24 hrs and successively diluted with respective solvent and concentration was measured using UV Spectrophotometer at 258 nm.
Ethanol: 23mg/ml at 25^0C
Water: (1 mg/ml at 25^0C)

7.1.2 UV Spectroscopy (Determination of λ max)
The Methodology Used In The Present Study Is UV - Visible Spectrophotometry

- **Potassium Dihydrogen Phosphate, 0.2M Solution**

Take accurately weighed 27.31gm of Potassium dihydrogen Phosphate and dissolvedin 1000 ml of distilled water, this will give 0.2MKH_2PO_4.

- **Sodium hydroxide 0.2N solution**

Take accurately weighed 8 gm of sodium hydroxide and dissolved in 1000 ml of distilled water, this will give 0.2N NaOH solution.

- **Preparation of pH 7.2 phosphate buffer**

Place 50 ml of the Potassium dihydrogen Phosphate solution in a 200 ml standard volumetric flask and add 39.1 ml of sodium hydroxide solution to this flask and make up the volume with distilled water.

PROCEDURE FOR STANDARD GRAPHS PREPARATION

Standard graphs preparation with phosphate buffer pH 7.2

Accurately weigh 100 mg of Sulfamethoxazole and transfer to a 100 ml volumetric flask and add minimum quantity of Methanol to solubilise the drug, and then add phosphate buffer pH 7.2 to make up the volume up to 100ml, this gives the stock solution I (1000µg/ml).

From stock solution I, pipette out 10ml and makeup the volume to 100ml with phosphate buffer pH 7.2, this gives the stock solution II (100µg/ml). From the stock solution II, pipette out 0.5, 1.0, 1.5, 2.0, and 2.5 ml into 5 separate10 ml volumetric flasks respectively, then make up the volume up to the mark to give 5,10, 15, 20 and 25 µg/ml concentration solutions and the phosphate buffer pH 7.2 was taken as blank.

The absorbance was measured at 258 nm and the graph was plotted against concentration (µg/ml) Vs absorbance.

7.1.3 Drug and excipient compatibility study

7.1.3.1 Fourier Transform Infrared (FTIR) spectrum interpretation

The Fourier Transform Infrared FTIR spectra of Sulfamethoxazole, PEG4000, HPMC were recorded using FTIR spectrophotometer (FTIR presties, Shimadzu). Sample were mixed with potassium bromide (spectroscopic grade) and compressed into disks using hydraulic press before scanning from 4000 to 600 cm^{-1}. The data were analyzed using IR Solution software (version 1.10).

7.1.3.2 Differential Scanning Calorimetry (DSC)

The possibility of any interaction between the drug and the carriers during preparation of solid dispersion was assessed by carrying out thermal analysis of drug and polymer alone as well as physical mixture and solid dispersion using DSC. DSC analysis was performed using Hitachi DSC 7020, on 5 to 15 mg samples. Samples were heated in sealed aluminum pan at a rate of 10°C/min conducted over a temperature range of 30 to 350°C under a nitrogen flow of 50 ml/min.

7.2 Enhancement study of drug by solid dispersion technique

Solid dispersion technology can be used to improve the invitro and invivo dissolution properties of poorly water soluble drugs. Sulfamethoxazole is poorly soluble in water. The dissolution rate from solid dispersion was affected by the carrier concentration. HPMC and PEG-4000 were used as carriers in the preparation of Sulfamethoxazole solid dispersion.

7.2.1 Procedure for preparation of Sulfamethoxazole solid dispersion by fusion method

In fusion method the polymer PEG4000, HPMC five different drug carrier ratio were used (1:1, 1:2, 1:3, 1:4, 1:5). PEG4000, HPMC has been taken in china disc and kept in a mantle a constant temperature programming for melting. After reaching melting point than add the Sulfamethoxazole with continuous stirring with the help of glass rod. After taking it out from the mantle, kept immediate for cooling in a ice bath, after cooling take it out and the resulting solid dispersion was store in desiccators until used.

Table 6: Formulation of solid dispersion (fusion method) showing various compositions.

Name	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Sulfamethoxazole	30	30	30	30	30	30	30	30	30	30
PEG4000	30	60	90	120	150	_	_	_	_	_
HPMC (mg)	_	_	_	_	_	30	60	90	120	150

7.2.2 Procedure for preparation of Sulfamethoxazole solid dispersion by solvent evaporation method

In solvent evaporation method solvent [methanol] is used. Sulfamethoxazole and polymer HPMC, PEG4000 use, drug**:** carrier five different ratios were used (1:1, 1:2, 1:3, 1:4, 1:5) to prepare solid dispersion of Sulfamethoxazole. Sulfamethoxazole And polymer HPMC, PEG4000 were dissolved in methanol and mixed with magnetic stirring. The resulting mixture was stirred at 20 rpm for 1 hour evaporate solvent temperature of 55ºC until dry. The solidified mass was scrapped, crushed, pulverized and passed through the mesh no.100.

Table 7: Formulation of solid dispersion (evaporation method solvent) showing various compositions.

Name	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10
Sulfamethoxazole	30	30	30	30	30	30	30	30	30	30
PEG4000	30	60	90	120	150	_	_	_	_	_
HPMC (mg)	_	_	_	_	_	30	60	90	120	150

7.3 Evaluation of Solid Dispersion

7.3.1 Micromeritic study

Measurement of Micromeritic Properties of Powders

7.3.1.1 Bulk density

The powder sample under test is screened through sieve No.18 and the sample equivalent to 25 gm is weighed and filled in a 100 ml graduated cylinder and the power is leveled and the unsettled volume, V_0 is noted. The bulk density is calculated in g/cm^3 by the formula.[56]

Bulk density = M/V_0

M = Powder mass

V_0 = apparent unstirred volume

7.3.1.2 Tapped density

The powder sample under test is screened through sieve No.18 and the weight of the sample equivalent to 25 gm filled in 100 ml graduated cylinder. The mechanical tapping of cylinder is carried out using tapped density tester at a nominal rate for 500 times initially and the tapped volume V_0 is noted. Tappings are proceeded further for an additional tapping 750 times and tapped volume, V_b is noted. The difference between two tapping volume is less the 2%, V_b is considered as a tapped volume V_f. The tapped density is calculated in g/cm^3 by the formula.[57]

Tapped density=M/V_f

M =weight of sample power taken

V_f =tapped volume

7.3.1.3 Angle of repose

The angle of repose of API powder is determined by the funnel method. The accurately weight powder blend are taken in the funnel. The height of the funnel is adjusted in a way that, the tip of the funnel just touched the apex of the powder blend. The powder blend is allowed to flow through the funnel freely on to the surface. The diameter of the powder cone is measured and angle of repose is calculated using the following equation.[55]

$\tan \theta = h/r$

Where, h and r are the height and radius of the powder cone.

Flow Properties and Corresponding Angle of Repose.

Flow Property	Angle of Repose (^{0})
Excellent	25-30
Good	31-35
Fair- aid not needed	36-40
Passable-may hang up	41-45
Poor-must agitate, Vibrate	46-55
Very Poor	56-65
Very, very Poor	>66

7.3.1.4 Compressibility Index / Carr's Index (%)

The Compressibility Index of the powder blend is determined by Carr's compressibility index to know the flow character of a powder. The formula for Carr's Index is as below.

Carr's Index (%) = [(TD-BD) /TD] x100

7.5.1.5 Hausner's ratio

The Hausner's ratio is a number that is correlated to the flow ability of a powder or granular material. The ratio of tapped density to bulk density of the powders is called the Hasner's ratio. It is calculated by the following equation. [58]

H = ρT / ρB

Where ρT = tapped density, ρB = bulk density

7.3.1.6 Scale of Flowability.

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

7.3.1.7 Percentage practical yield

Percentage practical yield was calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation.

$$PY(\%) = \frac{\text{Practical Mass (Solid dispersion)}}{\text{Theoretical Mass (Drug + carrier)}} \times 100$$

7.3.1.8 Drug content uniformity

Drug content estimation Solid dispersions equivalent to 10 mg of sulfamethoxazole were weighed accurately and dissolved in the 10 ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 258 nm by UV spectrophotometer. The Actual Drug Content was calculated using the following equation as follows.

$$\% \text{ Drug content} = \frac{M_{act}}{M_{ss}} \times 100$$

$$\frac{\text{Actual amount of drug in solid dispersion}}{\text{Theoretical amount of drug in solid dispersion}} \times 100$$

7.3.1.9 Solubility determination method

The solubility of the drug, physical mixture, and solid dispersions were determined in distil water. Excess of sample were transferred to flask before adding distil water. The mixtures then placed in mechanical shaker maintained at 37^0 C. Then measured quantity of the filtered drug solution was withdrawn after 24 hrs and successively diluted with respective solvent and concentration was measured using UV Spectrophotometer at 258 nm.

7.3.4 Dissolution Rate Studies of Different Solid Dispersions of Sulfamethoxazole

The dissolution studies are most important part of the evaluation of solid dispersions, where the dissolution of pure drug and solid dispersions were carried out, by using dissolution apparatus. Dissolution rate studies of various solid dispersions were carried out in 0.2M, pH 7.2 phosphate buffer using USP type II (paddle) Dissolution Testing Apparatus.

Dissolution method

In dissolution method 900 ml of 0.2M, pH 7.2 phosphate buffer was used as dissolution medium. SD equivalent to 40 mg of Sulfamethoxazole was taken in a hard gelatine capsule. The paddle type stirrer was adjusted to 75 rpm and the temperature was maintained at 37°±5°C. 5 ml of sample of dissolution medium were withdrawn at 0, 5, 10, 15, 20, 25, 30, 40, 45 min in temperature and volume with drawn was replaced with fresh quantity of dissolution media.

