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Formulation and Invitro Evaluation of Ambrisentan Solid Dispersions Using Melt Extrusion Method

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ABSTRACT
Ambrisentan is an orally active selective type A endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension. The main aim of present work is to formulate solid dispersions of poorly water soluble bcs class 2 drug Ambrisentan, which give the application of solid dispersions results in increasing the solubility of many poorly soluble drugs the objective of the present study, investigated to improve the solubility and rapidly increases bioavailability of and Ambrisentan by using PEG 6000, Ethyl cellulose, PEG 4000 and PVPK-30 to improve patient compliance. The Solid dispersions of Ambrisentan were prepared using melt extrusion method. Characterization of the prepared Solid dispersions was done with respect to saturation solubility, percentage yield, entrapment efficiency and in-vitro dissolution study. The results indicated that Increase in the stabilizer concentration of PEG 6000 at 1:3 ratio shows 98.68% of drug release, so the formulations prepared by using PEG 6000 releases more drug release at the end of 60mins than the other carriers and drug release kinetics follows Zero order kinetics.Solid dispersions seems to be a promising approach for bioavailability enhancement because of the simple method of its preparation and its universal applicability.
Keywords: Ambrisentan, PEG 6000, PEG 4000, HPMC K4M and PVPK-30.

I. INTRODUCTION

Oral bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be the rate determining step for the onset of therapeutic activity. Therefore efforts to increase drug dissolution of drug are often needed. Methods available to improve dissolution include salt formation, micronization and addition of solvent or surface active agents. Solid dispersion (SD) is one of such methods and it involves a dispersion of one or more active ingredients in an inner carrier or matrix in solid state prepared by melting, dissolution in solvent or melting solvent method.

The enhancements of oral bioavailability of such poorly water-soluble drugs often show poor bioavailability because of low and erratic levels of absorption. Drugs that undergo dissolution rate limited gastrointestinal absorption generally show improved dissolution and bio availability as a result of reduction in particle size. However, micronizing of drugs often leads to aggregation and agglomeration of particles, which results in poor wettability. Solid dispersions of poorly water-soluble drugs with water-soluble carriers have been reduced the incidence of these problems and enhanced dissolution. The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water-soluble drugs overcame the limitations of previous approaches such as salt formation, solubilization by co-solvents, and particle size reduction. Studies revealed that drugs in solid dispersion need not necessarily exist in the micronized state. A fraction of the drug might molecularly disperse in the matrix, thereby forming a solid dispersion. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles.

The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water soluble drugs. In addition, in solid dispersions, a portion of drug dissolves immediately to saturate the gastrointestinal tract fluid, and excess drug precipitates as fine colloidal particles or oily globules of submicron size. solid dispersion technique was firstly demonstrated by Sekiguchi and Obi. They proposed the faster absorption of poorly water-soluble drugs such as sulfathiazole by the formation of eutectic mixture with a water-soluble and physiologically inert carries like urea. Upon exposure to aqueous fluids the active drug released into fluids is fine, dispersed particles because of fine dispersion of the drug in the solid eutectic mixture and the faster dissolution of the soluble matrix. The eutectic mixture contained 52 per cent w/w of sulfathiazole and 48 per cent w/w of urea. The possibility of using solid solution approach in which a drug is molecularly dispersed in soluble carrier was subsequently introduced.

International Journal of Pharmaceutical Research and Applications
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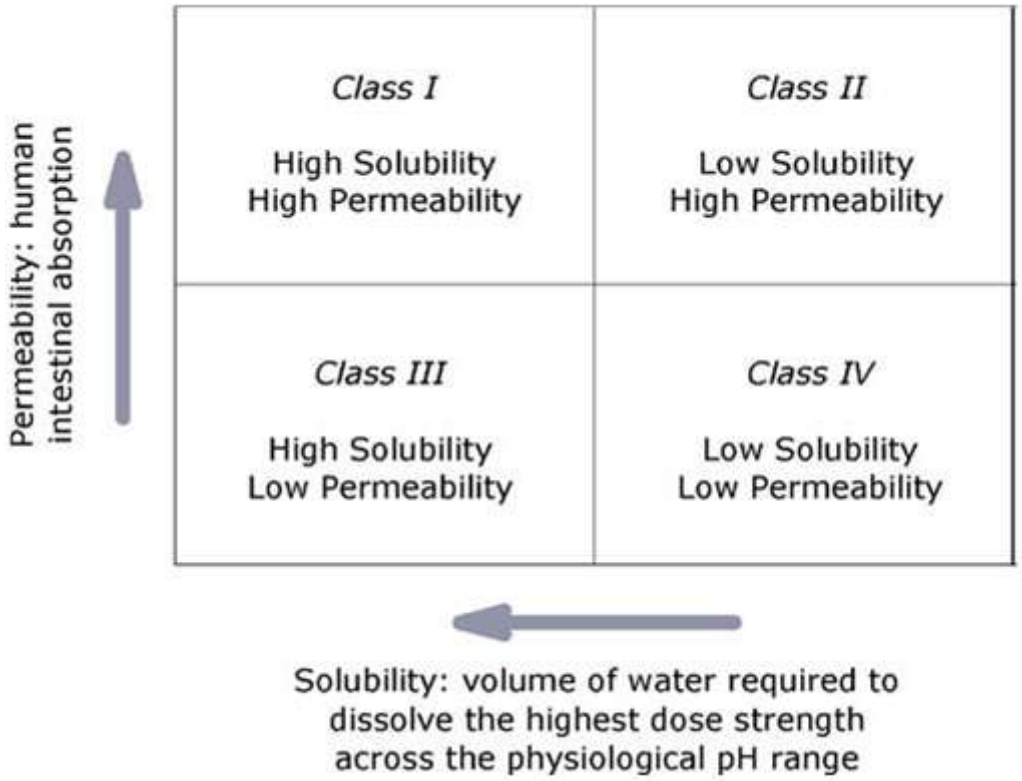

Fig: 1.1 Biopharmaceutical classification system chart

A solid dispersion technique has been used by various researchers who have reported encouraging results with different drugs The first drug whose rate and extent of absorption was significantly enhanced using the solid dispersion technique was sulfathiazole by Sekiguchi and Obi (Sekiguchi, 1961). Technique for the preparation of solid dispersions, Lyophilization has also been thought of as a molecular mixing technique where the drug and carrier were co-dissolved in cyclohexanol, frozen and then sublimed under vacuum to obtain a lyophilized molecular dispersion (Lin, 1980)[1].

Numerous solid dispersion systems have been demonstrated in the pharmaceutical literature to improve the dissolution properties of poorly water soluble drugs. Other methods, such as salt formation, complexation with cyclodextrins, solubilization of drugs in solvent(s), and particle size reduction have also been utilized to improve the dissolution properties of poorly water-soluble drugs; however, there are substantial limitations with each of these techniques. On the other hand, formulation of drugs as solid dispersions offers a variety of processing and excepient options that allow for flexibility when formulating oral delivery systems for poorly water soluble drugs.

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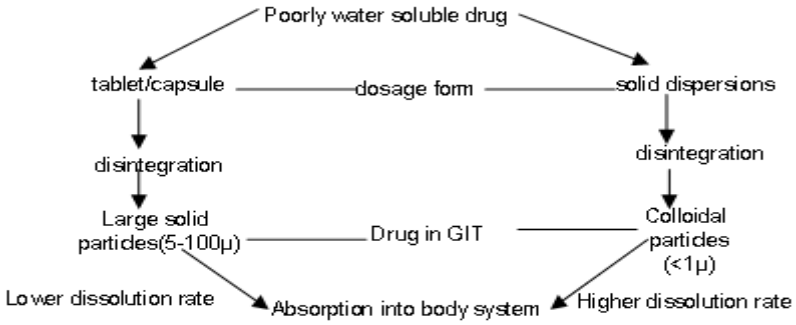

Schematic representation of the bioavailability enhancement of poorly Water soluble drug by solid dispersion technique

Fig:1.2 Schematic representation of bioavailability enhancement of poorly water soluble drug

Oral bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be the rate determining step for the onset of therapeutic activity. Therefore efforts to increase drug dissolution of drug are often needed. Methods available to improve dissolution include salt formation, micronization and addition of solvent or surface active agents. Solid dispersion (SD) is one of such methods and it involves a dispersion of one or more active ingredients in an inner carrier or matrix in solid state prepared by melting, dissolution in solvent or melting-solvent method4. The technique has been used for a wide variety of poorly aqueous soluble drug. Poorly soluble drugs represent a problem for their scarce availability related to their low dissolution rate. The major drawback of low aqueous solubility is delays its absorption from the gastrointestinal tract. Solubility behavior of a drug is one of the key determinants of its oral bioavailability. Noyes- Whitney equation provides some hints as to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral Availability[2].

$$\frac{dc}{dt} = \frac{AD(Cs - c)}{h}$$

Where,

dC/dt - is the rate of dissolution,

A -is the surface area available for dissolution,

D - is the diffusion coefficient of the compound,

Cs- is the solubility of the compound in the dissolution medium,

C -is the concentration of drug in the medium at time **t** and

h - is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.

To increase the dissolution rate from equation the following approaches are available.

- To increases the surface area available for dissolution Decreasing the particle size of drug.
- Optimizing the wetting characteristics of compound surface.
- To decrease the boundary layer thickness.
- Ensure sink condition for dissolution.
- Improve apparent solubility of drug under physiologically relevant conditions.
- Drug administered in fed state is a way to improve the dissolution rate.

Of these possibilities, changes in the hydrodynamics are difficult to invoke in-vivo and the maintenance of sink conditions will depend on how permeable the gastrointestinal mucosa is to the compound as well a soon the composition and volume of the luminal Fluids. Although some research effort has been directed towards permeability enhancement using appropriate excipients, results to date have not been particularly encouraging. Administration of the drug in the fed state may be an option to improve the dissolution rate and also to increase the time available for dissolution; the likely magnitude of the food effect can be forecasted from dissolution tests in bio relevant media[3,4].

The approaches that have commonly been used to overcome drawbacks associated with poorly water soluble drugs, in general includes micronization, salt formation, use of surfactant and use of pro- drug[5] however all these techniques have certain limitations. Techniques that have commonly been used to improve dissolution and bioavailability of poorly water-soluble drugs, in

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general, include micronization, the use of surfactant, and the formation of solid dispersions. Chiou and Riegelman outlined 6 types of drug carrier interactions in solid-state dispersions: simple eutectic mixtures, solid solutions, glass solutions and glass suspensions, amorphous precipitates, and compound or complex formation. Other factors such as increased wettability, solubilization of the drug by the carrier at the diffusion layer, and the reduction or absence of aggregation and agglomeration may also contribute to increased dissolution. Micronization has several disadvantages, the main one being the limited opportunity to control important characters of the final particle such as size, shape, morphology, surface properties and electrostatic charges. In addition micronization is a high-energy process, which causes disruptions in the drug s crystal lattice, resulting in the presence of disordered or amorphous regions in the final product. The amorphous regions are thermodynamically unstable and are therefore susceptible to recrystallization upon storage, particularly in hot and humid conditions[6] . All poorly water-soluble drugs are not suitable for improving their solubility by salt formation. The dissolution rate of a particular salt is usually different form that of parent compound. However sodium and potassium salts of weak acids dissolve more rapidly than the free salts. Potential disadvantages of salt forms include high reactivity with atmospheric carbon dioxide and water resulting in precipitation of poorly water-soluble drug, epigastric distress due to high alkalinity.

Use of co-solvents or surfactants to improve dissolution rate pose problems, such as patient compliance and commercialization. Even though particle size reduction increases the dissolution rate, the formed fine powders showing poor wettability and flow properties. Solid dispersion technique has come into existence to eliminate all these problems. However, the most attractive option for increasing the release rate is improvement of the solubility through formulation approaches[7].

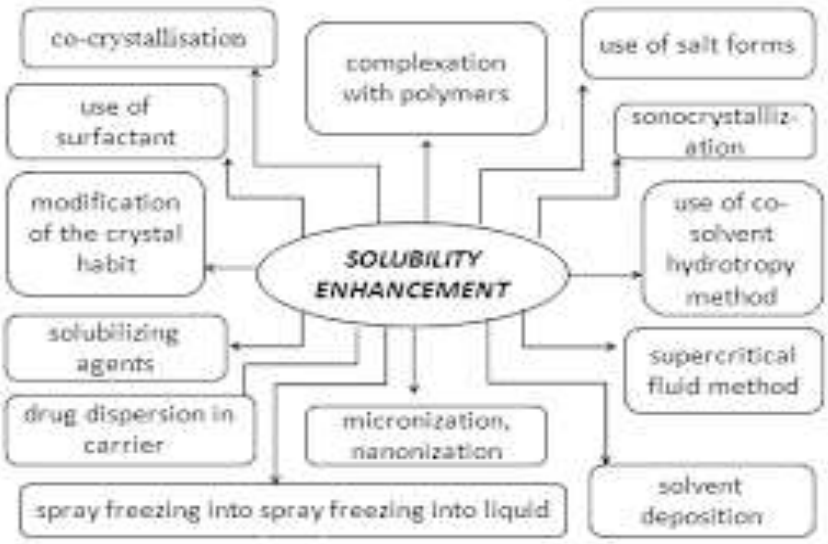

Fig: Summarizes the various formulation and chemical approaches that can be taken to improve the solubility or to increase the available surface area for dissolution

The dissolution of a drug from its solid oral dosage forms depends upon its release from the dosage form and its subsequent mixing into physiological fluids. It has been estimated that nearly 35-40% of the drugs suffer from poor aqueous solubility, thereby affecting their absorption from the gastrointestinal tract, which leads to poor oral bioavailability, high intra- and inter-subject variability, increase in dose, reduction in therapeutic efficiency and finally failure in formulation development. The development of solid dosage forms for water-insoluble drugs has been a major challenge for pharmaceutical scientists for decades. Various formulation strategies such as micronisation, micellar solubilization, complexation, dendrimers for drug solubilization, formation of solid solutions or dispersions with hydrophilic carriers, self-

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microemulsifying drug delivery systems, spray drying, nano approaches, pro-drug approaches and salt synthesis have been developed to increase the dissolution rate of water-insoluble drugs. An attractive possibility is employing a simple solid dispersion technique making use of various hydrophilic carriers. Solid dispersions (SDs) are defined as the dispersion of one or more active ingredients in an inert hydrophilic carrier or matrix in a solid state, and are prepared by the fusion, solvent or solvent-fusion method. This technique enables reducing particle size to a nearly molecular level, offers a variety of processing and excipient options that allow for flexibility when formulating oral delivery systems of poor water-soluble drugs that are cost-effective and significantly reduced in dosage. It has been widely demonstrated that a hydrophilic carrier dissolves rapidly, exposing the drug particles to the dissolution medium as fine particles facilitating quick dissolution and absorption[8]. The mechanisms for increased dissolution rate may include reduction of crystallite size, solubilization effect of the carrier, absence of aggregation of drug crystallites, improved wettability and dispersability of a drug from the dispersion, dissolution of the drug in the hydrophilic carrier or conversion of the drug to an amorphous state. Schizophrenia is a severe non-curable illness of the brain with serious consequences if not properly treated and kept under control. It is the most common form of severe mental illness. Olanzapine (OLZ;2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno-[2,3-b],[1,5]benzodiazepine) is a relatively new benzodiazepine atypical antipsychotic medication, which belongs to the class of the thienobenzodiazepines and has proven efficacy against the positive and negative symptoms of schizophrenia, bipolar disorder and other forms of psychosis. It exhibits poor water solublility and belongs to Biopharmaceutic Classification System (BCS) class II of drugs (low solubility and high permeability), highly bound to plasma protein (about 93%). Following oral administration, Cmax is reached within 5–6 h of dosing. OLZ Ashish et. al., Am. J. PharmTech Res. 2014; 4(5) ISSN: 2249-3387 www.ajptr.com 594 undergoes extensive pre-systemic metabolism in the liver, resulting in relatively very low oral bioavailability. The objective of this work is to enhance the aqueous solubility of poorly water-soluble drug OLZ by adopting a solid dispersion approach using mannitol as the hydrophilic carrier and to physico-chemically characterize the in vitro dissolution behavior of the solid dispersions[9].