The samples were analyzed for Sulfamethoxazole after suitable dilution by measuring absorbance at 258 nm using Dolphin, UV/Vis. spectrophotometer. 0.2M, pH 7.2 phosphate buffer was used as blank solution. The dissolution experiment work was conducted in triplicate. The percentage of Sulfamethoxazole dissolved at various time intervals was calculated and plotted against.
Details of parameters of dissolution test.

Table 9: Parameters of dissolution test for solid dispersion.

Sr. No.	Parameter	Detail
1	Apparatus	USP Type II
2	Volume of medium	900 ml
3	Temperature	37°±5°C
4	Paddle speed	75 rpm
5	Dissolution medium	0.2M Ph 7.2
6	Aliquot withdrawn	5ml

7.3 Formulation of Tablet

Prepared solid dispersion (180mg) equivalent to 300mg of Sulfamethoxazole was mixed with Magnesium stearate 6mg (as lubricant) Talc 6mg (as glidant) and directly compressible excipient as Microcrystaline cellouse 88mg (as diluents) triturated for 2 hours. The prepared mixture was then passed through a sieve no 80. The prepared granules were then compressed by using Rotatory tablet compression machine. Same prepared solid dispersion of F5, F10, S5, S9, S10 batches.

Table 10: Formulation of tablet.

Ingridient	F5	F10	S5	S9	S10
Solid dispersion ofSulfamethoxazole wt	180	180	180	150	180
Magnesium state	6	6	6	6	6
Talc	6	6	6	6	6
Sodium starch glycolate	20	20	20	20	20
Microcrystaline cellouse (mg)	88	88	88	118	88
Total wt	300	300	300	300	300

7.5 Evaluation of Tablets

7.5.1 Micromeritics study (Pre compression parameters)

Measurement of Micromeritic Properties of Powders

7.5.1.1 Bulk density

The powder sample under test is screened through sieve No.18 and the sample equivalent to 25 gm is weighed and filled in a 100 ml graduated cylinder and the power is levelled and the unsettled volume, V_0 is noted. The bulk density is calculated in g/cm^3 by the formula.[56]

Bulk density = M/V_0

M = Powder mass

V_0 = apparent unstirred volume

7.5.1.2 Tapped density

The powder sample under test is screened through sieve No.18 and the weight of the sample equivalent to 25 gm filled in 100 ml graduated cylinder. The mechanical tapping of cylinder is carried out using tapped density tester at a nominal rate for 500 times initially and the tapped volume V_0 is noted. Tapping are proced further for an additional tapping 750 times and tapped volume, V_b is noted. The difference between two tapping volume is less the 2%, V_b is considered as a tapped volume I_f. The tapped density is calculated in g/cm^3 by the formula.[57]

Tapped density=M/I_f

M =weight of sample power taken

I_f =tapped volume

7.5.1.3 Angle of repose

The angle of repose of API powder is determined by the funnel method. The accurately weight powder blend are taken in the funnel. The height of the funnel is adjusted in a way that, the tip of the funnel just touched the apex of the powder blend. The powder blend is allowed to flow through the funnel freely on to the surface. The diameter of the powder cone is measured and angle of repose is calculated using the following equation.[55]

Tan θ = h/r

Where, h and r are the height and radius of the powder cone.

7.5.1.4 Compressibility Index

The Compressibility Index of the powder blend is determined by Carr's compressibility index to know the flow character of a powder. The formula for Carr's Index is as below.

Carr's Index (%) = [(TD-BD) /TD] x100

7.5.1.5 Hausner's ratio

The Hausner's ratio is a number that is correlated to the flow ability of a powder or granular material. The ratio of tapped density to bulk density of the powders is called the Hasner's ratio. It is calculated by the following equation.[58]

H = ρT / ρB

Where ρT = tapped density, ρB = bulk density

7.5.1.6 Post compression parameters

a) Thickness

The thickness of tablets was determined by using Digital micrometer. Ten individual tablets from each batch were used and the results averaged.

b) Weight variation

Ten tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation three batches were calculated. It passes the test for weight variation test if not more than two of the individual tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the percentage shown. It was calculated on an electronic weighing balance.

c) Friability

The friability values of the tablets were determined using a Roche-type friabilator. Accurately weighed ten tablets were placed in Roche friabilator and rotated at 25 rpm for 4 min.

Percentage friability was calculated using the following equation.

Friability = $([w_O - w] / w_O) \times 100$

Where;

w_O = weight of the tablet at time zero before revolution.

w = weight of the tablet after 100 revolutions.

d) Disintegration test

Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets. Apparatus was run for 10 minutes and the basket was lift from the fluid, observe whether all of the tablets have disintegrated.

e) Dissolution Studies

The dissolution study of was performed over a 1 hr period using USP type II (paddle) Dissolution Testing Apparatus (Lab India) 900ml of pH 7.2 Phosphate buffer was used as dissolution medium agitated at 50 RPM, at temperature of 37^o± 0.5^{o}C. 5 ml samples were withdrawn at 5, 10, 15, 20, 30, 45 and 60 min to estimate the drug release. The samples were analyzed by UV Spectrophotometry at their respective λ max value.

8. RESULTS AND DISCUSSION

8.1 Preformulation study

Table 11: Physical characters of drug.

Sr. No.	Characters	Inference
1	Nature	Crystals or white powder
2	Color	Yellow – white powder
3	Odor	Practically odorless
4	Taste	Bitter
5	Melting point	167 °C
6	Solubility – In water In ethanol In dimethyl formamide	Practically insoluble Soluble Soluble

The physical characters of Sulfamethoxazole were found to be identical with
standards given in analytical profile of drug substances.

- Solubility determination.

Name	Solubility	Temprature
Dimethylsulfoxide (DMSO)	51mg/ml	at 25^0C
Water	<1mg/ml	at 25^0C
Ethanol	23mg/ml	at 25^0C

8.2 UV Spetroscopy (Determination of λmax)

Table 12: Standard Graph of Sulfamethoxazole with phosphate buffer pH 7.2.

Sr. No.	Concentration (µg/ml)	Absorbance at 258nm
1	0	0.0000
2	5	0.1249
3	10	0.2490
4	15	0.3730
5	20	0.4920
6	25	0.6202

The λ max of sulfamethoxazole was found to be at 258 nm. This complies with the standard.
On the basis of the above tests, it was confirmed that the drug sample of sulfamethoxazole was an authentic one.

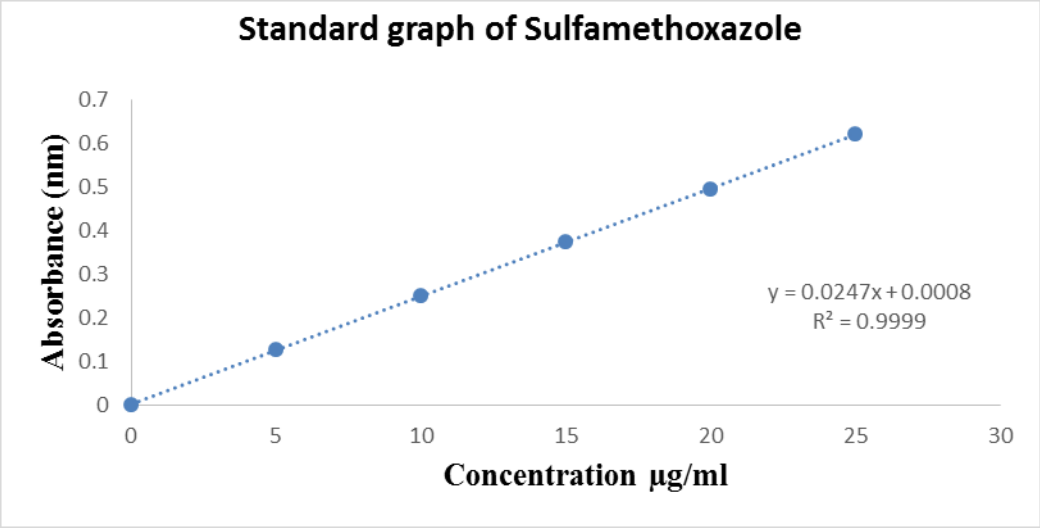


Fig 11: Standard calibration curve of sulfamethoxazole.

Equation of line (y = mx + c) of calibration curve of sulfamethoxazole in PH 7.2 was,
$Y = 0.024x + 0.0000$ and $R^2 = 0.999$
Where,
M = slop of the line
C = constant
R^2 = Regression coefficient

8.3 Drug – Excipient Compatibility Studies By FTIR Studies

The FTIR spectra of sulfamethoxazole PEG4000, HPMC and their mixture are shown in fig. The FTIR spectram of pure sulfamethoxazole was identical for the unprocessed powder and for powder obtained after drying in the drug solution used to prepared the solid dispersion.

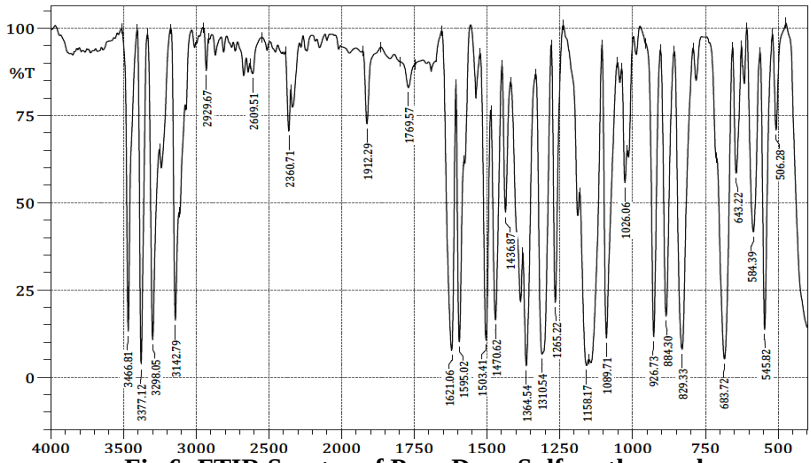


Fig 6: FTIR Spectra of Pure Drug Sulfsmethoxazole.