1.2 Solid dispersions

Solid dispersions(SDs) traditionally have been used as an effective method to improve the dissolution properties and bioavailability of poorly water-soluble drugs. Since 1961, many investigators have studied SDs of poorly water-soluble drugs with various pharmacologically inert carriers to increase the dissolution and oral absorptionof poorly water-soluble drug show ever, only a few systems are useful commercially. Different types of drug–carrier interactions in solid-state dispersions have been suggested by Chiou and Riegelman:simple eutectic mixtures, solid solutions, glass solutions and glass suspensions, amorphous precipitates in a crystalline carrier, and compound or complex formation. In SD systems, a drug may exist as an amorphous form in polymeric carriers, and this may result in improved solubility and dissolution rates compared with crystalline material. The mechanisms for the enhancement of the dissolution rate of SDs have been proposed by several investigators. Molecular dispersion of drug in polymeric carriers may lead to particle size reduction and surface area enhancement, which result in improved dissolution rates. Furthermore, no energy is required to breakup the crystal lattice of a drug during dissolution process and improvement in drug solubility and wettability due to surrounding hydrophilic carriers. Reduction or absence of aggregation and agglomeration may also contribute to increased dissolution. The methods used to prepare SDs include the melting method, the solvent method, and the solvent wetting method. Among the various approaches employed to improve the dissolution of poorly soluble drugs, solid dispersion has been proven successful. Fast or immediate drug dissolution from solid dispersions has been observed due to increased wettability, improved dispersibility of drug particles, existence of the drug in amorphous form with improved solubility and absence of aggregation of drug particles .Literature shows that the solvent evaporation method has been used for the preparation of solid dispersions for dissolution enhancement .Earlier studies show that solid dispersion systems increased the drug dissolution due to improved solubility, wet ability and dispersibility using hydrophilic carriers In the

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present work, physical mixtures,co-grinding and co-precipitation or solvent evaporaration method was used to prepare solid dispersions of prednisolone. This method requires the minimal amountof solvent in dissolving the drug. We used various polymeric carriers it his study. Polyvinylpyrrolidone(PVP) and polyethyleneglycol(PEG) were chosen as water-soluble polymers.

The physicochemical properties of prednisolone in solid dispersions were characterized by differential scanning calorimetry and FTIR and various hydrophilic solid dispersion carriers on its dissolution properties were investigated[10].

Chiou and Riegelman defined the term solid dispersion as "a dispersion involving the formation of eutecticmixtures of drugs with water soluble carriers by melting of their physical mixtures"[11].The term solid dispersion refers to the dispersion of one or more active ingredient in an inert carrier or matrix at solid state prepared by melting (fusion),solvent, or the melting solvent method. Sekiguchiet.al. Suggested that the drug was present in a eutectic mixture in a microcrystalline state [8], after few years Goldberg et.al. reported that all drug in solid dispersion might not necessarily be presents in a microcrystalline state, a certain fraction of the drug might be molecular dispersion in the matrix, thereby forming a solid solution. Once the solid dispersion was exposed to aqueous media & the carrier dissolved, the drug was released as very fine, colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water soluble drugs were expected to be high. The commercial use of such systems has been limited primarily because of manufacturing problems with solid dispersion systems may be overcome by using surface active and self-emulsifying carriers. The carriers are melted at elevated temperatures and the drugs are dissolved in molten carriers. 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, in amorphous particles(clusters) or in crystalline particles. Solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or melting solvent method. The dispersion of a drug or drugs in a solid diluent or diluents by traditional mechanical mixing is not included in this category. The solid dispersion, a first stated by Mayersohn and Gibaldi.

The term "solid dispersions" refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the melting (fusion) method, solvent method or fusion solvent method. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. The poor solubility of drug substances in water and their low dissolution rate in aqueous G.I.T fluid often leads to insufficient bioavailability. The present investigation is an attempt to improve the solubility and dissolution rate of methyldopa (a poorly soluble drug) by solid dispersion technique. Binary solid dispersions were made using PEG-4000 or PEG-6000 as carriers with varying drug: carrier ratios 1:1 and 1:3 by the fusion method. Binary solid dispersions were also prepared by the solvent evaporation method using PEG-4000 or PEG-6000 as carriers with varying drug: carrier ratios 1:0.5 and 1:2. Also ternary solid dispersions were made by both the fusion and the solvent evaporation method using the PEG-4000 or PEG-6000 and the poloxamer 407 in the ratios of 1:5:1, 1:5:2, 1:1:1 and 1:2:2. Twelve formulations were prepared and evaluated for drug content, in vitro release studies and compared with the marketed formulation of methyldopa. All formulae showed marked significant improvement in the solubility and dissolution rate of the drug. The interaction studies showed no interaction between the drug and any of the used carriers. Formulation FT6 (1:5:2) in phosphate buffer pH 6.8 showed the best in vitro release rate of 86.21% in 60 minutes. Also this formulation showed the highest drug content of 98.64%. It was concluded that combination of PEG- 6000 and poloxamer 407 can be well utilized to improve the solubility of poorly soluble drugs.

Numerous solid dispersion systems have been demonstrated in the pharmaceutical literature along with various hydrophilic carriers, such as polyethylene glycols, polyvinylpyrrolidone, hydroxypropyl methylcellulose, gums, sugar, mannitol and urea. Water insoluble drugs comprise nearly one-third of drugs in development and one-half of these fail in trials because of underprivileged pharmacokinetics (Savicetal., 2006). Mostly Poorly water soluble drugs belong toBCS class II and Class IV group of compounds (Amidonet al., 1995). In the process of absorption of drug from oral route, dissolution is the rate limiting step for lipophilic drugs.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

Therefore improving of dissolution is of great importance in order to ensure maximum therapeutic effect of these drugs. It has been estimated that 40% of new chemical entities currently being discovered are poorly water soluble. Among the various approaches to improve solubility, the solid dispersion (SD) technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble drugs because it is simple, economic, and advantageous. The carrier can be either crystalline or amorphous in nature. Most commonly used carriers for the preparation of SDs are different grade of polyethyleneglycols (PEGs) and polyvinylpyrrolidone (PVPs), Glacier44/14, Labra sol, sugars, and urea. The first drug whose rate and extent of absorption was significantly enhanced using the solid dispersion technique was sulfathiazole by Sekiguchi and Obi. This technique has been used by many researchers/scientists for a wide variety of poorly aqueous soluble drugs to enhance the solubility of the drugs and hence bioavailability. Literature reviews on solid dispersion of past four decades suggests that there is an increasing interest in using this approach. Despite an active research interest, the number of marketed products arising from this approach is really disappointing. Only few commercial products were marketed during the last four decades. Methyldopa {chemically 2-amino-3-(3,4-dihydroxyphenyl)-2-methyl-propanoic acid} is a antihypertensive drug which is used for treatment of moderate to severe hypertension usually in combination with diuretic or a beta-blocking agent. Methyldopa has molecular weight of 238.215 g/mol, oral bioavailability approximately 50%, protein binding is 70-76% and elimination half-life is 0.8-1 hr. The present work was conducted to improve the solubility of methyldopa using solid dispersion technique with PEGs and the poloxamer 407.

1.3 Classification of solid dispersion

Based on their molecular arrangement, six different types of solid dispersions can be distinguished. (In Table 1.1) Moreover, in various studies the designation of solid dispersions is based on the method of preparation. However, since different preparation methods can result in the same subtypes or similar preparation methods can result in different subtypes, it can be argued that solid dispersions should preferably be designated according to their molecular arrangement. Moreover, not the preparation method but the molecular arrangement governs the properties of solid dispersions. Therefore, it is essential to use terms that indicate the molecular arrangement in the solid dispersion. Knowledge about the molecular arrangement will enlarge comprehension of the properties and behavior of solid dispersions. Furthermore, it will facilitate optimization of their properties required for a specific application. For example, the mechanism underpinning the dissolution of solid dispersions is poorly understood. Many case studies showed accelerated dissolution of hydrophobic compounds using solid dispersions but mechanisms are rarely discussed. The most important reason for that is the lacking knowledge about the mode of incorporation of the hydrophobic drug in the matrix, despite numerous efforts to clarify this. A question like, “is the drug present as a crystalline phase or as amorphous nano-particles or molecularly dispersed throughout the matrix” is rarely discussed. All three situations result in different drug concentrations at the dissolving interface. Still it has not been fully elucidated how this affects dissolution behaviour of solid dispersions. Secondly, the physical and chemical stability of the matrix or the incorporated drug depends on the mode of incorporation. If drug molecules, for example, are present in amorphous nano-particles, crystallization requires only rotational rearrangement. On the other hand, for a molecularly dispersed drug, translational diffusion is necessary before crystallization can occur by rotational rearrangements[12].

1. Eutectic mixtures:

A simple eutectic mixture consists of two compounds which are completely miscible in the liquid state but only to a very limited extent in the solid state. It is prepared by rapid solidification of fused melt of two components that show complete liquid miscibility but negligible solid-solid solution[13].

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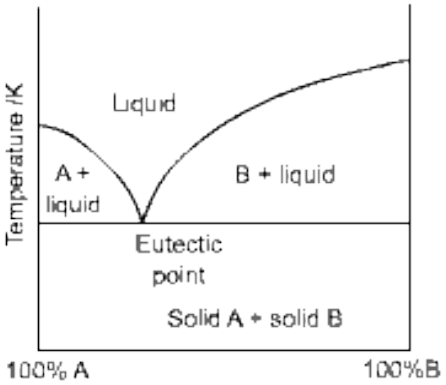

Fig: 1.3Phasediagram of eutectic mixture

2. Amorphous precipitation in crystalline matrix:

This is similar to simple eutectic mixtures but only difference is that drug is precipitated out in an amorphous form[14].

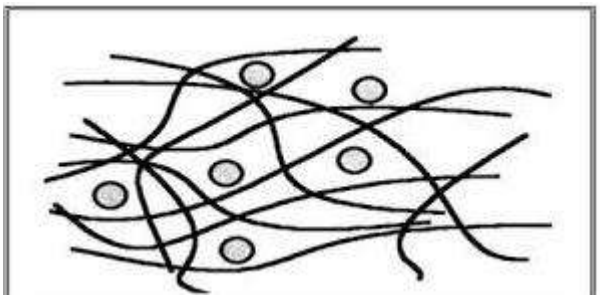

Fig:1.4 Amorphous soliddispersions

3.Solid solution: Solid solutions are comparable to liquid solutions, consisting of just one phase irrespective of the number of components. In the case of solid solutions, the drug's particle size has been reduced to its absolute minimum viz. the molecular dimensions14 and the dissolution rate is determined by the dissolution rate of the carrier. Classified according to their miscibility (continuous versus discontinuous solid solutions) or second, according to the way in which the solvate molecules are distributed in the solvendum (substitutional, interstitial or amorphous)[15].

4.Continuous solid solutions:

In a continuous solid solution, the components are miscible in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components. Solid solutions of this type have not been reported in the pharmaceutical world till date[16].

5.Discontinuous solid solutions:

In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. Due to practical considerations it has been suggested by Goldberg et al.14 that the term `solid solution' should only be applied when the mutual solubility of the two components exceeds 5%.

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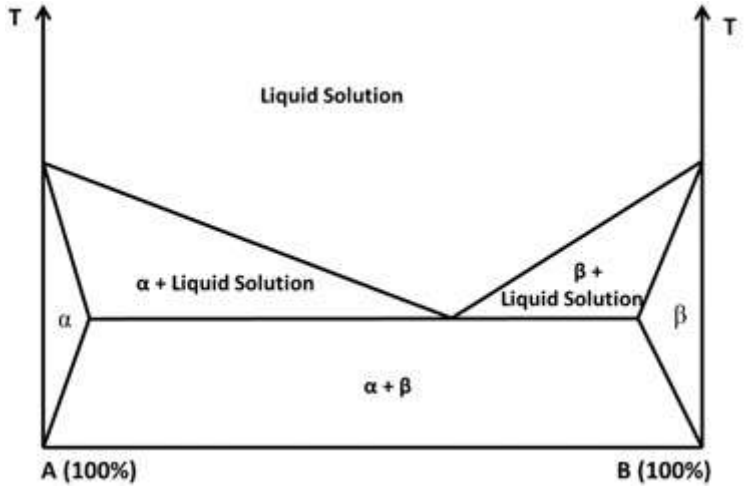

Fig: 1.5 Phase diagram of discontinuous solid solutions

6.Subsitutional solid dispersions:

Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules15. Classical solid solutions have crystalline structure, in which the solute molecules can either substitute for solvent molecules in the crystal lattice or fit into the intrsticies between the solvent molecule.

7. Interstitial solid solutions:

In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. Solute molecule diameter should be less than 0.59 times than that of solvent molecular diameter.

8. Glass solution and suspensions:

Glass solutions are homogeneous glassy system in which solute dissolves in glass carrier. Glass suspensions are mixture in which precipitated particles are suspended in glass solvent. Lattice energy is much lower in glass solution and suspension.