Sr. No.	Wave number (Cm-1)	Functional group
1	3298.05	NH stretching of group
2	3142.79	C-H stretching aromatic group
3	2929.67	C-H stretching aliphatic group
4	2609.51	C=O stretching carboxyl ion
5	1769.57	C-N stretching in oxazole group
6	1621.06	C-C stretching group
7	1503.41	C=N stretching in oxazole group
8	1470.62	C=C stretching aromatic group
9	11364.54	S=O stretching group
10	1158.17	C-N symmetric SO2 stretching group

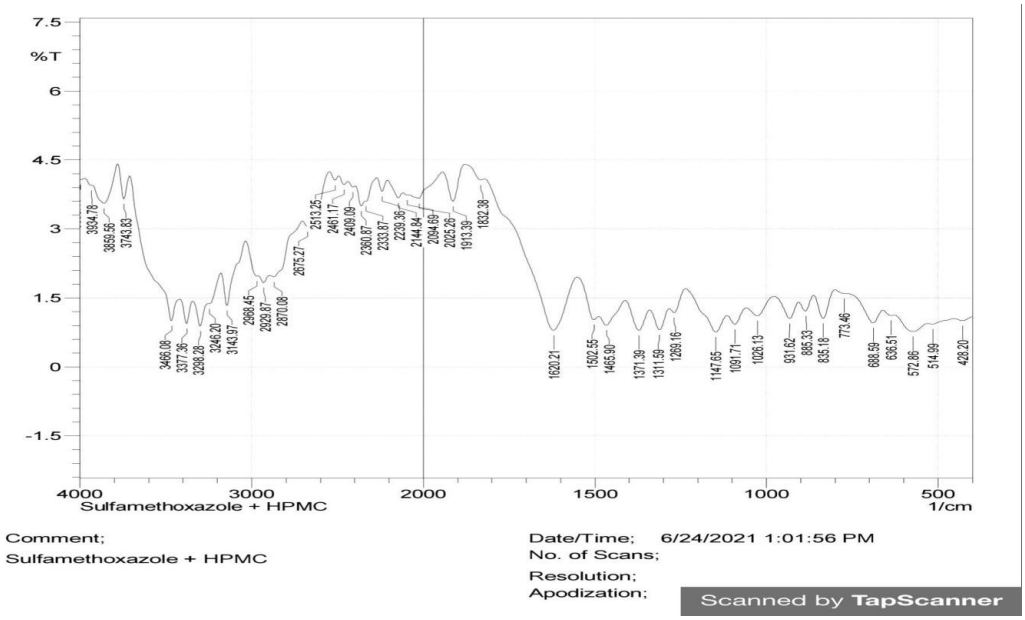


Fig 7: FTIR Spectra of Sulfamethoxazole + HPMC.

Sr. No.	Wave number (Cm-1)	Functional group
1	28700.08	Alkane C-H stretching group
2	1913.39	Aromatic C-H Group
3	1620.21	CarboxylicC=O stretching group
4	1465.90	Aromatic C-H stretching group.
5	1147.65	C-O stretching group
6	835.18	C-Cl stretching group

From the above graphs it was showed no interactions between drug and excipients. Both API and excipients compatibility with each other. . From figure it was found that the functional group associated with pure drug sulfamethoxazole with polymer HPMC are same. It shows that there was no interaction between sulfamethoxazole and HPMC.

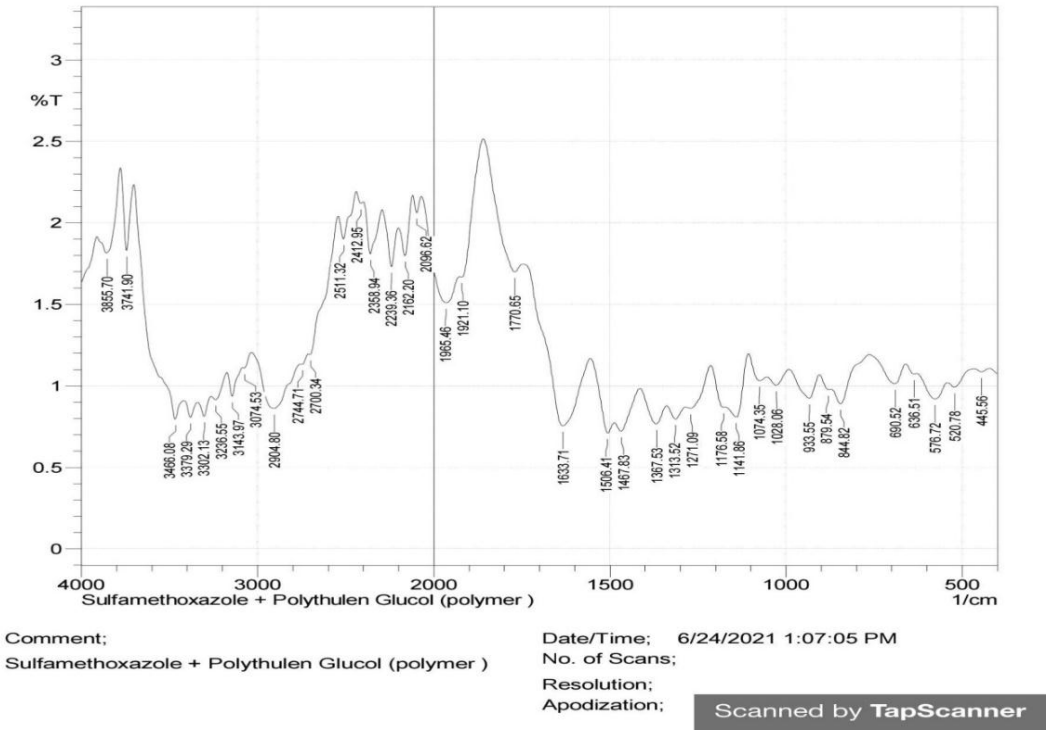


Fig 8: FTIR SPECTRA OF SULFAMETHOXAZOLE + PEG4000.

Sr. No.	Wave number (Cm-1)	Functional group
1	3466.08	Amine N-H stretching group
2	2904.80	Alkane C-H stretching group
3	1965.46	Aromatic C-H Group
4	1770.65	Carboxylic C=O stretching group.
5	1467.83	Aromatic C-H stretching group.
6	1141.86	C-O stretching group
7	844.82	C-Cl stretching group

From the above graphs it was showed no interactions between drug and excipients. Both API and excipients compatibility with each other. From figure it was found that the functional group associated with pure drug sulfamethoxazole with polymer PEG4000 are same. It shows that there was no interaction between sulfamethoxazole and PEG4000

DIFFERENTIAL SCANNING CALORIMETRY (DSC)

The DSC of pure drug, polymer and all solid dispersion formulations were performed using Meffler—TeledoDSC831e (Meffler-TeldoGmbh,Switzerland). From the DSC thermogram of Sulfamethoxazole solid dispersion containing drug and PEG^{4000} the melting was found to be and 215^0C which is different from the pure drug Melting point of Sulfamethoxazole (207^0 C) from the DSC thermo gram of Sulfamethoxazole solid dispersion with HPMC which is prepared by solvent evaporation method was found to be 200^0C which shows that the crystalline nature of compound getting changed. From the DSC studies of solid dispersions conclude that there was a change in nature of the compound.

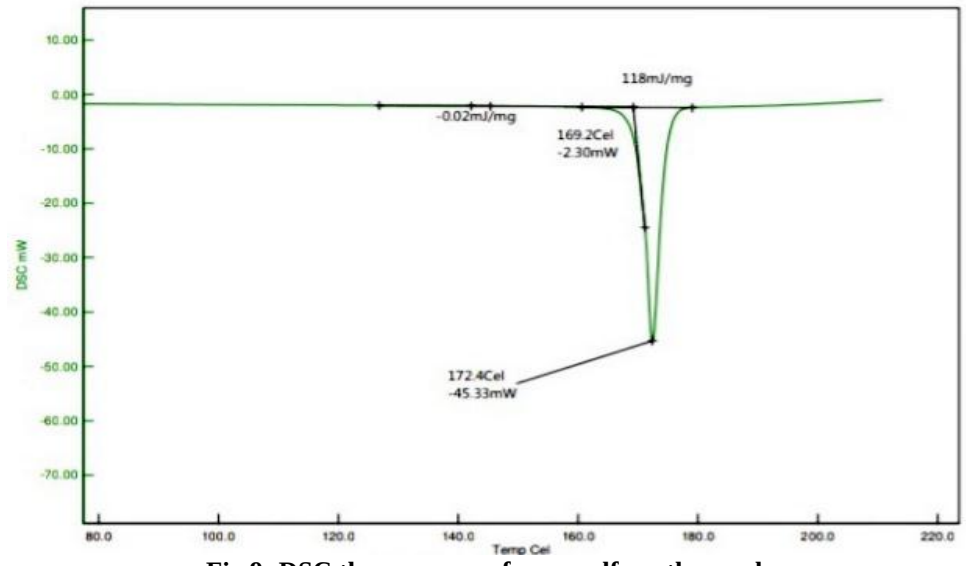


Fig.9: DSC thermogram of pure sulfamethoxazole.