1.4 Current trends in solid dispersions techniques

New manufacturing processes to obtain solid dispersions have also been developed to reduce the drawbacks of the initial process. It is intended to discuss the recent advances related on the area of solid dispersions. The classification of solid dispersions according to implementation and recent advancement.

First generation solid dispersions

The first description of solid dispersions was from Sekiguchi and Obi in 1961. They noted that the formulation of eutectic mixtures improves the rate of drug release and consequently, the bioavailability of poorly water soluble drugs. These solid dispersions produced faster release and higher bioavailability than conventional formulations of the same drugs. The small particle size and the better wettability of the drug were the main reasons for the observed improvements in bioavailability[17].

Later, Levy and Kaning developed solid dispersion systems, containing mannitol as carrier, by preparing solid solutions through molecular dispersions instead of using eutectic mixtures. The observed improvements were attributed to a faster carrier dissolution, releasing microcrystals or particles of drug .These solid dispersions, which could be designed as first generation solid dispersions, were prepared using crystalline carriers. Crystalline carriers include urea and sugars, which were the first carriers to be employed in solid dispersions. They have the disadvantage of forming crystalline solid dispersions, which were more thermodynamically stable and did not release the drug as quickly as amorphous ones[18].

Second generation solid dispersions

In the late sixties it was observed that solid dispersions, where the drug was maintained in the crystalline state, might not be as effective as the amorphous, because the former were more thermodynamically stable. Therefore, a second generation of solid dispersions appeared, containing amorphous carriers instead of crystalline. Indeed, the most common solid dispersions do not use crystalline carriers but amorphous. In the latter, the drugs are molecularly dispersed in an irregular form within an amorphous carrier, which are usually polymers. Polymeric carriers have been the most successful for solid dispersions, because they are able to originate

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amorphous solid dispersions[19]. They are divided into fully synthetic polymers and natural product-based polymers. Fully synthetic polymers include povidone (PVP, polyethyleneglycols (PEG) and polymethacrylates. Natural product based polymers are mainly composed by cellulose derivatives, such as hydroxypropylmethylcellulose (HPMC), ethylcellulose or hydroxypropylcellulose or starch derivates, like cyclodextrins. Amorphous solid dispersions can be classified according to the molecular interaction of drug and carriers in solid solutions, solid suspensions or a mixture of both. In amorphous solid solutions, drug and carrier are totally miscible and soluble, originating a homogeneous molecular interaction between them. In these systems, the drug and carrier interaction energy is extremely high, resulting in a really true solution. The use of polymers in the preparation of a true solid solution creates an amorphous product in which the crystalline drug is dissolved. This type of amorphous solid dispersion is homogeneous on a molecular level. Therefore, only one phase is present. Amorphous solid suspensions occur when the drug has limited carrier solubility or an extremely high melting point. Molecularly, the obtained dispersion does not have a homogeneous structure, but is composed of two phases. Small drug particles, when dispersed in polymeric carriers, are able to provide an amorphous final product. When a drug is both dissolved and suspended in the carrier, a heterogeneous structure is obtained with mixed properties of amorphous solid solutions and amorphous solid suspensions. In second generation solid dispersions, the drug is in its supersaturated state because of forced solubilization in the carrier. These systems are able to reduce the drug particle size to nearly a molecular level, to solubilize or co-dissolve the drug by the water soluble carrier, to provide better wettability and dispersibility of the drug by the carrier material, and to produce amorphous forms of the drug and carriers. In these solid dispersions, the carrier dissolution (or mixtures of carriers) dictates the drug release profile[20].

Third generation solid dispersions

Recently, it has been shown that the dissolution profile can be improved if the carrier has surface activity or self-emulsifying properties, therefore third generation solid dispersions appeared. These contain a surfactant carrier, or a mixture of amorphous polymers and surfactants as carriers. These third generation solid dispersions are intended to achieve the highest degree of bioavailability for poorly soluble drugs and to stabilize the solid dispersion, avoiding drug recrystallization. The use of surfactants such as inulin, inutec SP1, compritol 888 ATO, gelucire 44/14 and poloxamer-407 as carriers was shown to be effective in originating high polymorphic purity and enhanced in vivo bioavailability. The association of amorphous polymers and surfactants has also been reported. For instance, the dissolution rate and bioavailability of LAB68, a poor water soluble drug, were improved after being dispersed in a mixture of PEG and polysorbate 80. The bioavailability of this solid dispersion was 10-fold higher compared to the dry blend of micronized drug. In addition, the solid dispersion system was physically and chemically stable for at least 16 months. HPMC was also associated with poloxamer and polyoxyethylenehydrogenated castor oil to prepare an amorphous felodipine solid dispersion. The inclusion of surfactants in the formulation containing a polymeric carrier may help to prevent precipitation and/or protect a fine crystalline precipitate from agglomeration into much larger hydrophobic particles.[21]

1.5 The advantageous properties of solid dispersions

Management of the drug release profile using solid dispersions is achieved by manipulation of the carrier and solid dispersion particles properties. Parameters, such as carrier molecular weight and composition, drug crystallinity and particle porosity and wettability, when successfully controlled, can produce improvements in bioavailability

Particles with reduced particle size and increased dissolution rate

Molecular dispersions, as solid dispersions, represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers. A high surface area is formed, resulting in an increased dissolution rate and, consequently, improved bioavailability. The fact that more than 40% of newly discovered drugshave little or negligible water solubility presents a serious challenge to the successful development andcommercialization of new drugs in the pharmaceuticalindustry (Connors & Elder, 2004). Solubility andpermeability are the main factors that control oralbioavailability of a drug substance. Generally, whenthe drug solubility

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

in water is less than 10 mg/ml,dissolution is the rate-limiting step in the process ofdrug absorption (Habib, 2000). Factors influencingdrug dissolution rate in aqueous solution are describedin Noyes-Whitney equation:where dC/dT is the rate of dissolution, A is the surfacearea available for dissolution, D is the diffusioncoefficient of the drug, Cs is the solubility of the drugin the dissolution medium, C is the concentration ofdrug in the medium at time t and h is the thickness ofthe diffusion boundary layer adjacent to the surface ofthe dissolving drug (Leuner&Dressman, 2000).According to this equation, dissolution rate can beincreased through increasing the surface area, and thiscan be achieved through reducing the particle size.Different methods have been used to reduce theparticle size, such as micronization, recrystallization,freeze drying and spray drying. Micronization ofpoorly soluble drugs by milling has been used for manyyears in the pharmaceutical industry in order

To enhance the dissolution rate of those drugs. For example the dissolution rate of micronizedspironolactone was higher than that of the standard form (McInneset al., 1982). However, fine particles may not always produce the expected faster dissolution. This primarily results from the aggregation and agglomeration of fine particles. In addition, poor wettability of fine powders may reduce the dissolution rate (Bloch &Speiser, 1987; Rippie, 1986). Solid dispersion techniques have been used to enhance the dissolution rate of many poorly water soluble drugs. Particle size reduction and reduced agglomeration would both increase the exposed surface area of thedrug. When solid solutions or amorphous precipitation sare formed, particle size of the active ingredient Isreduced to the minimum level. In addition, the carrier material may contribute to increasing the dissolution rate through its solubilizing and wettability-enhancing properties. It was reported that urea increased the dissolution rate of chlorpropamide incorporated into urea, through its solubilizing properties. The enhancement in dissolution rate as a result of solid dispersion formation, relative to pure drug, varies from as high as 400-fold to less than two-fold [22].

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. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects. Recently, the inclusion of surfactants in the third generation solid dispersions reinforced the importance of this property[23].

Particles with higher porosity

Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity alsodepends on the carrier properties, for instance, solid dispersions containing linear polymers produce largerand more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release profile[24].

Drugs in amorphous state

Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility. The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that, if drugs precipitate, it is as a metastable polymorphic form with higher solubility than the most stable crystal form.For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them.

Strategies to avoid drug recrystallization

Recrystallization is the major disadvantage of solid dispersions. As amorphous systems, they are thermodynamically unstable and have the tendency to change to a more stable state under recrystallization. Molecular mobility is a key factor governing the stability of amorphous phases, because even at very high viscosity, below the glass transition temperature (Tg), there is enough mobility for an amorphous system to crystallize over pharmaceutically relevanttime scales. Furthermore, it was postulated that crystallization above Tg would be governed by the configurational entropy, because this was a measure ofthe

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

probability of molecules being in the appropriate conformation, and by the mobility, because this was related to the number of collisions per unit time.Several experiments have been conducted to understand the stabilization of solid dispersions. Recentstudies observed very small reorientation motions insolid dispersions showing a detailed heterogeneity of solid dispersions and detecting the sub-glass transitionbeta-relaxation as well as alpha-relaxation, whichmay lead to nucleation and crystal growth.Molecular mobility of the amorphous system depends, not only on its composition, but also on the manufacturing process as stated by Bhugraet al. .Soliddispersions exhibiting high conformational entropy and lower molecular mobility are more physically stable. Polymers improve the physical stability of amorphous drugs in solid dispersions by increasing theTg of the miscible mixture, thereby reducing themolecular mobility at regular storage temperatures, orby interacting specifically with functional groups of thedrugs. For a polymer to be effective in preventingcrystallization, it has to be molecularly miscible with the drug. For complete miscibility, interactionsbetween the two components are required. It isrecognized that the majority of drugs containhydrogen-bonding sites, consequently, several studieshave shown the formation of ion–dipole interactionsand intermolecular hydrogen bonding between drugsand polymers, and the disruption of the hydrogenbonding pattern characteristic to the drug crystallinestructure. These lead to a higher miscibility andphysical stability of the solid dispersions Specific drugpolymer interactions were observed by Teberekidisetal., showing that interaction energies, electron density,and vibrational data revealed a stronger hydrogen bondof felodipine with PVP than with PEG, which was inagreement with the dissolution rates of the corresponding solid dispersions.

1.6 Methods of preparation of solid dispersions

Various methods used for preparation of solid dispersion system. These methods are given bellow.

1 kneading method
2 Solvent evaporation method
3 Melting solvent method (melt evaporation)
4 Melt extrusion methods
5 Lyophilization techniques
6 Melt agglomerations Process
7 The use of surfactant
8 Electrospinning
9 Super Critical Fluid (Scf) technology

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

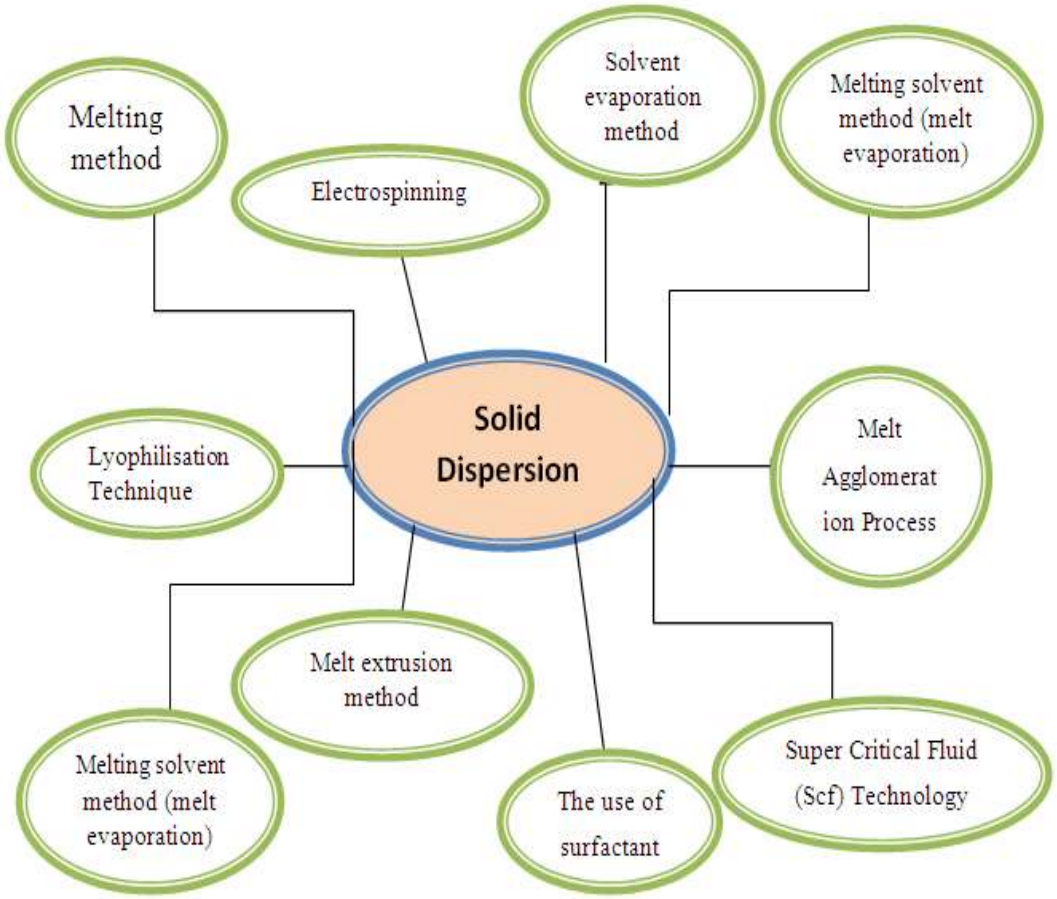


Fig:1.6 schematic representation of various methods of solid dispersions

1. Kneading method

In the kneading method Solid dispersions were prepared by weighed quantities of drug and polymers were placed in a mortar and then the mixtures were kneaded with small volume water for 30 min to produce a homogeneous dispersion. Once homogeneous slurry was obtained, samples where dried in oven at 45^0C until dryness. The dispersions after drying were pulverized using a glass mortar and pestle. The pulverized mass was then sifted through a #60 sieve to obtain a uniform particle size and stored in a desiccator at room temperature until further use[25].

2. Solvent evaporation method[26]

In this method, the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents. However, some disadvantages are associated with this method such as

1) The higher cost of preparation.
2) The difficulty in completely removing liquid solvent.
3) The possible adverse effect of traces of the solvent on the chemical stability
4) The selection of a common volatile solvent.
5) The difficulty of reproducing crystal form.
6) In addition, a super saturation of the solute in the solid system cannot be attained except in a System showing highly viscous properties.

3. Melting solvent method (melt evaporation)

It involves preparation of solid dispersions by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The 5

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

–10% (w/w) of liquid compounds can be incorporated into polyethylene glycol 6000 without significant loss of its solid property. It is possible that the selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. Also the liquid solvent used mayaffect the polymorphic form of the drug, which precipitates as the solid dispersion. This technique possesses unique advantages of both the fusion and solvent evaporation methods. From a practical standpoint, it is only limited to drugs with a low therapeutic dose e.g. below 50 mg[27].

4. Melt extrusion method

The drug/carrier mix is typically processed with a twinscrew extruder. The drug/carrier mix is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. Theintermediates can then be further processed into conventional tablets. An important advantage of the hot melt extrusion method is that the drug/carrier mix isonly subjected to an elevated temperature for about 1 min, which enables drugs that are somewhat thermo labile to be processed. Solid dispersion by this method is composed of active ingredient and carrier, and prepare by hot-stage extrusion using a co-rotating twin-screw extruder. Theconcentration of drug in the dispersions is always 40% (w/w). The screw-configuration consist of two mixing zones and three transport zones distribute over the entire barrel length, the feeding rate is fix at 1 kg/h and the screw rate is set at 300 rpm. The five temperature zones are set at 100, 130, 170, 180, and 185C from feeder to die. The extrudates are collect after cooling at ambient temperature on a conveyer belt. Samples are milled for 1 min with a laboratory cutting mill and sieve to exclude particles >355μm[28].

5. Lyophilization Technique

Lyophilization involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative technique to solvent evaporation. 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[29].

6. Melt Agglomeration Process

This technique has been used to prepare solid dispersion wherein the binder acts as a carrier. In addition, solid dispersion are prepared either by heating binder, drug and excipient to a temperature above the melting point of the binder (melt- in procedure) or by spraying a dispersion of drug in molten binder on the heated excipient (spray-on procedure) by using a high shear mixer [83]. The rotary processor might be preferable to the high melt agglomeration because it is easier to control the temperature and because a higher binder content can be incorporated in the agglomerates. The effect of binder type, method of manufacturing and particle size are critical parameters in preparation of solid dispersion by melt agglomeration. It has been found that the melt in procedure gives a higher dissolution rates than the spray-on procedure with PEG 3000, poloxamer 188 and gelucire 50/13 attributed toimmersion mechanism of agglomerate formation and growth. In addition the melt in procedure also results inhomogenous distribution of drug in agglomerate. Larger particles results in densification of agglomerates while fine particle cause complete adhesion to the mass to bowl shortly after melting attributed to distribution and coalescence of the fine particles[30].

7. Melt Agglomeration Process by The use of surfactants

The utility of the surfactant systems 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, floatation, 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[31].

8. Electrospinning

Electrospinning is a process in which solid fibers are produced from a polymeric fluid stream solution ormelt delivered through a millimeter-scale nozzle.This process involves the application of a strongelectrostatic field over a conductive capillary attachingto a reservoir containing a polymer solution or melt anda conductive collection screen. Upon increasing theelectrostatic field strength up to but not exceeding acritical value, charge species accumulated on thesurface of

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

a pendant drop destabilize the hemisphericalshape into a conical shape (commonly known as Taylors cone). Beyond the critical value, a charged polymerjet is ejected from the apex of the cone (as a way ofrelieving the charge built-up on the surface of thependant drop). The ejected charged jet is then carriedto the collection screen via the electrostatic force. TheCoulombic repulsion force is responsible for thethinning of the charged jet during its trajectory to thecollection screen. The thinning down of the charged jetis limitedIf the viscosity increases, the charged jet is dried.This technique has tremendous potential for thepreparation of nanofibres and controlling the release ofbiomedicine, as it is simplest, the cheapest thistechnique can be utilized for the preparation of solid dispersions in future[32].

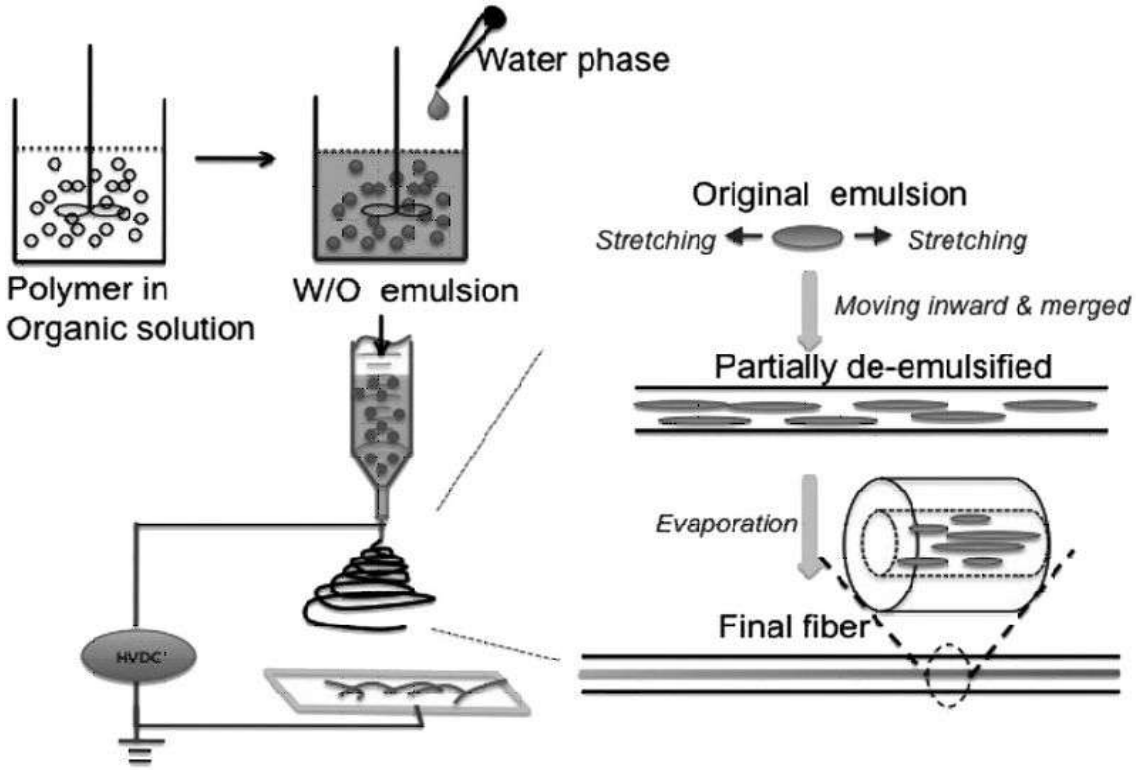


Fig:1.7 Schematic representation of electrospinning method

9. Super Critical Fluid (Scf) Technology

The supercritical fluid antisolvent techniques, carbondioxide are used as anantisolvent for the solute but as asolvent with respect to the organic solvent. Differentacronyms were used by various authors to denotemicronization processes: aerosol solvent extractionsystem, precipitation with a compressed fluidantisolvent, gas anti-solvent, solution enhanceddispersion by supercritical fluids, and supercritical antisolvent.The SAS process involves the spraying of thesolution composed of the solute and of the organic solvent into a continuous supercritical phase flowing concurrently. Use of supercritical carbon dioxide isadvantageous as it is much easier to remove from thepolymeric materials when the process is complete,even though a small amount of carbon dioxide remainstrapped inside the polymer; it poses no danger to thepatient. In addition the ability of carbon dioxide toplasticize and swell polymers can also be exploited andthe process can be carried out near room temperature.Moreover, supercritical fluids are used to lower thetemperature of melt dispersion process by reducing themelting temperature of dispersed active agent. Thereason for this depression is the solubility of the lightercomponent (dense gas) in the forming phase (heavier component)[33].

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

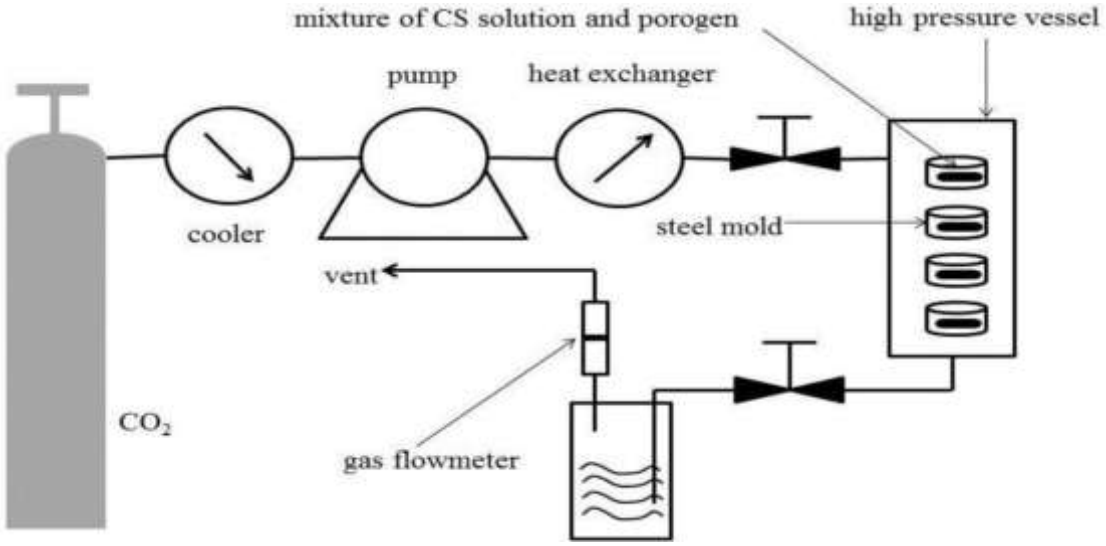


Fig:1.8 Schematic representation of Super Critical Fluid (Scf) Technology

Advantages of solid dispersion:

Particles with Reduced Particle Size

Molecular dispersions, as solid dispersions, represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers. A high surface area is formed, resulting in an increased dissolution rate and, consequently, improved bioavailability.

Particles with Improved Wettability

Carriers with surface activity, such as cholic acid and bile salts. When used, can significantly \increase the wettability property of drug. Even carriers without any surface activity, such as urea, improved drug wettability. Carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects.

Particles with Higher Porosity

Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity also depends on the carrier properties; 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. The increased porosity of solid dispersion particles also hastens the drug release profile.

Drugs in Amorphous State

Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility. The enhancement of drug release can usually be achieved using the drug in itsamorphous state, because no energy is required to break up the crystal lattice during the dissolution process For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier24. For drugs with high crystal energy, higher amorphous compositions Jaskirat et al Journal of Drug Delivery & Therapeutics; 2013, 3(5), 148-155 152 © 2011, JDDT. All Rights Reserved ISSN: 2250-1177 CODEN (USA): JDDTAO can be obtained by choosing carriers, which exhibit specific interactions with them.

Rapid disintegration of oral tablets

Drug is formulated with hydrophilic carrier (e.g. PEG) as a solid dispersion to increase its aqueous solubility and dissolution. Then superdisintegrant (e.g. croscarmellose sodium) is used in tablet formulation to achieve rapid disintegration of tablets prepared by wet granulation method. These rapidly disintegrating tablets can be used as an alternative to parenteral therapy enabling patient for self-medication even without the aid of water.

As a formulation vehicle

Solid dispersions can be used as formulation vehicle to facilitate the preclinical safety and early clinical studies on new chemical entities with very low aqueous solubility. It provides a means to rapidly assess the safety and

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

efficacy profile of the drug substance that may be otherwise difficult to obtain.

Disadvantages of solid dispersions

- The major disadvantages of solid dispersion are related to their instability. Several systems have shown changes in crystallinity and a decrease in dissolution rate with aging. The crystallization of ritonavir from the supersaturated solution in a solid dispersion system was responsible for the withdrawal of the ritonavir capsule (Norvir, Abboft) from the market.
- Moisture and temperature have more of a deteriorating effect on solid dispersions than on physical mixtures. Some solid dispersion may not lend them to easy handling because of tackiness.They are not broadly used in commercial products because there is the possibility that during processing (mechanical stress) or storage (temperature and humidity stress) the amorphous state may undergo crystallization.
- The effect of moisture on the storage stability of amorphous pharmaceuticals is also a significant concern, because it may increase drug mobility and promote drug crystallization.
- Most of the polymers used in solid dispersions can absorb moisture, which may result in phase separation, crystal growth or conversion from the amorphous to the crystalline state or from a metastable crystalline form to a more stable structure during storage. This may result in decreased solubility and dissolution rate. Therefore, exploitation of the full potential of amorphous solids requires their stabilization in solid state, as well as during in vivo performance.
- Poor scale-up for the purposes of manufacturing.
- Laborious and expensive methods of preparation.
- Reproducibility of physicochemical characteristics.
- Difficulty in incorporating into formulation of dosage forms.
- Scale-up of manufacturing process.
- Stability of the drug and vehicle.

Applications of Solid Dispersions[34-43]

Solid dispersion systems can provide numerous additional benefits; some of them are as follows

- In improving immunosuppressive therapy in lung transplant patients, dry powder formulation consisting of a solid dispersion (e.g. Cyclosporine A) for inhalation is prepared. It can avoid many problems like use of local anaesthesia and irritating solvents
- Solid dispersion formulations were demonstrated to accelerate the onset of action for drugs such as nonsteroidalantiinflammatory drugs (NSAIDS) where immediacy of action is crucial in relieving acute pain and inflammation. .
- Solid dispersion systems were shown to provide bio available oral dosage forms for anti-cancer drugs, which could be substituted for standard injections to improve patient comfort and compliance.
- Solid dispersion systems were also found to reduce food effect on drug absorption, thus increasing the convenience of drug therapy as the need for some drugs to be taken with food was eliminated.
- Solid dispersion- based dosage form allowed for greater drug loading per dose and improved stability over a soft gelatin capsule formulation which thereby improved the convenience of drug therapy by reducing the dosing regime and eliminating the need for refrigerated storage.
- Improved absorption efficiency demonstrated for solid dispersion systems allows for a reduction in the content of active agent per dose, thus decreasing the cost associated with these drug therapies.
- It also act as a functional carriers that offer the added benefit of targeting the release of highly soluble forms of poorly water soluble drugs to an optimum site for absorption. These benefits demonstrate the current contributions and future potential of solid dispersion systems toward improving drug therapies for a variety of important medical conditions whose treatment involves poorly water soluble drugs.
- To obtain a homogeneous distribution of a small amount of drug in solid state.
- To stabilize the unstable drug.
- To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
- To formulate a fast release primary dose in a sustained released dosage form.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

- 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 isomorphous, solid solution, eutectic or molecular addition compounds.
- To increase the solubility of poorly soluble drugs thereby enhance the dissolution rate, absorption and bioavailability.
- To obtain a homogeneous distribution of a small amount of drug in solid state.
- To stabilize unstable drugs and protect against decomposition by processes such as hydrolysis, oxidation, racemization, photo oxidation etc.
- To dispense liquid or gaseous compounds;
- To formulate a fast release priming dose in a sustained release dosage form;
- To formulate sustained release preparation of soluble drugs by dispersing the drug in poorly soluble or insoluble carrier;
- To reduce side effects-(a) the binding ability of drugs for example to the erythrocyte
- membrane is decreased by making its inclusion complex, (b) the damage to the stomach mucous membranes by certain non-steroidal anti-inflammatory drugs can be reduced by administration as an inclusion compound;
- To mask unpleasant taste and smell and avoid undesirable incompatibilities.
- To convert liquid compounds into formulations. 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.
- To reduce pre systemic inactivation of drugs like morphine and progesterone.