The unprocessed sulfamethoxazole showed a characteristic endothermic melting peak at 170^0 indicating that the drug sulfamethoxazole highly crystalline in nature.

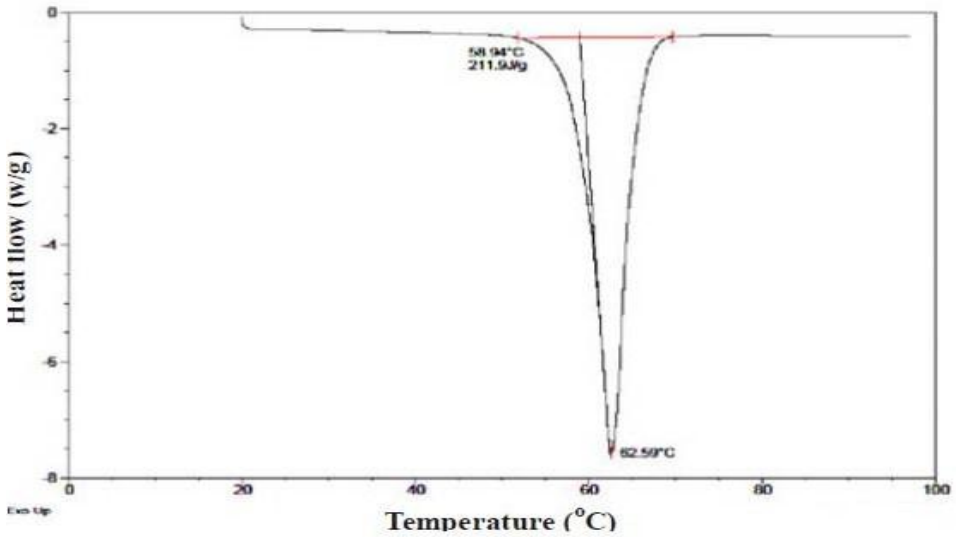


Fig. 10: DSC thermogram of Drug and PEG400.

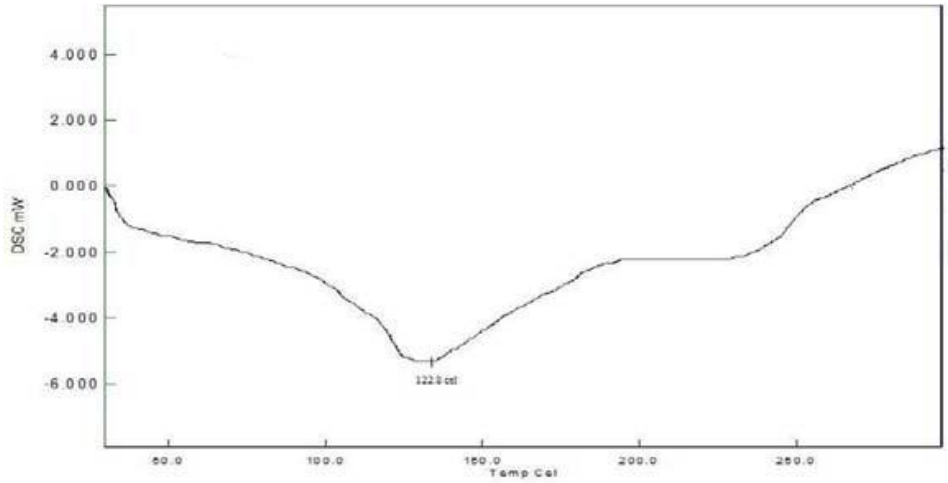


Fig.11: DSC Thermogram of Drug and HPMC.

7. Preformulation of solid dispersion

The solid dispersion of sulfamethoxazole was preparaed by fusion method:

Table 13: Physical properties.

Formulation Code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Angle of repose (Ɵ)	Carr's Index (%)	Hausner's ratio
F1	0.53	0.59	25.10	10.16	1.10
F2	0.54	0.64	25.43	15.62	1.16
F3	0.54	0.58	25.41	6.89	1.07
F4	0.51	0.61	26.40	16.39	1.17
F5	0.58	0.63	27.12	17.12	1.18
F6	0.59	0.64	25.31	7.81	1.08
F7	0.56	0.63	26.11	11.11	1.12
F8	0.53	0.58	26.15	8.62	1.09
F9	0.54	0.61	26.10	11.47	1.12
F10	0.57	0.62	27.13	17.14	1.19

Solid dispersions of Sulfamethoxazole by fusion method were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. Angle of repose was less than 28^0, Carr's index values were less than 11 for the precompression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.25 for all the batches indicating good flow properties.

Percentage yield

The result of percentage yield of solid dispersion of sulfamethoxazole was preparaed by fusion method were as below

Table 14: percentage yield of solid dispersion of sulfamethoxazole.

Sr. No.	Formulation	% yield + S.E.M
1	F1	63.23 ± 0.91
2	F2	69.01 ± 0.11
3	F3	65.22 ± 0.52
4	F4	70 ± 0.91
5	F5	72.23 ± 0.47
6	F6	62.55 ± 0.11
7	F7	65.47 ± 0.91
8	F8	69.57 ± 0.51
9	F9	70.59 ± 0.44
10	F10	71.03 ± 0.98

The prepared solid dispersion gives good percentage yield. The maximum percentage yield was found to be of F5 batch and was noted to be 72.23%. It was found that percentage yield was greater than 62.55% for all the batches.

Drug content

The results of drug content solid dispersion of sulfamethoxazole were as below.

Table 15: Drug contentof solid dispersion of sulfamethoxazole.

Sr. No.	Formulation	% drug content + S.E.M
1	F1	87.77 ± 0.61
2	F2	89.37 ± 0.66
3	F3	91.36 ± 0.01
4	F4	93.29 ± 0.21
5	F5	95.01 ± 0.61
6	F6	89.33 ± 0.51
7	F7	90.74 ± 0.41
8	F8	92.37 ± 0.61
9	F9	94.45 ± 0.64
10	F10	96.17 ± 0.66

Drug content was found to be in range of 87.77% to 96.17%. The maximum drug content solid dispersion of sulfamethoxazole was found to be of F10 batch and was notated to be 97.17%.

Solubility study

The results of solubility study of solid dispersion of sulfamethoxazole were as below:

Table 16: Solubility (µg/ml) of solid dispersion of sulfamethoxazole.

Sr. No.	Formulation	Solubility (µg/ml) ± S.E.M
1	F1	22.64 ± 0.24
2	F2	23.44 ± 0.45
3	F3	25.35 ± 0.29
4	F4	24.04 ± 0.30
5	F5	25.92 ± 0.77
6	F6	23.99 ± 0.40
7	F7	24.84 ± 0.60
8	F8	24.67 ± 0.55
9	F9	25.03 ± 0.42
10	F10	26.84 ± 0.29

The result of solubility study indicates that pure sulfamethoxazole has a vey low solubility. The drug solubility from the solid dispersion increased significantly, demonstrating that the incorporation of HPMC enhances the solubility than PEG4000. This may be due to capacity of HPMC to avoid recrystallization during cooling of solid dispersion. As the concentration of HPMC increase the solubility also increase, the maximum solubility was observed in F10 batch.

The solid dispersion of sulfamethoxazole was preparaed by Solvent evaporation method:

Table 17: Physical properties

Formulation Code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Angle of repose (Ɵ)	Carr's Index (%)	Hausner's ratio
S1	0.52	0.58	25.09	10.15	1.09
S2	0.54	0.62	25.42	15.61	1.15
S3	0.54	0.58	25.41	6.89	1.07
S4	0.52	0.62	26.42	16.39	1.17
S5	0.59	0.61	27.13	17.14	1.19
S6	0.55	0.62	25.10	9.81	1.08
S7	0.56	0.63	26.11	11.11	1.12
S8	0.53	0.58	26.15	8.62	1.09
S9	0.57	0.64	26.12	11.51	1.20
S10	0.59	0.69	27.40	17.42	1.21

Sulfamethoxazole solid dispersions of Solvent evaporationmethod were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. Angle of repose was less than 28^0, Carr's index values were less than 11 for the precompression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.25 for all the batches indicating good flow properties.

Percentage yield

The result of percentage yield of solid dispersion of sulfamethoxazole waspreparaed by fusion method were as below.

Table 18: percentage yield of solid dispersion sulfamethoxazole.

Sr. No.	Formulation	% yield ± S.E.M
1	S1	63.55 ± 0.45
2	S2	67.88 ± 0.96
3	S3	65.52 ± 0.72
4	S4	69.29 ± 0.38
5	S5	70.42 ± 0.11
6	S6	63.38 ± 0.44
7	S7	64.77 ± 0.11
8	S8	69.94 ± 0.99
9	S9	73.29 ± 0.49
10	S10	75.09 ± 0.22

The prepared solid dispersion gives good percentage yield. The maximum percentage yield was found to be of F5 batch and was noted to be 75.09%. It was found that percentage yield was greater than 63.38% for all the batches.

Drug content

The results of drug content solid dispersion of sulfamethoxazole were as below.

Table 19: Drug contentof solid dispersion of sulfamethoxazole

Sr. No.	Formulation	Drug content + S.E.M
1	S1	87.33 ± 0.68
2	S2	88.83 ± 0.74
3	S3	90.88 ± 0.44
4	S4	93.83 ± 0.69
5	S5	95.91 ± 0.44
6	S6	89.83 ± 0.60
7	S7	91.80 ± 0.74
8	S8	93.83 ± 0.50
9	S9	95.11 ± 0.66
10	S10	97.83 ± 0.82

Drug content was found to be in range of 87.33% to 97.83%. The maximum drug content solid dispersion of sulfamethoxazole was found to be of F10 batch and was notated to be 98.83%.

Solubility study

The results of solubility study of solid dispersion of sulfamethoxazole were as below.

Table 20: Solubility (µg/ml) of solid dispersion of sulfamethoxazole

Sr. No.	Formulation	Solubility + S.E.M
1	S1	22.73± 0.99
2	S2	24.39 ± 0.77
3	S3	24.22± 0.52
4	S4	25.73± 0.88
5	S5	25.01± 0.94
6	S6	23.30± 0.91
7	S7	24.73± 0.22
8	S8	25.37± 0.11
9	S9	27.22 ±0.52
10	S10	28.73± 0.52

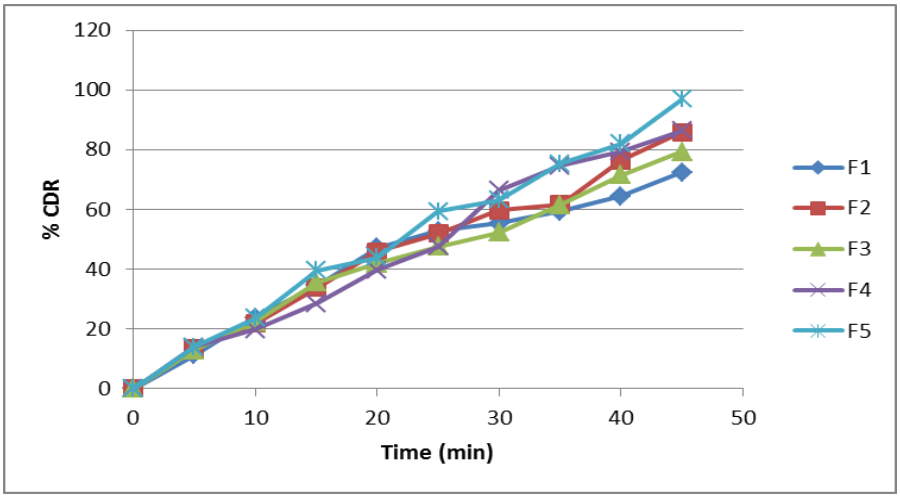
The result of solubility study indicates that pure sulfamethoxazole has a very low solubility. The drug solubility from the solid dispersion increased significantly, demonstrating that the incorporation of HPMC enhances the solubility than PEG4000. This may be due to capacity of HPMC to avoid recrystallization during cooling of solid dispersion. As the concentration of HPMC increase the solubility also increase, the maximum solubility was observed in F10 batch.

In vitro release studies of solid dispersion:

The drug release rate was studied using the USP type II dissolution test apparatus. The dissolution medium was 900 ml of pH 7.2 phosphate buffer at 50 rpm at a temperature of 37 ± 0.5 °C. Samples of 5 ml were collected at different time intervals up to 1 hr and analysed after appropriate dilution by using UV Spectrophotometer at 264 nm.

Table 21: Invitro drug release of solid dispersion with PEG4000 (Fusion method) results.

Time(Min)	F1	F2	F3	F4	F5
0	0	0	0	0	0
5	11.25	13.56	12.91	13.85	14.02
10	23.65	21.67	22.32	19.77	23.57
15	34.41	33.74	35.61	28.45	39.45
20	47.21	45.91	41.89	39.74	43.97
25	52.74	51.94	47.52	47.44	59.37
30	55.31	59.74	52.22	66.41	63.14
35	59.37	61.74	61.45	74.55	75.32
40	64.44	76.44	71.41	79.31	81.98
45	72.36	85.74	79.23	86.44	96.99



Figuer12: Invitro drug release of solid dispersion with PEG4000 (Fusion method) results.

In solid dispersion of sulfamethoxazole with PEG4000 show increase in drug dissolution than dissolution of pure drug. In which F5 show that increase the drug dissolution.

Table 22: Invitro drug release of solid dispersion with HPMC (Fusion method) results

Time(Min)	F6	F7	F8	F9	F10
0	0	0	0	0	0
5	12.32	14.25	13.95	12.98	14.90
10	22.15	21.41	20.96	22.65	29.21
15	29.32	30.87	31.45	32.87	32.20
20	33.62	35.74	36.44	39.78	41.22
25	51.73	42.39	45.82	47.33	51.81
30	59.91	55.76	57.55	58.51	71.70
35	63.65	67.99	61.95	63.44	80.29
40	72.37	74.92	74.44	76.92	82.18
45	78.45	81.32	85.65	89.43	96.31

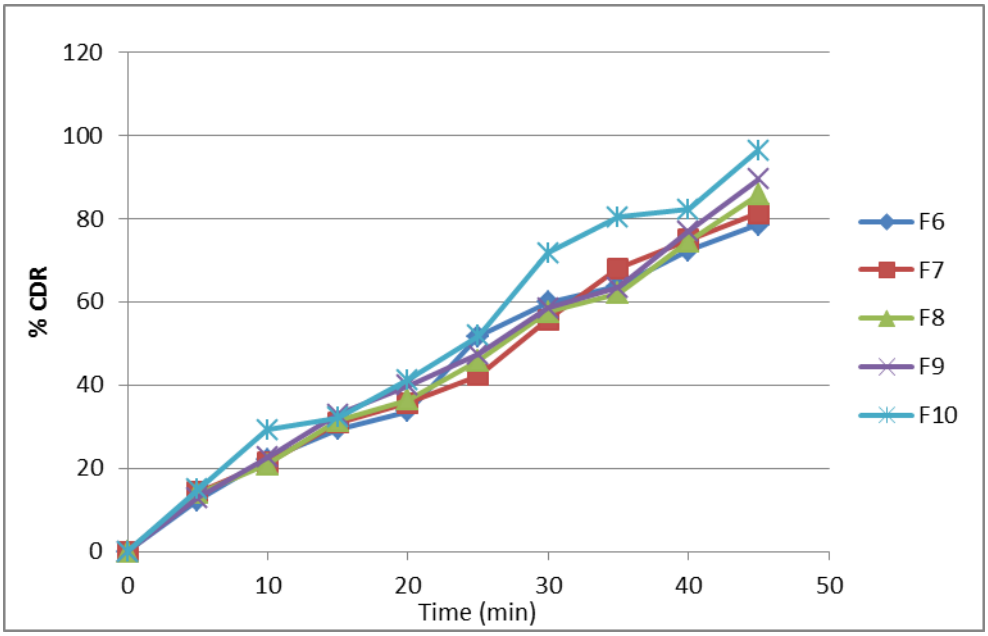


Figure13: Invitro drug release of solid dispersion with HPMC (Fusion method) results.

In solid dispersion of sulfamethoxazole with HPMC show increase in drug dissolution than dissolution of pure drug. In which F10 show that increase the drug dissolution as compare to other.

Table 23: Invitro drug release of solid dispersion with PEG4000 (Solvent evaporation method) results

Time(Min)	S1	S2	S3	S4	S5
0	0	0	0	0	0
5	14.29	13.24	15.55	15.98	16.38
10	28.42	29.12	29.52	29.21	30.62
15	32.12	33.22	35.25	32.20	36.31
20	40.10	41.22	41.11	41.22	43.29
25	51.12	52.32	52.98	51.81	56.91
30	70.50	72.52	71.62	71.70	72.63
35	76.52	78.24	81.30	80.29	81.31
40	77.52	81.13	82.95	82.18	85.52
45	81.15	85.21	91.01	91.31	95.62

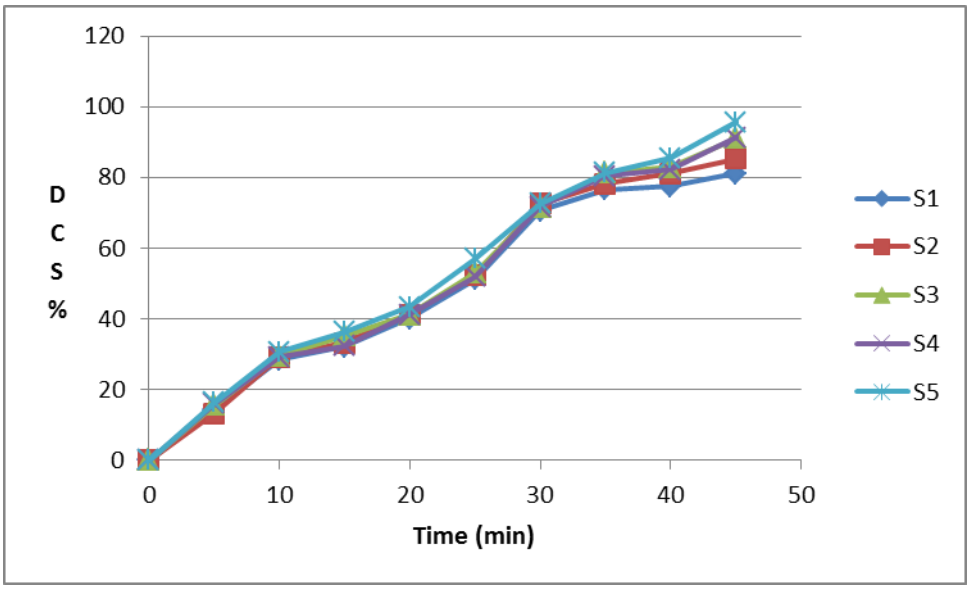


Figure14: Invitro drug release of solid dispersion with PEG4000 (Solvent evaporation method) results.