II. LIMITATIONS:

The limitations of this technology have been a drawback for the commercialization of solid dispersions. The limitations include

- Laborious and expensive methods of preparation,
- Reproducibility of physicochemical characteristics,
- Difficulty in incorporating into formulation of dosage forms,
- Scale-up of manufacturing process, and
- Stability of the drug and vehicle.

Characterization of Solid dispersions:

Several different molecular structures of the drug in the matrix can be encountered in solid dispersions. Several techniques have been available to investigate the molecular arrangement in solid dispersions. However, most effort has been put into differentiate between amorphous and crystalline material. Many techniques are available which detect the amount of crystalline material in the dispersion.

Drug -carrier miscibility

- Differential scanning calorimetry
- Powder X-ray diffraction

Drug carrier interactions

- FT-IR spectroscopy

Dissolution enhancement

- Dissolution

Powder X-ray diffraction

Powder X-ray diffraction can be used to qualitativelydetect material with long range order. Sharperdiffraction peaks indicate more crystalline material.

Infrared spectroscopy (IR)

Infrared spectroscopy (IR) can be used to detect thevariation in the energy distribution of interactionsbetween drug and matrix. Sharp vibrational bandsindicate crystallinity. Fourier Transformed InfraredSpectroscopy (FTIR) was used to accurately detectcrystallinity ranging from 1 to 99% in pure material

Differential Scanning Calorimetry (DSC)

Frequently used technique to detect the amount of crystalline material is Differential Scanning Calorimetry (DSC). In DSC, samples are heated with a constant heating rate and the amount of energy necessary for that is detected. With DSC the temperatures at which thermal events occur can be detected. Thermal events can be a glass to rubber transition, (re)crystallization, melting or degradation. Furthermore, the melting- and (re)crystallization energy can be quantified. The melting energy can be used to detect the amount of crystalline material.

In Vitro Dissolution Studies

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

In vitro dissolution studies are done for the find out dissolution behavior. The in-vitro dissolution study can be used to demonstrate the bioavailability or bioequivalence of the drug product through in vitro – in vivo correlation (IVIVC). On the other hand if absorption of the drug is dissolution rate limited that means the drug in the gastrointestinal fluid passes freely through the bio-membranes at a rate higher than it dissolves or is released from the dosage form. The specifically designed in-vivo dissolution study will be required in solid dispersion system to access the absorption rate, and hence its bioavailability and to demonstrate the bioequivalence ultimately. There are some apparatus used in United States pharmacopoeia for dissolution testing these are following.

III. AIM & OBJECTIVES

- To perform preformulation studies forAmbrisentan.
- To perform Drug-Excipient Compatibility Studies.
- To formulate and develop the solid dispersions for Ambrisentan with various proportions by melt extrusion method.
- To determine the drug content uniformity of all the prepared formulations.

To determine the drug entrapment efficiency of all the prepared formulations. The main aim of present work is to formulate solid dispersions of poorly water soluble BCS class 2 drug Ambrisentan, which give the application of solid dispersions results in increasing the solubility of many poorly soluble drugs.

The objective of the present study, investigated to improve the solubility and bioavailability of Ambrisentan solid dispersions by melt extrusion method using PEG 6000, HPMC K4M, PEG 4000 and PVPK-30 to improve patient compliance.

Ambrisentan is an orally active selective type A endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension.

IV. OBJECTIVES:

- Selection of suitable carriers for preparing solid dispersions.
- To establish In–vitro drug release compliance with the established criteria.
- To evaluate drug release kinetics for the formulated solid dispersions.

V. DRUG PROFILE

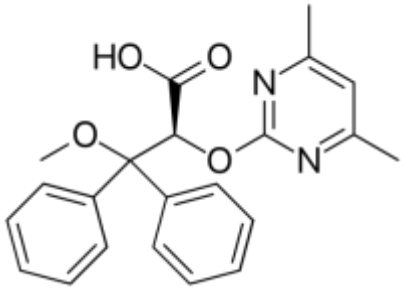
DRUG
AMBRISENTAN

Description: Ambrisentan is an orally active selective type A endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension. It is approved in Europe, Canada and the United States for use as a single agent to improve exercise ability and delay clinical worsening. In addition, it is approved in the United States for use in combination with tadalafil to reduce the risks of disease progression, hospitalization and to improve exercise ability. Studies establishing the efficacy of Ambrisentan included patients with both idiopathic or heritable pulmonary arterial hypertension and those with pulmonary arterial hypertension associated with connective tissue diseases. Patients studied displayed symptoms and etiologies predominantly of WHO Functional Class II-III. As an endothelin receptor antagonist, Ambrisentan prevents endogenous endothelin peptide from constricting the muscles in blood vessels, allowing them to relax and permit a reduction in blood pressure.

Synonym: Ambrisentan.
Brand Names: Ambrican, Endobloc, Pulmonext, Zambri.
Chemical Name: Chemically AMBRISENTAN is (2S)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid

Structure 1. AMBRISENTAN:

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781



Molecular formula: $C_{22}H_{22}N_2O_4$
Molecular weight: 378.428 g/mol
Solubility: practically insoluble in aqueous solutions at low pH. Solubility increases at higher pH.
Melting Point:165-168°C

Categories:
- Acids, Carbocyclic,
- Antihypertensive Agents,
- Antihypertensives for Pulmonary Arterial Hypertension.

UV absorption maxima (λ max): The solution shows an absorption maximum at 262 nm.
CAS number:177036-94-1

VI. PHARMACOLOGY:

Pharmacodynamics: Ambrisentan 10 mg daily had no significant effect on the QTc interval, whereas a 40 mg daily dose of ambrisentan increased mean QTc at tmax by 5 ms with an upper 95% confidence limit of 9 ms. Significant QTc prolongation is not expected in patients taking ambrisentan without concomitant metabolic inhibitors. Plasma concentrations of B-type natriuretic peptide (BNP) in patients who received ambrisentan for 12 weeks were significantly decreased. Two Phase III placebo-controlled studies demonstrated a decrease in BNP plasma concentrations by 29% in the 2.5 mg group, 30% in the 5 mg group, and 45% in the 10 mg group ($p < 0.001$ for each dose group) and an increase by 11% in the placebo group.
Mechanism of action: Endothelin-1 (ET-1) is an endogenous peptide that acts on the endothelin type A (ETA) and endothelin type B (ETB) receptors in vascular smooth muscle and endothelium. ETA-mediated actions include vasoconstriction and cell proliferation, whereas ETB predominantly mediates vasodilation, anti-proliferation, and ET-1 clearance. In patients with pulmonary arterial hypertension, ET-1 levels are increased and correlate with increased right arterial pressure and severity of disease. Ambrisentan is one of several newly developed vasodilator drugs that selectively target the endothelin type A (ETA) receptor, inhibiting its action and preventing vasoconstriction. Selective inhibition of the ETA receptor prevents phospholipase C-mediated vasoconstriction and protein kinase C-mediated cell proliferation. Endothelin type B (ETB) receptor function is not significantly inhibited, and nitric oxide and prostacyclin production, cyclic GMP- and cyclic AMP-mediated vasodilation, and endothelin-1 (ET-1) clearance is preserved.

Pharmacokinetics:
Absorption:
Ambrisentan is rapidly absorbed with peak plasma concentrations occurring around 2 hours after oral administration. Cmax and AUC increase proportionally with dose across the therapeutic dosing range. Absolute oral bioavailability of ambrisentan is unknown. Absorption is not affected by food.
Volume of distribution: Ambrisentan has a low distribution into red blow cells, with a mean blood: plasma ratio of 0.57 and 0.61 in males and females, respectively.
Metabolism: Ambrisentan is a metabolized primarily by uridine 5'-diphosphate glucuronosyltransferases (UGTs) 1A9S, 2B7S,1A3S to form ambrisentan glucuronide. Ambrisentan is also metabolized to a lesser extent by CYP3A4, CYP3A5 and CYP2C19 to form 4-hydroxymethyl ambrisentan which is further glucuronidated to 4-hydroxymethyl ambrisentan glucuronide.
Excretion: Ambrisentan is primarily cleared by non-renal pathways. Along with its metabolites, ambrisentan is primarily found in the feces following hepatic and/or extra-hepatic metabolism. Approximately 22% of the administered dose is recovered in the urine following oral administration with 3.3% being unchanged ambrisentan.
Half life: Mean terminal elimination half-life is 15 hours in young healthy adults.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

Clearance: The mean oral clearance of ambrisentan was found to be 38 mL/min in healthy subjects and 19 mL/min in patients with pulmonary artery hypertension.

Indications and Usage: Ambrisentan is indicated for treatment of idiopathic ('primary') pulmonary arterial hypertension (IPAH) and pulmonary arterial hypertension (PAH) associated with connective tissue disease in patients with WHO functional class II or III symptoms. In the United States of America, ambrisentan is also indicated in combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability.

Toxicity:

Ambrisentan is teratogenic and has a high risk of embryo-fetal toxicity. LD50 was found to be greater than or equal to 3160 mg/kg when studied in rats. There was no evidence of carcinogenic potential in 2 year oral daily dosing studies in rats and mice.

POLYMER PROFILE

PEG – 4000

Synonyms:

Carbowax; Carbowax Sentry; Lipoxol; LutrolE; PEG; PluriolE;
polyoxyethylene glycol.

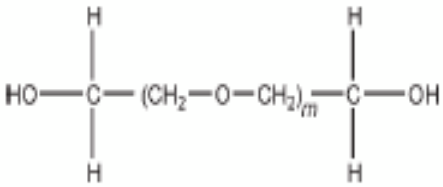
Chemical Name and CAS Registry Number:

a-Hydro-o-hydroxypoly(oxy-1,2-ethanediyl)

Empirical Formula and Molecular Weight:

$HOCH_2(CH_2OCH_2)mCH_2OH$ where m represents the average number of oxyethylene groups.

StructuralFormula:



FunctionalCategory:

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology:

Polyethylene glycols can also be used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersions with an appropriate polyethylene glycol. Polyethylene glycol grades with molecular weights of 6000 and above canbe used as lubricants,particularlyfor soluble tablet. In solid-dosageformulations,higher-molecular-weightpolyethyleneglycols can enhance the effectiveness of tablet binders and impart plasticity to granules. However,they have only limited binding action when used alone, and can prolong disintegration if present in concentrations greater than 5%w/w. When used for thermoplastic granulations,(5–7)a mixture of the powdered constituents with10–15%w/w PEG 6000 is heated to70–75^{0C}.The mass becomes paste like and forms granules if stirred while cooling. This technique is useful for the preparation of dosage forms such as lozenges when prolonged disintegration is required.

Description:

TheUSPNF23describespolyethyleneglycolas being addition polymer of ethylene oxide and water.

Typical Properties: Density:

1.11–1.14 g/cm3 at 258C for liquid PEGs;
1.15–1.21 g/cm3 at 258C for solid PEGs.

Melting point:

55–63^{0}Cfor PEG 4000;

Solubility:

All grades of polyethylene glycolare soluble in water and miscible in all proportions with other polyethyleneglycols (after melting, if necessary) Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol (95%),and methanol; they are slightly soluble in aliphatic hydrocarbons and ether, butin soluble in fats, fixed oils, and mineral oil.

Stability and Storage Conditions:

Polyethylene glycols are chemically stable in air and in solution, although grades with a molecular weight lessthan 2000arehygroscopic.Polyethyleneglycols do not support microbial growth, and they do not become

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

rancid. Polyethylene glycols should be stored in well-closed containers in a cool, dry place

Incompatibilities:

All grades can exhibit some oxidizing activityowing to the presence of peroxide impurities and secondary products formed by autoxidation. Liquidandsolid polyethylene glycol grades may be incompatible with some coloring agents.

PVP K30 [92]

Synonyms:

E1201; Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl)ethylene];
polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer.

Chemical Name and CAS Registry Number:

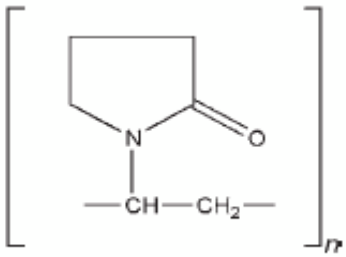
1-Ethenyl-2-pyrrolidinone homopolymer (9003-39-8)

Empirical Formula and Molecular Weight:

$(C_6H_9NO)_n$ 2500–3000000

PVP K 30: 50000

StructuralFormula:



FunctionalCategory:

Disintegrant; dissolution aid; suspending agent; tablet binder.

Applications in Pharmaceutical Formulation or Technology:

Although povidone is used in a variety of pharmaceutical formulations, It is primarily used in solid-dosageforms. In tableting, povidone solutions are used as binders in wet granulation processes.(2,3) Povidone is also added to powder blends in the dry form and granulated in situ by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosageforms.(4–6) Povidone solutions may also be used as coating agents. Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing

Agent in a number of topical and oral suspensions and solutions.The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone.

Description:

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with K-values equal to or lower than 30 are manufactured by spray-drying and occur asspheres. Povidone K-90 and higher K- value povidones are manufactured by drumdrying and occur as plates.

Typical Properties:

Acidity/alkalinity:pH = 3.0–7.0 (5% w/v aqueous solution).
Density (bulk): 0.29–0.39 g/cm3 for Plasdone.
Density (tapped): 0.39–0.54 g/cm3 for Plasdone.
Density (true): 1.180 g/cm3
Flowability: 20 g/s for povidone K-15;

16 g/s for povidone K-29/32.

Melting point:

Softens at 150^0C.

Moisture content:

Povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humidities.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

Solubility:
Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the K-value.