In solid dispersion of sulfamethoxazole with PEG4000 show increase in drug dissolution than dissolution of pure drug. In which S5 show that increase the drug dissolution as compare to other.

Table 24: Invitro drug release of solid dispersion with HPMC (Solvent evaporation method) results

Time(Min)	S6	S7	S8	S9	S10
0	0	0	0	0	0
5	12.30	12.24	14.55	16.98	20.38
10	29.42	28.12	28.50	29.42	33.62
15	32.12	33.22	36.23	32.20	37.31
20	41.10	43.22	42.11	44.22	45.29
25	52.12	55.32	53.98	56.81	66.91
30	63.50	61.52	72.62	71.70	72.63
35	69.52	72.24	85.30	80.29	81.30
40	72.85	81.13	88.95	87.18	89.52
45	79.54	85.01	91.11	95.31	98.62

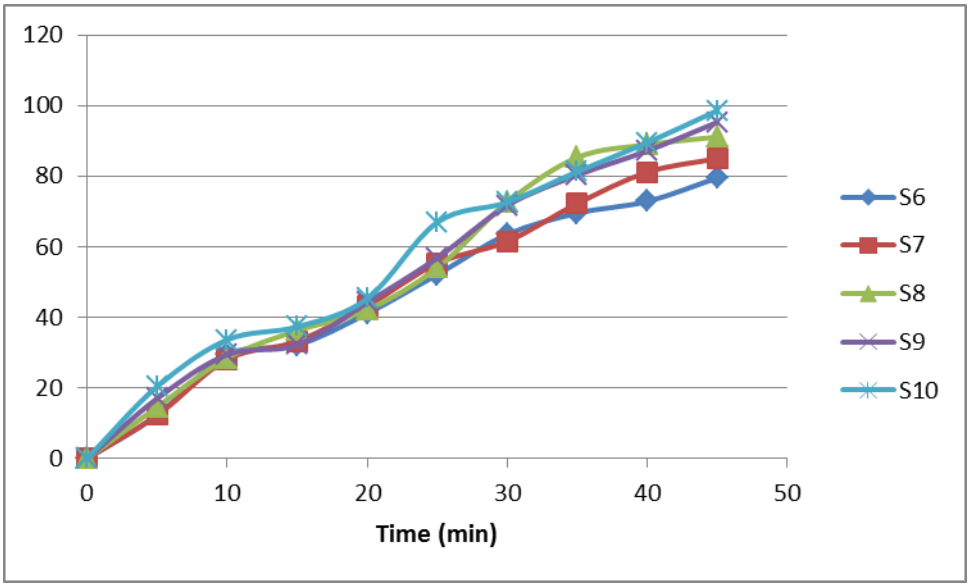


Figure 15: Invitro drug release of solid dispersion with HPMC (Solvent evaporation method) results.

In solid dispersion of sulfamethoxazole with HPMC show increase in drug dissolution than dissolution of pure drug. In which S10 show that increase the drug dissolution as compare to other.

On the basis of above study we concluded that F5, F10, S5, S9, S10 show good result as compared to other. F5, F10, S5, S9, S10 which show that increased drug dissolution rate as well as their flow property also good as compared to F1, F2, F3, F4,F6,F7,F8,S1,S2,S3,S4,S6,S7,S8.

On the basis of above study we selected 5 batches (Solvent evaporation method and fusion method) with sulfamethoxazole and polymer HPMC, PEG4000 with different ratios.

Formulation of tablet

Prepared solid dispersion (260mg) equivalent to 300mg of Sulfamethoxazole was mixed with Magnesium stearate 6mg (as lubricant) Talc 6mg (as glidant), Sodium starch glycolate 28mg (as disintegrating agent) and directly compressible excipient as Microcrystalinecellouse 28mg (as diluents) triturated for 2 hours. The prepared mixture was then passed through a sieve no 80. The prepared granules were then compressed by using CADMACH single station punching machine. Same prepared solid dispersion of F5, F10, S5, S9, S10 batches.

Table25: Formulation of 300mg Sulfamethoxazole tablet.

Ingridient	F5	F10	S5	S9	S10
Solid dispersion ofSulfamethoxazole wt	180	180	180	150	180
Magnesium sterate	6	6	6	6	6
Talc	6	6	6	6	6
Sodium starch glycolate	20	20	20	20	20
Microcrystalinecellouse	88	88	88	118	88
Total wt	300	300	300	300	300

Micromeritics studies of mixture blend

Table 26: Micromeritics Evaluation of mixture blend.

Parameters	F5	F10	S5	S9	S10
Bulk Density Gm/cm^2	0.591±0.006	0.571±0.004	0.567±0.008	0.578±0.001	0.591±0.009
Tapped Density Gm/cm^2	0.599±0.002	0.582±0.001	0.574±0.004	0.581±0.005	0.625±0.006
% Compressibility (cars index)	17.11	16.22	16.01	17.28	18.82
Hausners Ratio	1.19	1.15	1.17	1.15	1.19
Angle of Repose	$27^0$13’	$28^0$34’	$27^0$16’	$30^0$74’	$31^0$64’

(Means of three sample ± SEM)

The physical characters of Sulfamethoxazole mixture blend were found to be identical with standards given in analytical profile of drug substances.

Evaluation of Sulfamethoxazole tablet.

Table 27: Evaluation of Sulfamethoxazole tablet.

Parameters	F5	F10	S5	S9	S10
Thickness (mm)	3.1±0.07	3.1±0.10	3.3±0.19	3.4±0.12	3.4±0.17
Weight Variation (mg)	300±1.54	299±1.33	301±1.57	299±1.41	300±1.22
Friability (%W/W)	0.34	0.38	0.42	0.33	0.410
Hardness (kg/cm^2)	2.5±0.24	2.2±0.55	2.6±0.14	2.8±0.24	2.4±0.34
Disintegration Time (min)	17±0.85	18±0.62	17±0.92	18±0.11	18±0.67
Percent Drug Content	95.02±0.11	97.52±0.41	97.12±0.55	98.12±0.12	98.91±0.46

(Means of three sample ± SEM)

In- Vitro Dissoution of Sulfamethoxazole tablet

Table 28: % CDR Vs Time (min) of prepared Sulfamethoxazole tablet with different polymer and ratio.

Time (min)	F5	F10	S5	S9	S10
0	0	0	0	0	0
5	12.85± 0.40	14.66± 0.11	13.91± 0.41	15.15± 0.22	16.20± 0.10
10	29.01± 0.11	18.85± 0.61	29.24± 0.89	22.66±0.32	35.18± 0.34
15	38.77 ±0.56	22.80± 0.55	38.76± 0.85	37.41± 0.22	51.74± 0.87
20	42.81±0.11	37.02±0.41	52.38± 0.38	44.87± 0.61	68.45±0.52
25	58.85± 0.49	44.88± 0.43	64.22± 0.63	52.85± 0.62	71.53± 0.61
30	61.11± 0.91	52.19±0.61	71.66± 0.81	65.19± 0.43	85.18± 0.42
35	66.55± 0.35	61.22± 0.91	79.15± 0.39	72.14± 0.37	92.41± 0.38
40	76.15± 0.41	77.46±0.84	88.85± 0.48	87.75± 0.11	98.4± 0.09
45	88.80± 0.48	89.21±0.34	96.41± 0.71	98.18± 0.22	99.92± 0.14

(Means of three sample ± SEM)

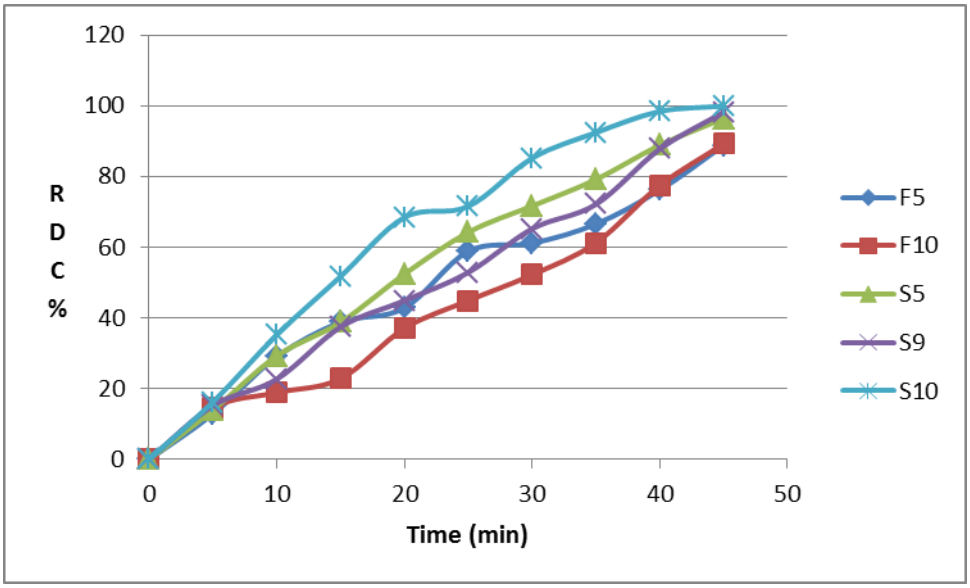


Figure 16: % CDR Vs Time (min) of prepared Sulfamethoxazole tablet with different polymer and ratio.

On the basis of above study we can say that S10 show good result as compared to F5, F10, S5, S9. which show that increased drug dissolution rate as well as their flow property also good as compared to F5, F10, S5, S9. Among all the formulations solvent evaporation method S10 formulation containing, Sulfamethoxazole and HPMC in the ratio of 1:5 showed good result as compared to fusion method.

Kinetic Analysis of In Vitro Release Rate of Formulation

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

- Zero order kinetic model cumulative percentage drug release vs time.
- First order kinetic model log cumulative percentage drug release remaining vs time.
- Higuchi's model cumulative percentage drug release vs square root time

- Korsmeyer's equation/Peppa's model log cumulative percentage drug release vs log time

1. Zero order kinetic

Zero order release would be predicted by the following equation:

$At = A_0 – K_0 t$

Where,

A_t = Drug release at time 't'

A_0 = Initial drug concentration

K_0 = Zero order rate constant (hr^{-1})

When the data is plotted as cumulative percent drug release vs time, if the plot is linear then the data obeys Zero order release kinetics, with a slope equal to K_0

2. First order kinetic

First order release would be predicted by the following equation:

$Log\ C = log\ C_0 - K_t/2.303$

Where,

C =Amount of drug remained at time 't'

C_0 =Initial amount of drug

K_0 =First order rate constant (hr^{-1})

When the data is plotted as cumulative percent drug remained vs time yields a straight line, indicating that the release follow first order release kinetics. The constant K can be obtained by multiplying 2.303 with slop values.

3. Higuchi's model

Drug release from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation.

$Q = [D£ / \tau(2A - £Cs)\ Cst]^{1/2}$

Where,

Q = Amount of drug release at time 't'

D = Diffusion coefficient of drug in the matrix

A = Total amount of drug in the matrix

C_S = The solubility of drug in the matrix

£ = Porosity of the matrix

T = Tortuosity

T = Time (hrs) at which Q amount of drug is released

Above equation may be simplified if one assumes that D, Cs, and A, are constant.

Then equation becomes.

$Q = K\ t^{½}$

When the data is plotted according to equation i.e. cumulative drug release vs square root of time yield a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K'.

4. Korsmeyer's equation/Peppa's model

To study the mechanism of the drug release from the solid dispersion, the release data were also fitted to the well- known exponential equation (Korsmeyer's equation/Peppa's law equation), which is often used to describe the drug releasebehavior from polymeric systems.

$M_t/M_a = Kt^n$

Where,

M_t/M_a = The fraction of drug release at time 't'

K = Constant incorporating the structural and geometrical characteristics of the drug/polymer

N = Diffusion exponent related to the mechanism of release

Above equation can be simplified by appiying log on both side and we get:

$Log\ M_t/M_a = Log\ K + n\ Log\ t$

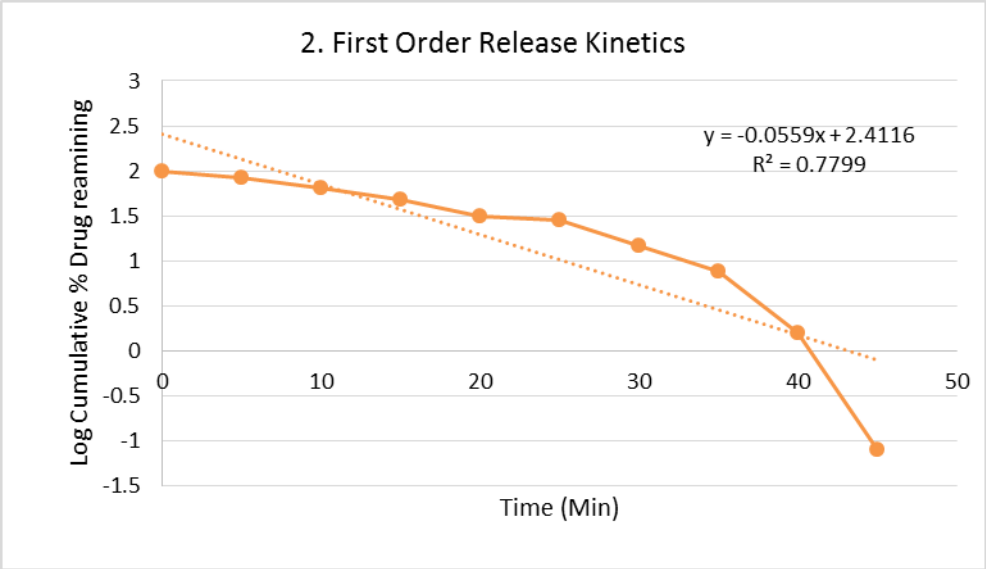
When the data is plotted as log of drug released vs log time, yield a straight line with a slope equal to 'n' and the 'k' can be obtained from y intercept. For Fickian release 'n' = 0.5 while for anomalous (non Fickian) transport 'n' range from 0.5 to 1.0.

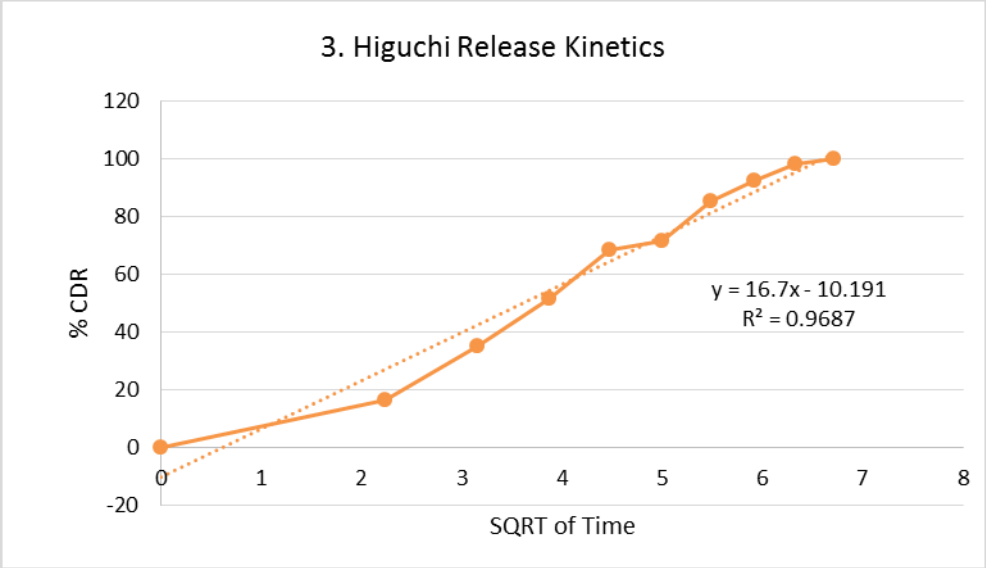
Table 29: Mechanism of drug release as per Korsmeyer's equation/Peppa's model.

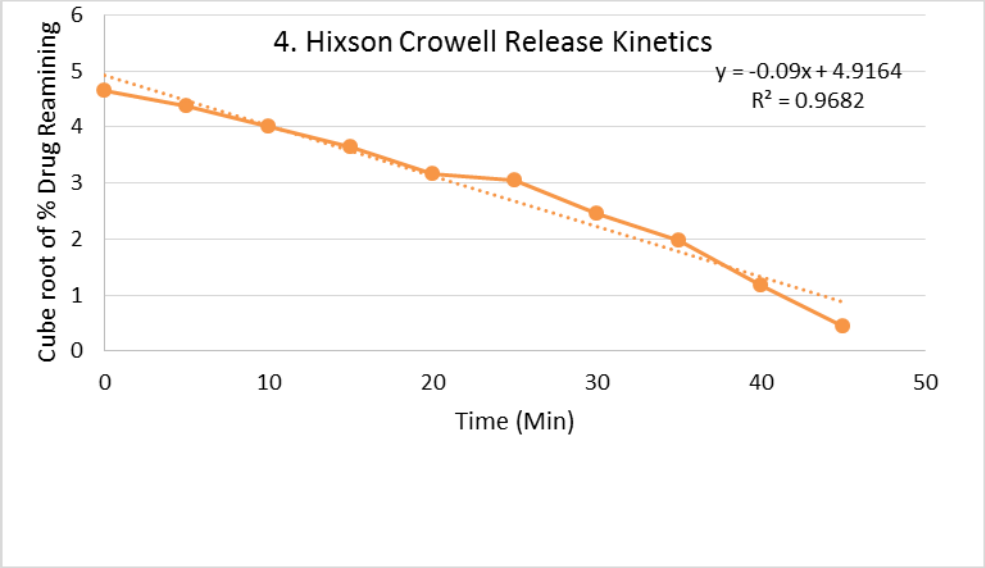
Sr. No.	n Value	Drug Release
1	N<0.5	Fickian release
2	0.5<n<1	Non Fickian release
3	n>1	Case II transport