Viscosity (dynamic):
The viscosity of aqueous povidone solutions depends on both the concentration and the molecular weight of the polymer employed. PVP K 30Viscosity (dynamic) is 5.5–8.5

Stability and Storage Conditions
Povidone darkens to some extent on heating at 1508C, with a reduction in aqueous olubility. It is stable to a short cycle of heat exposure around 110–1308C. Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an air tight container in a cool, dry place.

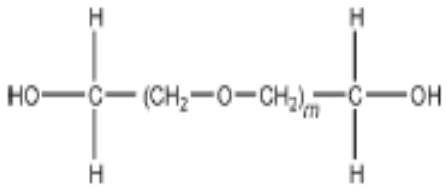
Incompatibilities
Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylicacid, phenobarbital, tannin, and other compounds. The efficacy of some preservatives, e.g. thimerosal, may be adversely affected by the formation of complexes with povidone.

PEG – 4000 [91]
Synonyms:
Carbowax; Carbowax Sentry; Lipoxol; LutrolE; PEG; PluriolE;polyoxyethylene glycol.

Chemical Name and CAS Registry Number:
a-Hydro-o-hydroxypoly(oxy-1,2-ethanediyl)

Empirical Formula and Molecular Weight:
$HOCH_2(CH_2OCH_2)mCH_2OH$ where m represents the average number of oxyethylene groups.

StructuralFormula:



FunctionalCategory:
Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology:
Polyethylene glycols can also be used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersions with an appropriate polyethylene glycol. Polyethylene glycol grades with molecular weights of 6000 and abovecanbe used as lubricants,particularlyfor soluble tablet. In solid-dosage formulations, higher-molecular-weight polyethyleneglycols can enhance the effectiveness of tablet binders and impart plasticity to granules. (4)However, they haveonlylimitedbindingactionwhenused alone,andcanprolongdisintegrationif present in concentrations greaterthan 5% w/w. When used for thermoplastic granulations, (5–7) –15% w/w PEG 6000 is heated to 70–758C. The mass becomes paste like and forms granules if stirred while cooling. This technique is useful for the preparation of dosage forms such as lozenges when prolonged disintegration is required.

HYDROXYPROPYL METHYLCELLULOSE:
Non proprietary names: B.P: Hypromellose.
Eur Ph: Methylhydroxypropylcellulosim.
USP: Hydroxypropyl methylcellulose.

Synonyms: Cellulose, Hydroxypropylmethyl ether, Methocel, HPMC, Methylcellulose, Propylene glycol ether, Methylhydroxy Cellulose, Pharmacoat.

Chemical Name: Cellulose,2-Hydroxypropylmethylether.
Molecular Weight: 10,000-15,000.
Category: Coating agents, Film formers, Stabilizing agents, Suspending agents, Tablet binder, and Viscosity increasing agent.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

Description: HPMC is an odourless tasteless, white or creamy-white coloured, fibrous or granular powder.
Solubility: Soluble in cold water, insoluble in Chloroform, Ethanol and Ether, but soluble in mixtures of Ethanol and Dichloromethane and mixtures of Methanol and Dichloromethane.
Viscosity: The viscosity of polymer ranges from 75-140% of declared value.
Stability: It is a stable material although it is hygroscopic after drying. Increase in temperature reduces the viscosity of solutions. It undergoes a reversible solution to get transformation upon heating and cooling respectively. The powder should be stored in a well closed container in a cool, dry place.
Safety: It is generally regarded as a non-toxic and non-irritant material although excessive consumption may have a laxative effect.

VII. 4. REVIEW OF LITERATURE

Subhash Deshmane et.al., enhancement of solubility and bioavailability of ambrisentan by solid dispersion technique using natural Daucus carota extract as drug carrier. Drug carrier was evaluated for solubility, swelling index, viscosity, angle of repose, hydration capacity, and acute toxicity test (LD50). Ambrisentan was studied for the saturation solubility, phase solubility, and Gibbs free energy change. Compatibility of drug and the natural carrier was confirmed by DSC, FTIR, and XRD. Solid dispersions were evaluated for drug content, solubility, morphology, in vitro, and in vivo study. Screening of the natural carrier showed the desirable properties like water solubility, less swelling index, less viscosity, and acute toxicity study revealed no any clinical symptoms of toxicity. Drug and carrier interaction study confirmed the compatibility to consider its use in the formulation. Formed particles were found to be spherical with smooth surface. In vitro studies revealed higher drug release from the solid dispersion than that of the physical mixture. Bioavailability study confirms the increased absorption and bioavailability by oral administration of solid dispersion. Hence, it can be concluded that the natural Daucus carota extract can be the better alternative source for the preparation of solid dispersion and/or other dosage forms for improving solubility and bioavailability.

K. Wlodarski et.al.,[45] improve solubility of tadalafil (Td), a poorly soluble drug substance (3 lg/ml) belonging to the II class of the Biopharmaceutical Classification System, its six different solid dispersions (1:1, w/w) in the following polymers: HPMC, MC, PVP, PVP-VA, Kollicoat IR and Soluplus were successfully produced by freeze-drying. Scanning electron microscopy showed a morphological structure of solid dispersions typical of lyophilisates. Apparent solubility and intrinsic dissolution rate studies revealed the greatest, a 16-fold, increase in drug solubility (50 lg/ml) and a significant, 20-fold, dissolution rate enhancement for the Td/PVP-VA solid dispersion in comparison with crystalline Td. However, the longest duration of the supersaturation state in water (27 lg/ml) over 24 h was observed for the Td solid dispersion in HPMC. The improved dissolution of Td from Td/PVP-VA was confirmed in the standard dissolution test of capsules filled with solid dispersions. Powder X-ray diffraction and thermal analysis showed the amorphous nature of these binary systems and indicated the existence of dispersion at the molecular level and its supersaturated character, respectively. Nevertheless, as evidenced by film casting, the greatest ability to dissolve Td in polymer was determined for PVP-VA. The crystallization tendency of Td dispersed in Kollicoat IR could be explained by the low Tg (113 _C) of the solid dispersion and the highest difference in Hansen solubility parameters (6.8 MPa0.5) between Td and the polymer, although this relationship was not satisfied for the partially crystalline dispersion in PVP. Similarly, no correlation was found between the strength of hydrogen bonds investigated using infrared spectroscopy and the physical stability of solid dispersions or the level of supersaturation in aqueous solution

Krasnyuk Jr.et.al.,[46] The effects of solid dispersions (SD) on the solubility of antibiotics were studied. Rifampicin, amoxycillin trihydrate and their SD with polyethylene glycol 1500, polyvinylpyrrolidone 10,000, and β-cyclodextrin were investigated. Preparation of SD increased the solubility and rate of dissolution of antibiotics. The solubility of rifampicin from SD increased by a factor of 2 – 2.7. The rate of dissolution from SD increased by factors o 2 – 2.7. Previous studies using a variety of physicochemical study methods have suggested that improvements in antibiotic release from SD occur as a result of decreases in crystallinity and the formation of intermolecular complexes.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

M.R.Shivalingam et.al.[47] Glipizide is a class-II antidiabetic drug which is purely insoluble in water. Since only dissolved drug can pass the gastro intestinal membrane, proper solubility of the drug is ultimately desired. Solubility of the poorly soluble drug is enhanced by formulating solid dispersion using solvent evaporation method. Drug and carrier in different ratios like 1: 1, 1: 2, 1: 3 by keeping drug weight constant was considered for formulating solid dispersions. Then prepared solid dispersions were evaluated for their routine tests like Phase solubility, Invitro dissolutoion study and the results were observed and tabulated. FT-IR study was also done for drug, polymers and formulated solid dispersion having(1: 3) ratios of drug:carrier by KBr pellet method. From the study it was concluded that 1: 3 ratio of drug:carrier shows better phase solubility and invitro dissolution rate. Also it was confirmed from the FTIR Spectra that no extra peaks were observed indictes no interaction between drug and polymers in the formulated solid dispersions.

Koji Takeda et.al.,[48] The suspension of the sugar and the model hydrophobic component was vacuum foam dried to give a solid powder. Four types of sugars and methanol were used as representative sugars and the organic medium. Four model drugs (indomethacin, ibuprofen, gliclazide, and nifedipine) were employed. Differential scanning calorimetry analyses indicated that the sugar and model drug (100:1) did not undergo segregation during the drying process. The dissolution of the hydrophobic drugs in water from the solid dispersion was then evaluated, and the results indicated that the C_{max} and $AUC_{0–60\ min}$of the hydrophobic drug in water were increased when the surfactant-free solid dispersion was used. Palatinose and/or α-maltose were superior to the other tested carbohydrates in increasing C_{max} and $AUC_{0–60\ min}$ for all tested model drugs, and the model drug with a lower water solubility tended to exhibit a greater extent of over-dissolution.

Kristine Opsvik Wikene et.al.,[49]develop rapidly dissolving formulations of curcumin that could photoinactivate both Gram-positive and Gram-negative bacteria.Curcumin solid dispersions with methyl-β-cyclodextrin and hyaluronic acid (HA), hydroxypropyl methylcellulose (HPMC) or both HA and HPMC were prepared through lyophilization. The lyophilizates were characterized by curcumin drug load [% (w/w)], differential scanning calorimetry, photostability, thermalstability, theirabilityto form supersaturated solutions
andby invitro photoinactivationof Enterococcus faecalis and Escherichia coli.The lyophilizates were amorphous solid dispersions with a curcumin drug load in the range of 1.4–5.5% (w/w) depending on the included polymer and the ratio between curcumin and the cyclodextrin. The lyophilizates were photolabile, but thermally stable and dissolved rapidly in contact with water to form supersaturated solutions. Selected lyophilizates demonstrated >log 6 reduction of colony forming units/ml of both E.faecalis and E. coli after exposure to low curcumin concentrations (0.5–10 μM) and blue light dose (1116 J/cm^2). The high drug load of the lyophilizates, rapid dissolution, ability to form relatively stable supersaturated solutions and the very high phototoxicity towards both E. faecalis and E. coli make these lyophilizates suitable for in vivo aPDT.This treatment with optimized curcumin formulations should be explored as an alternative to topical antibiotics in the treatment of wound infections.

Pankaj Vijay Dangre et.al.,[50] Solid dispersion (SD) was prepared by melting, solvent evaporation and kneading method using different ratios of drug and polymers (PEG-4000, Eudragit E-100, PVP K-30, Poloxamer-407, and Eudragit L-100). Phase solubility study revealed highest solubility in PVP K-30 at 1:2 ratios. The solid state characterizations of selected solid dispersion formulation (SD-15) were performed by infrared spectroscopy, differential scanning calorimeter, X-ray diffraction study and scanning electron microscopy. In vitro dissolution was carried out in phosphate buffer (pH 7.4) at 50 rpm in 900 ml of volume. The in vivo pharmacokinetic study of selected formulation (SD-15) was carried out in male Wistar rats using non-compartment analysis by linear trapezoidal method after a single oral dose of 10 mg/kg of EM. Results: The solid state characterization revealed no such drug-polymer interactions and rapid transformation of crystalline drug in an amorphous state, which amplifies the aqueous solubility and hence the dissolution rate. The in vitro dissolution study of the dispersions prepared by PVP K-30 (1:2) was found to be 95.5% after 1 hr. In vivo pharmacokinetic study in Wistar rats showed significant improvement in oral bioavailability of EM in SD-15 with the 2.4 fold increments than the pure drug.

Momoh et.al.,[51] Vernonia amygdalina solid dispersions SDs containing varying concentrations0:1, 1:0 1:1, 1:3 and 3:1, of Vernonia

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

amygdalina: PEG 4000 were prepared using the fusion -solvent evaporation method. Wound contraction ability in excision wound model was measured at different time intervals and study was continued until wound is completely healed. The effects of the preparation on the activities of liver were similarly assessed. Tensile strength was measured in 9th –dayold incision wound. Preparation (d) containing 1:3 of PEG : V. amygdalina showed statistically significant response, in terms of wound contracting ability, wound closure time, period of epithelization, tensile strength of the wound, when compared with the individual components and the control group (negative control), the results were comparable to those of a commercial neomycin formulation (positive control). The liver parameters and hematological studies did not show much variation to that of the control. It is believe that SDs of this extracted could be formulate into pharmaceutical dosage form and used as an alternative in wound healing.

Alka Ahuja et.al.,[52] solid dispersions of poorly soluble drugs like Cefixime, Valsartan and Ibuprofen were prepared and evaluated. Suitable carriers such as PVP K30 and HMPC etc. in different ratios were chosen. They were prepared by physical mixing and kneading method. The standard curves were prepared for cefixime, ibuprofen and valsartan in methanol. The release studies were carried out and compared. The results showed a marked increase in release of the drug from solid dispersions compared to the drug in its pure form. The percentage of the drug released for Ibuprofen increased from 12.78 to 52.4% (1:1 ratio), 70.2% (1:2 ratio) and 68.2% (1:3 ratio). The use of cefixime with hydroxypropymethylcellulose (HPMC) greatly improved the solubility of the drug and enhanced its dissolution rate. The percentage of the drug released increased from 13.2 to 31.4% (1:1 ratio), 34.9% (1:2 ratio) and 43.9% (1:3 ratio). The ratios which showed the best release were considered as the optimized formulations.

Tejal Soni et al.,[53] the development of meaningful dissolution procedure for drug products with limited water solubility have been a challenge to the pharmaceutical industry. In the present study, parameters such as solubility, medium PH, surfactant type, dissolution behavior of formulations, influence of sink conditions, stability and discriminatory effect of dissolution testing were studied for the selection pf proper dissolution medium. The discriminating dissolution method for aceclofenac formulation is paddle at 50 rpm; 900 ml pH 6.8-phosphate buffer, greater than 80% of the label amount is released over 60 minutes.

Ashok R. Patel et al.,[54] The present investigation aims atstudying the effect of mixed surfactant system of sodium lauryl sulphate (SLS) and alkyl polyglucosides (C_{10}APG, C_{12}APG and $C_{12/14}$APG) on dissolution rate enhancement of poorly water-soluble drug. Aceclofenac —a non-steroidal anti-inflammatory agent was used as a model drug as it has limited water solubility. The influence of the surfactant concentration in various blends on dissolution rate of Solid Dispersion (SD), prepared using solution method with ethanol as the solvent, The observed results in the dissolution rate enhancement could be attributed to the drug—surfactant interactions as evident from FT-IR, SEM and XRD results.

Sandrien Janssens et al.,[55] studied the characterization ofternary solid dispersions of itraconazole in PEG-6000/PVPVA 64 blends, it concluded that the influence of PEG-6000 on the dissolution of itraconazole from a PEG-6000/PVPVA 64 martix is composition dependent.

Yongmei Xie et al.,[56] they aimed to enhance the bioavailability of process included fast dissolving esomeprazole co-granulated with PEG-4000 by using solvent method. it was found that the absorption rate of SDEZ enteric capsule is lower than that Nexium in oral administration study, which corresponds with in-vitro dissolution.

H. de Waard et al.,[57] studied what are the unexpected differences observed in dissolution behaviour of poorly water soluble drug, tablets prepared from solid dispersions with a surfactant sodium laulyl sulphate, physically mixed or incorporated.

Sandrien Janssens et al.,[58] studied the physical stability of ternary solid dispersions of itraconazole PEG-6000/HPMC 2910 E5 blends, finally the dissolution data showed that an increase in the crystallinity of itraconazole was directly related to a decrease in the extent of dissolution.

Patel V.P et al.,[59] these are revealed that the dissolution behaviour of glipizide- cyclodextrin polymer systems in highly dependent on polymer type and concentration . incorporation of 5% PEG 4000 in glipizide-HP-B-CD complex improves significantly the dissolution behaviour of drug.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

Phuong HA Lien Trana et al.,[60] studied the modulation of micro-environmental Ph and crystallinity of ionizable telmisartan using alkalizers in solid dispersion for controlled release.

S.T. Prajapati et al.,[61] studied to enhance dissolution properties of carbamazepine with solid dispersion, solvent evaporation technique by using different types of carriers- PVP-K30, PEG-6000 and PEG-4000, finally it concluded that this solid dispersion technique had been shown a successful approach to improve dissolution.

P.Srinivasa Babu et al.,[62] studied the enhancement of dissolution rate of piroxicam with crosscarmellose sodium, pregelatinized starch, primojel , cros povidone, MCC, PVP and PEG., finally concluded that solid dispersions in super disintegrates an effective and efficient technique for enhancing the dissolution rate of piroxicam a poorly soluble drug.

Asyaries. et al.,[63] Gliclazide is insoluble in water and has low dissolution rate. Asyaried S. et al., used PEG as a matrix to disperse gliclazide in the solid state. The solid dispersion of Gliclazide: PEG6000 (1:4) was prepared by solvent evaporation method. In vivo study was carried out in healthy rats and results indicated that the rapid T_{max} was due to rapid absorption of gliclazide across the GI tract membrane. Increased C_{max}, AUC, (0-12) ,and AUC(0- ∞) indicate a better absorption of gliclazide in solid dispersion and physical mixture than gliclazide alone.

VIII. METHODOLOGY

Materials:

Table 1.1: List of chemicals used:

S. No.	Material	Manufacturer
1.	Ambrisentan	DR.REDDYS
2.	PEG 4000	Loba chemie, Mumbai
3.	HPMC K4M	Loba chemie, Mumbai
4.	PVP K-30	Loba chemie, Mumbai
5.	PEG 6000	Loba chemie, Mumbai
6.	Methanol	Rankem chemicals
7	Dichloromethane	Rankem chemicals

Table 1.2: List of equipments used:

S. No.	Instrument used	Manufacturer

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

1.	Electronic weighing balance	Shimadzu 2000
2.	UV-Visible Spectrophotometer	Shimadzu-1700, Mumbai
3.	Dissolutiontest apparatus USP23 (LABINDIA DISSO 8000)	Tab machines, Mumbai
4.	Hot air oven	Tapman, Mumbai
5.	Dessicator	Hindustan Apparatus mfg. Company

5.1 Preformulationstudies:

Preformulation testing is the first step in the rational development of dosage forms of a drug substance.

Definition: It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients.

Objective: Overall objective of preformulation testing isto generate information useful to the formulator in developing stable and bio-available dosage forms.

The following preformulation studies were carried out for Ambrisentan

a) Determination of melting point of Ambrisentan

b) Solubility studies

c) Drug–excipient compatibility studies

a) Determination of melting point

Melting point of the drug was determined by taking small amount of drug inacapillary tube closed at one end. The capillary tube was placed in an electrically operated melting point apparatus and the temperature at which the drug melts was recorded. This was performed thrice and average value was noted.

b) Solubility studies: Solubility of Ambrisentan was carried out in different buffers. Saturated solutions were prepared by adding excess drug to the vehicles and shaking on the shaker for 24 hrs at 25°C under constant vibration. Filtered samples (1ml) were diluted appropriately with suitable buffer and solubility of Ambrisentan was determined spectrophotometrically at suitable nm.

c) Drug–polymer compatibility studies

In the preparation of tablet formulation, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Preformulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between Ambrisentan, and the selected polymers. The pure drug and drug with excipient were scanned separately.

FT-IR studies

Sample/KBr ratio

The concentration of the sample in KBr should be in the range of 0.2% to 1%. The pellet is much thicker than a liquid film, hence a lower concentration in the sample is required (Beer's Law). Too high a concentration usually causes difficulties obtaining clear pellets. The IR beam is absorbed completely, or scattered from the sample which results in very noisy spectra.

Sample preparation

Completely dried potassium bromide was transferred into a mortar. About 2 % of drug sample was weighed in digital balance, mixed and grind to a fine powder. Two stainless steel disks were taken out of the desiccator. A piece of the precut cardboard (in the tin can next to the oven) on top of one disk was placed and cutout hole was filled with the finely ground mixture. The second stainless steel disk was kept on top and transfers the sandwich onto the pistil in the hydraulic press. With a pumping movement, hydraulic pump handle moved downward. The pistil will start to move upward until it reaches the top of the pump chamber. Then, the pump handle moved upwards and continued pumping until the pressure reaches 20,000 prf. Rest for a few seconds and with the small lever on the left side, the pressure was released. Removing of the disks and pulling apart. Obtained film was homogenous and transparent in appearance. Than inserted into the IR sample holder and attach with scotch tape and run the spectrum.

The physical mixtures of drugs were prepared in 1:1 ratio and then passed through sieve # 30. Samples of drug and excipients were placed

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

in vial, closed and labelled. Then the vials were stored under two different conditions at 4˚C and at 40˚C±75% RH. Observations of all the mixtures were done on 0th day, 7th day, 15th day and 30th day. The compatibility of drugs with excipients was studied by FT-IR. X-Ray Diffractometry the solid state of the drugs was investigated.

Experimental Methods:

Preparation of Buffers and Reagents

pH 7.4 Phosphate buffer Solution:

Dissolve 8.5ml of Concentrated HCL in 1000ml volumetric flask with distilled water and the final volume was made up to the mark with distilled water.

Phosphate buffer solution(pH7.4):

50 ml of 0.2M potassium dihydrogen ortho phosphate was taken in a 200 ml volumetric flask, to which 39.1 ml of 0.2M sodium hydroxide was added and volume was made upto the mark with distilled water.

5.2 Analytical method development by U.V. Spectroscopy:

UV-Visible spectrophotometry is one of the most frequently employed technique in pharmaceutical analysis. It involves measuring the amount of ultraviolet or visible radiation absorbed by a substance in solution. Instrument which measure the ratio, or function of ratio, of the intensity of two beams of light in the U.V-Visible region are called Ultraviolet-Visible spectrophotometers.

In qualitative analysis, organic compounds can be identified by use of spectrophotometer, if any recorded data is available, and quantitative spectrophotometric analysis is used to ascertain the quantity of molecular species absorbing the radiation. Spectrophotometric technique is simple, rapid, moderately specific and applicable to small quantities of compounds. The fundamental law that governs the quantitative spectrophotometric analysis is the Beer -Lambert law.

Scanning of λ_{max} of Ambrisentan:

Preparation of Stock Solution: 10 mg of Ambrisentan was taken in a 10ml volumetricflask. To that 5ml of methanol was added and shaken well to dissolve the drug. The solution was made up to the mark with pH 7.4 Phosphate buffer to give 1000 µg /ml concentration.

From the above solution 1ml is diluted to 10 ml with pH 7.4 Phosphate buffer to give 100 µg /ml concentration. From the above solution, take 1ml, and diluted to 10 ml with pH 7.4

Phosphate buffer,to give 10 µg /ml concentration. The prepared solution i.e.,10 µg/ml concentration was scanned for λ_{max} from 200-400 nmin UV/Visible spectrophotometer.

Calibration curve of Ambrisentan in pH 7.4 Phosphate buffer:

Preparation of stock solution:

10mgofAmbrisentanwastakenina10ml volumetricflask.ToThe solution was made up to the mark with pH 7.4 Phosphate buffer to give 1000 µg /ml concentration. From this Solution 1ml is diluted to 10ml with, pH 7.4 Phosphate buffer to give 100 µg /ml concentration. From the above stock solution subsequent dilutions containing 5 to 30 µg/ml solutions were prepared. The absorbance of each test solution was measured at λ_{max} i.e., 270nm of Ambrisentan in UV/Visiblespectroscopy against blank.

5.3 PREPARATION OF SOLID DISPERSIONS OF AMBRISENTAN:

There are several carriers, which have been reported for the preparation of solid dispersions by using different carriers by melt extrusion method.

Melt extrusion method:

In order to mimic the process of HME, a technique was developed wherein drug, polymer, and plasticizer in a fixed ratio (as mentioned in below tables) were geometrically mixed in a ground glass test tube. The mixture was heated in liquid paraffin(Q.S) contained in a beaker which was heated on a hot plate (REMI 1MHL) maintained at 170∘C with concomitant mixing. The hot mass obtained was immediately removed, allowed to cool, and stored in glass vials at 2–8∘C. Microscopic analysis was performed for solid dispersions prepared by hot melt mixing, physical mixture of polymer-plasticizer, and physical mixture of drug-polymerplasticizer, the last two prepared by simple geometric mixing.The % yield and % content of was determined by UV spectroscopy at 270 nm. Then the sample is collected and kept at room temperature in a screw capped glass vial until use.

Table :1.3

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

Formulation code	Drug: polymer ratio (Ambrisentan:PEG 4000)
F1	1:1
F2	1:2
F3	1:3

Formulation code	Drug : polymer ratio (Ambrisentan:HPMC K4M)
F4	1:1
F5	1:2
F6	1:3

Formulation code	Drug : polymer ratio (Ambrisentan: PVP K30)
F7	1:1
F8	1:2
F9	1:3

Formulation code	Drug : polymer ratio (Ambrisentan: PEG 6000)
F10	1:1
F11	1:2
F12	1:3

5.4 Evaluation of Solid Dispersions:

Prepared polymer drug conjugates were evaluated by

1) Estimation of drug content
2) Entrapment efficiency
3) Saturation Solubility
4) In- vitro dissolution studies

5.4.1 Estimation of Drug Content:

A quantity, which was equivalent to 10mg of drug, was accurately weighed and transferred to 100 ml volumetric flask. Then the volume was make up with pH 7.4 phosphate buffer and shaken or 10 min to ensure complete solubility of the drug. Then the solution was filtered. Same concentration of standard solution was prepared by dissolving 10mgof standard drug in 0.1 N HCL buffer. For both the sample and standard solutions absorbance was measured at 215nm for Ambrisentan inUV-Visible spectrophotometer.

5.4.2 Entrapment efficacy:

Entrapment efficiency of the solid dispersions was an important characteristic to assess the quantity of material entrapped inside solid dispersions before the study of behaviour of this entrapped drug in physical and biological systems, since the effects observed experimentally are usually dose related. Solid dispersions formulation of a drug can only be developed if the encapsulation efficiency of therapeutic doses can be delivered with a reasonable amount of drug, since the lipids in higher doses may be toxic and also result in non-linear (saturable) pharmacokinetics of formulation. An optimized loading procedure would achieve trapping efficiencies of 90% and more. This obviates the need for removal of non-entrapped material because loading doses of 10% or less of free drug can usually be tolerated. Procedures such as dialysis and passage through exclusion column, for removal of non-entrapped material are often time consuming, tedious, costly and recovery of non-entrapped material is usually difficult.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

Entrapment efficacy was calculated by following formula:

%Entrapment efficiency= Drug content *100/Drug added in each formulation

5.4.3 Determination of Saturation Solubility.

To evaluate the increase in solubility of Ambrisentan from solid dispersions, saturation solubility measurements were conducted and compared these data with that of pure Ambrisentan and physical mixtures of respective ratios. The known excess samples (Ambrisentan solid dispersions, physical mixtures, and pure Ambrisentan) containing 10 mg equivalent weight of Ambrisentan were added to 10m L of phosphate buffer, pH = 7.4,and these samples were rotated at 20 rpm in a water bath(37 ± 0.5°C) for 48 hours. The samples were then filtered,suitably diluted, and analyzed by UV-VIS spectrophotometer at 270 nm wavelength.

5.4.4 In vitro dissolution study:

The prepared solid dispersions were subjected to in vitro dissolution. Dissolution test was carried out using USP type 2paddle method [apparatus2]. The stirring rate was 50rpm,pH 7.4 phosphate buffer was used as dissolution medium and dissolution medium was maintained at 37±0.5^{O}C. Samples of 5ml were withdrawn at regular intervals of time, filtered and replace with 5ml of fresh dissolution medium, dilutions were made wherever necessary and were analysed for Ambrisentan at 270 nm by using UV-visible spectrophotometer.

5.5 KINETICS OF DRUG RELEASE

The mechanism of drugrelease for the Ambrisentan solid dispersions was determined using zero order and first order.

The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows:-

1. Zero – order kinetic model – Cumulative % drug released versus time.
2. First – order kinetic model – Log cumulative percent drug remaining versus time.

- **Zero Order Kinetic**

It describes the system in which the drug release rate is independent of its concentration.

$$Qt = Qo + Ko\ t$$

Where,

Qt= Amount of drug dissolved in time t

Qo = Initial amount of drug in the solution, which is often zero

and

Ko = zero order release constant.

If the zero-order drug release kinetic is obeyed, then a plot of Qt versus twill give a straight line with a slope of Ko and an intercept at zero.

- **First Order Kinetic**

It describes the drug release from the systems in which the release rate is concentration dependent.

$$Log\ Qt = log\ Qo + kt/2.303$$

Where,

Qt = amount of drug released in time t.

Qo = initial amount of drug in the solution k = first order release constant If the first order drug release kinetic is obeyed, then a plot of log (Qo- Qt)versus twill be straight line with a slope of kt/ 2.303and an intercept at t=0 of log Qo.

IX. 6.RESULTS & DISCUSSION

PREFORMULATION STUDIES

Determination of melting point

The melting point of Ambrisentan was found to be 165-168^{O}C which was determined by capillary method.