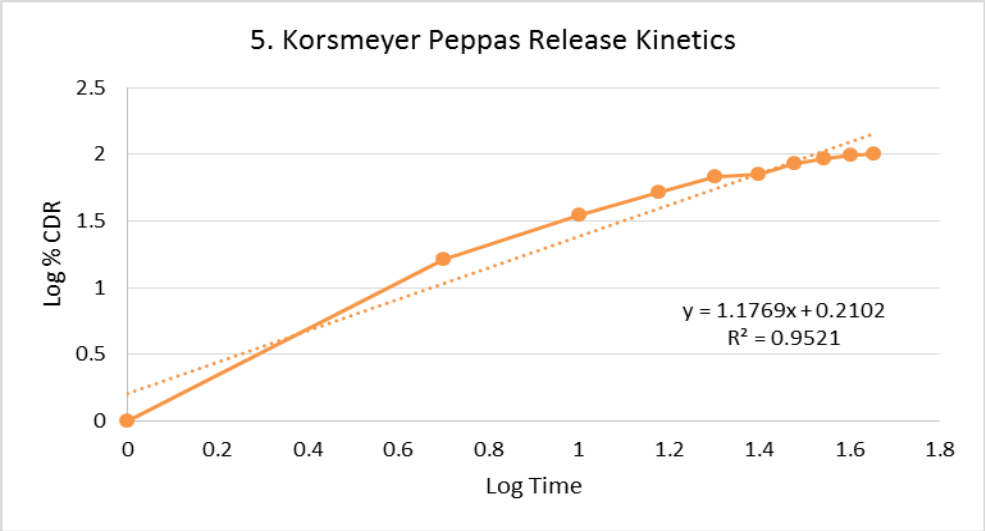
Time (min)	%CDR	Log Cumulative % Drug remaining	SQRT of Time	Cube root of % Drug Remaining	Log time	Log %CDR
0	0	2	0	4.641588834	-	-
5	16.2	1.923244019	2.236067977	4.376040569	0.69897	1.209515
10	35.18	1.811709027	3.16227766	4.017010888	1	1.5462958
15	51.74	1.683587318	3.872983346	3.640791198	1.17609	1.7138264
20	68.45	1.498999364	4.472135955	3.15984991	1.30103	1.8353735
25	71.53	1.454387467	5	3.053485221	1.39794	1.8544882
30	85.18	1.170848204	5.477225575	2.456307501	1.47712	1.9303376
35	92.41	0.880241776	5.916079783	1.965232444	1.54407	1.965719
40	98.4	0.204119983	6.32455532	1.169607095	1.60206	1.9929951
45	99.92	-1.096910013	6.708203932	0.430886938	1.65321	1.9996524


1. Zero Order Release Kinetics
% CDR
Time (Min)
y = 2.2597x + 11.058
R² = 0.9468
0
20
40
60
80
100
120
0
10
20
30
40
50


2. First Order Release Kinetics
Log Cumulative % Drug reamining
Time (Min)
y = -0.0559x + 2.4116
R² = 0.7799
3
2.5
2
1.5
1
0.5
0
-0.5
-1
-1.5
0
10
20
30
40
50


3. Higuchi Release Kinetics
% CDR
SQRT of Time
y = 16.7x - 10.191
R² = 0.9687
120
100
80
60
40
20
0
-20
0
1
2
3
4
5
6
7
8





Sr. No.	Model Name	R^2 Value
1	Zero Order	0.9468
2	First Order	0.7799
3	Higuchi	0.9687
4	Hixson Crowell	0.9682
5	KorsmeyerPeppas	0.9521

Base on the regression coefficients (R^2), the Higuichi model displayed the best linearity for majority of the formulations with an R^2 value of between 0.7799 And 0.9687, indicating that the drug release mechanism was based on a square root of a time dependent process based on Fickian diffusion .

Accelerated Stability Study

Stability studies of tablets were performed at 45 ± 2^0C and 75% RH for one month. Then the thickness, hardness, release profile and drug content of tablets was determined and calculated. It indicates that irrespective of concentration of polymer, these formulations are able to retain their stability for a month.

Table 30: Evaluation of Sulfamethoxazole tablet after stability study.

Parameters	Before Stability (0 Days)	After Stability (30 days)
Thickness (mm)	3.4±0.007	3.4±0.012
Hardness (kg/cm^2)	3.2±0.09	3.1±0.01
Disintegration Time (min)	18±0.41	18±0.59
Percent Drug Content	98.91±0.64	98.22±0.09

(Means of three sample ± SEM)

Dissolution study

Table 31: In – vitro release study of Sulfamethoxazole tablet after stability study.

Time	Before Stability (0 Days)	After Stability (30 days)
0	0	0
5	16.20±0.11	16.11±0.09
10	28.88±0.95	27.45±0.48
15	37.45±0.77	36.33±0.38
20	42.10±0.13	41.05±0.14
25	55.07±0.15	55.14±0.11
30	62.08±0.75	61.10±0.80
35	72.34±0.46	71.52±0.14
40	85.80±0.22	83.10±0.85
45	99.92±0.14	99.75±0.05

(Means of three sample ± SEM)

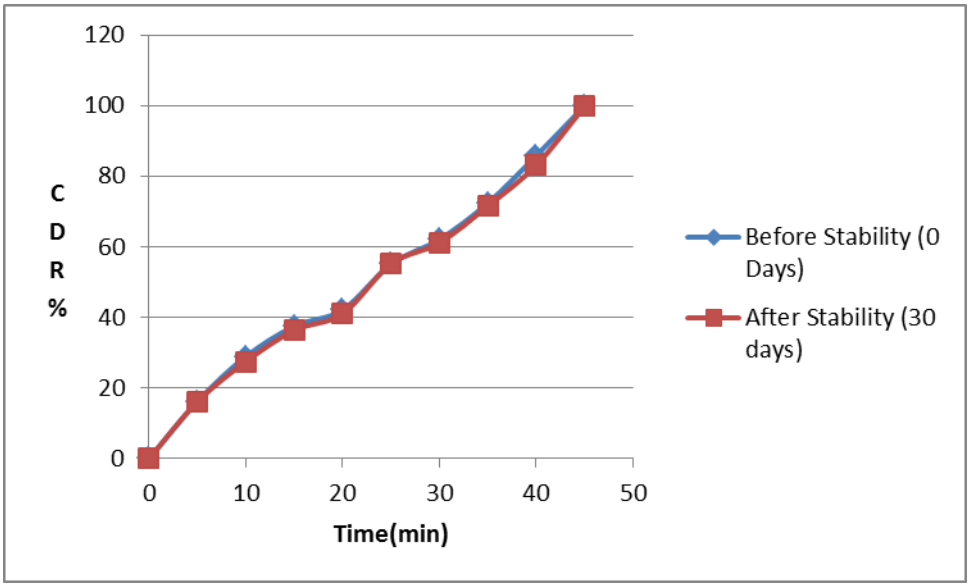


Figure17: In – vitro release study of Sulfamethoxazole tablet after stability study.

From stability data it was found that there is no considerable change in the thickness, hardness, disintegration time, drug content and dissolution profile of the tablet. This signifies that the above formulation is stable at temp 45± 2^0C and 75%.

9. CONCLUSION

Solubility is the key parameter for the oral bioavailability of poorly water soluble drugs. Dissolution of drug is rate determining step for oral absorption of poorly water soluble drug which subsequently affect the in vivo absorption of drug. Studies were under taken on the preparation and evaluation of solid dispersion of Sulfamethoxazole with a view to develop fast release formulation of Sulfamethoxazole. In the prepration of solid dispersion carries such as PEG ^{4000} and HPMC were used. In this present study solid dispersions were prepared by solvent evaporation and fusion methods.

The standard curve of Sulfamethoxazole was obtained and good correlation was obtained with R^2 value 0f 0.999. The medium selected was pH 7.2 phosphate buffer.

FTIR studies revealed that no interactions between drug and excipients.

The pre compression blend of Sulfamethoxazole soild dispersions were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio**.** The precompression blend of all the batches indicating good to fair flowability and compressibility.

10. Solid dispersions were prepared with various concentrations of carriers, the prepared solid dispersions were compressed into tablets. The formulated tablets were evaluated for various quality control parameters. The tablets were passed all the tests. The product obtained by all these means were appropriately characterized and evaluated for enhancement of solubility and for their in vitro dissolution. The optimized solid dispersion batch was used to formulate and evaluate conventional tablet and compare with Solid dispersion of Sulfamethoxazole by fusion method using HPMC polymer show that increase in solubility and good dissolution as compared to PEG4000.

Methods and fusion methods

Successful solubilization of Sulfamethoxazole was achieved using solid dispersion technique. In the present study synergism of two polymer i.e. HPMC, PEG4000 was evaluated for the enhancement of solubility and dissolution rate as well as flowability of Sulfamethoxazole.

1. The poorly water soluble drug Sulfamethoxazole used in the preparation of solid dispersions was characterized for preformulation and spectral analysis by UV spectroscopy and FTIR spectroscopy.
2. Solid dispersion were prepared using two different method solvent evaporation method and fusion methods with different ratio of different polymer.
3. Solid dispersion were prepared using hydrophilic polymer. The hydrophilic carriers used were HPMC, PEG4000.
4. These hydrophilic polymer and Sulfamethoxazole were check for compatibility by FTIR spectroscopy.
5. From the FTIR of all these polymers and drug Sulfamethoxazole, it was evident that there was no probable interaction found between drug and polymer.
6. Dissolution studies of (solvent evaporation method) S10 batch showed definite increase in the dissolution rate of all Solid dispersion of Sulfamethoxazole as compared to fusion methods formulation.
7. S10 batch showed maximum dissolution rate.
8. Solid dispersion of Sulfamethoxazole by fusion method using HPMC polymer show that increase in solubility and good dissolution as compared to PEG4000.
9. Solid dispersion of Sulfamethoxazole by solvent evaporation method using HPMC polymer show that increase in solubility and good dissolution as compared to PEG4000.
10. The optimum dissolution was shown by the F5, F10, S5, S9, S10 batches.
11. S10 batch of (solvent evaporation method) 1:5 ratio using HPMC polymer enhance the dissolution rate showing dissolution efficiency comparable to that obtained with F5, F10 batches of fusion method.
12. The study thus presented a system capable of increasing the dissolution rate of Sulfamethoxazole, immediate release formulation is a solution to overcome the variable bioavailability problem of Sulfamethoxazole

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