Solubility:

Solubility of Ambrisentan was carried out at 25^{0}C using 0.1 N HCL, 6.8 phosphate buffer, and purified water.

Table : 1.4

S.NO	MEDIUM	SOLUBILITY (mg/ml)
1	water	0.059
2	0.1 N HCL	0.316
3	6.8 pH buffer	0.524
4	7.4 pH buffer	0.721

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

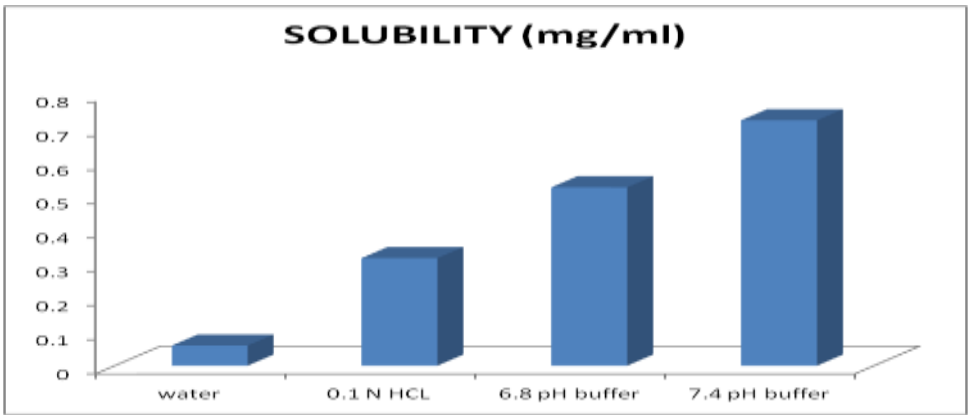


Fig :1.9Solubility studies of Ambrisentan

Discussion:

From the above conducted solubility studies in various buffers, we can say that 7.4 pH buffer solution has more solubility when compared to other buffer solution

Analytical method development by U.V. Spectroscopy:

Fig : 2.0 Uv Scan Spectrum of Ambrisentan

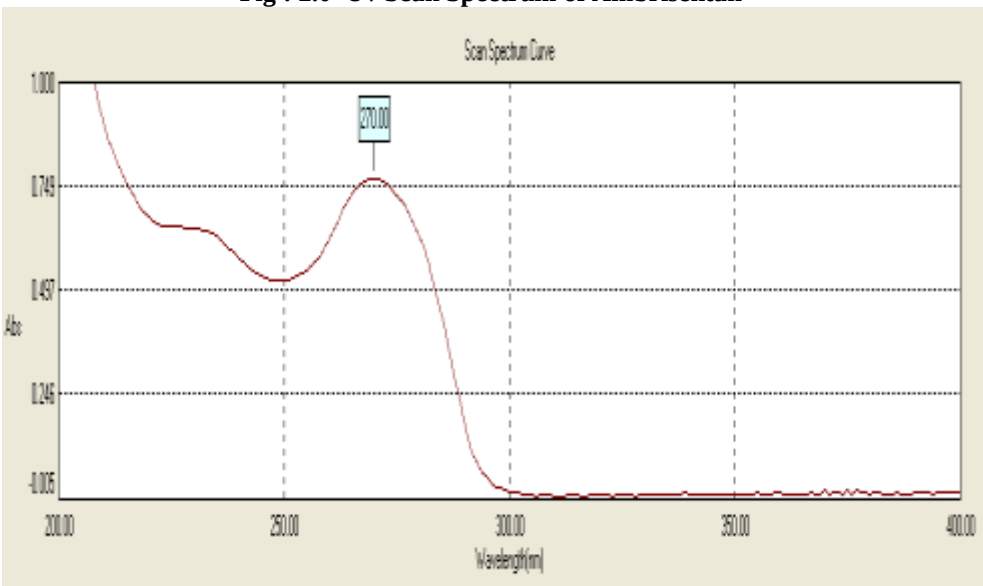


Table :1.5 Calibration curve data of Ambrisentan

Concentration(µg/ml)	Absorbance

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

0	0
5	0.123
10	0.247
15	0.371
20	0.509
25	0.638
30	0.785

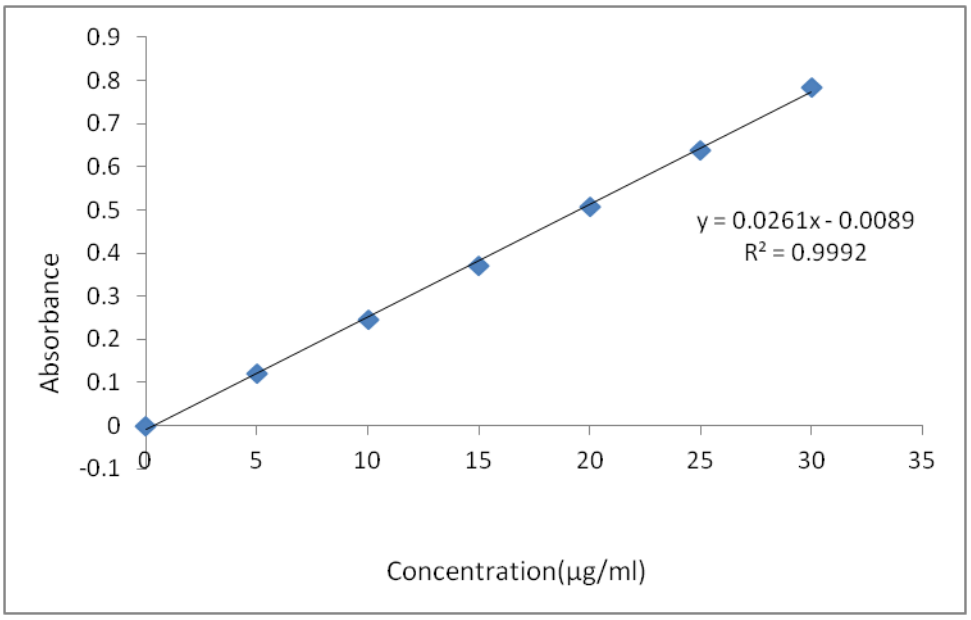


Fig:2.1 Calibration curve of Ambrisentan

Drug excipient compatibility:

Drug and excipient compatibility was confirmed by comparing spectra of FT-IR analysis of pure drug with that of various excipients used in the formulation.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

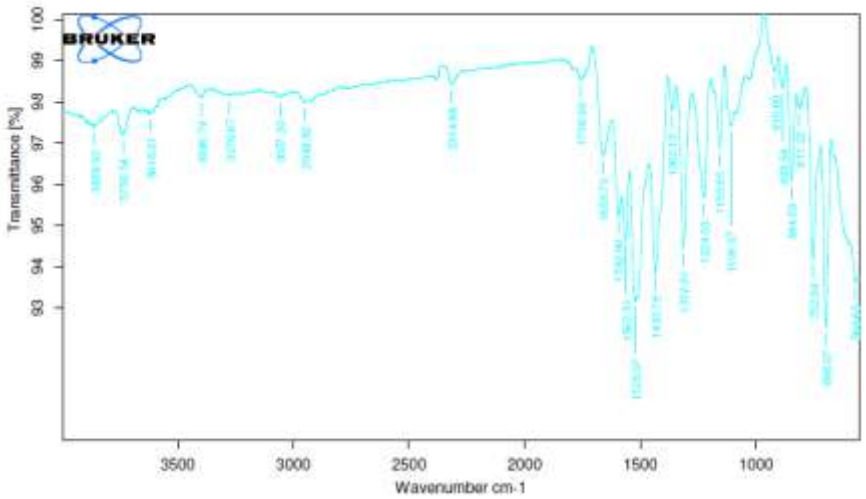


Fig:2.2 IR spectrum of pure Ambrisentan

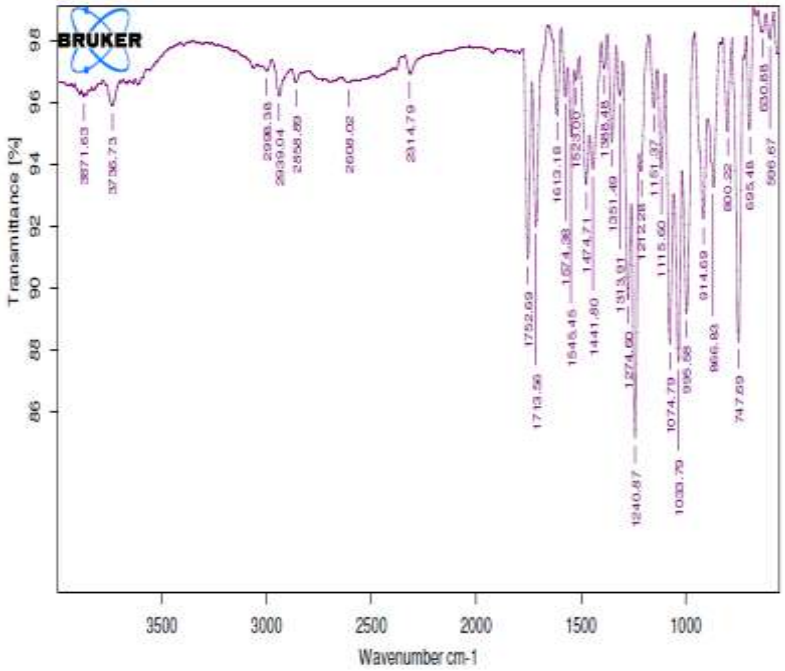


Fig: 2.3IR spectrum of Ambrisentan Optimised Formulation

Discussion: From the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Ambrisentan) and optimized formulation (Ambrisentan: excipients) which indicates there are no physical changes.

DISCUSSION: % Drug content values of all the formulation (F1-F12) were in the range of 72.89 – 98.18%.

Entrapment efficiency of solid dispersions by physical mixture method

Table: Entrapment efficiency of solid dispersions by physical mixture method

Table :1.6 :

Formulation	Percentage	%Entrapment efficacy	Saturation solubility

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

			Physical mixture	Solid dispersion
F1	84.28	90.45	68.72	90.78
F2	86.22	90.27	74.22	98.21
F3	85.22	95.34	85.21	100.28
F4	87.12	97.49	74.22	96.28
F5	88.26	98.76	80.18	100.28
F6	90.28	91.51	91.26	110.22
F7	95.22	99.34	78.92	92.85
F8	94.28	96.32	80.20	105.42
F9	96.11	93.51	86.22	120.14
F10	98.02	95.71	80.22	110.68
F11	96.26	99.68	85.16	125.78
F12	98.22	97.69	92.22	130.22

Discussion:
The Percentage yield of the formulated solid dispersions were found to be in the range of 84.2827- 98.22% respectively.
The entrapment efficacy of the formulated solid dispersions were found to be in the range of 90.27-99.68% respectively.
Saturation solubility study reveals that solid dispersions have more solubility than the physical mixtures, among them PEG 600 shows more solubility than the other polymers.

INVITRO DRUG RELEASE STUDIES OF SOLID DISPERSIONS:
Physical mixture method (F1-F12)
Invitro drug release studies for formulations (F1-F12)

Table :1.7

Time (Min)	Percentage drug release Release											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
5	23.42	26.48	31.37	29.48	31.59	34.51	20.32	23.38	25.39	25.29	28.42	29.47
10	30.89	33.92	35.49	35.99	38.78	41.49	27.69	30.79	32.78	33.68	36.82	42.79
15	36.61	39.33	40.63	40.12	43.01	45.32	33.23	36.31	38.31	39.11	40.97	54.61
30	53.23	55.61	56.95	50.61	53.89	57.11	48.81	51.99	54.63	65.71	72.98	78.89
45	70.82	72.96	74.39	61.52	64.91	67.69	64.92	67.92	70.92	82.42	85.82	87.64
60	90.31	92.54	93.99	72.41	75.24	78.71	82.21	85.31	88.32	91.91	94.15	96.28

DISCUSSION: Invitro drug release of Ambrisentan solid dispersions with PEG 4000 in

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

various ratios were observed which shows at the end of 60 mins, the formulation F1 releases 90.31, formulation F2 releases 92.54, F3 releases93.99%.

In vitro drug release of Ambrisentan solid dispersions with HPMC K4M in various ratios were observed which shows at the end of 60 mins, the formulation F4 releases 72.41, formulation F5 releases 75.24, formulation F6 releases 78.71%.

In vitro drug release of Ambrisentan solid dispersions with PVP K30in various ratios were observed which shows at the end of 60 mins, the formulation F7 releases 82.21, formulation F8 releases 85.31, F9 releases 88.32%.

In vitro drug release of Ambrisentan solid dispersions with PEG 6000in various ratios were observed which shows at the end of 60 mins, the formulation F10 releases 91.91, formulation F11 releases 94.15, and formulation F12 releases 96.28%.

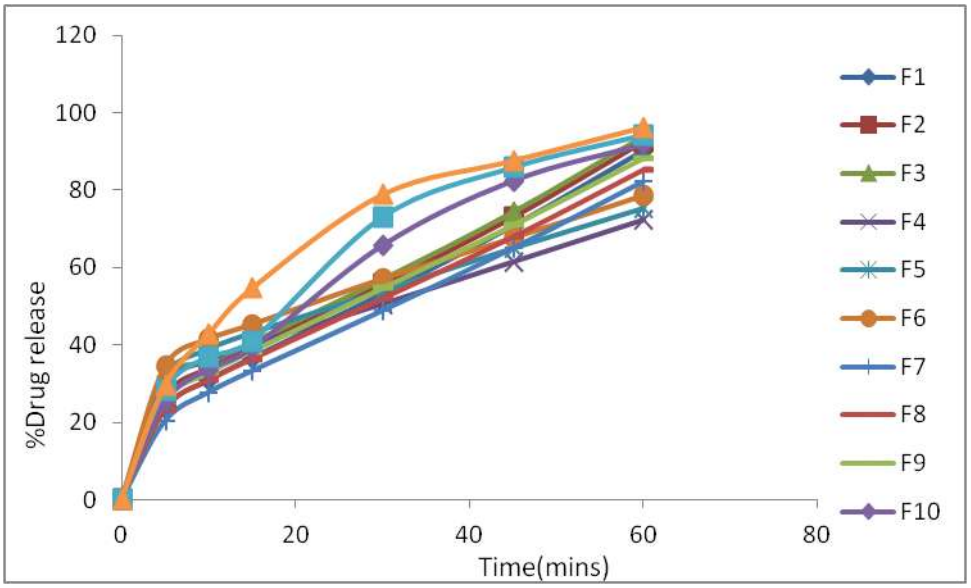


Fig:2.4 Invitro drug release profile for (F1-F12)

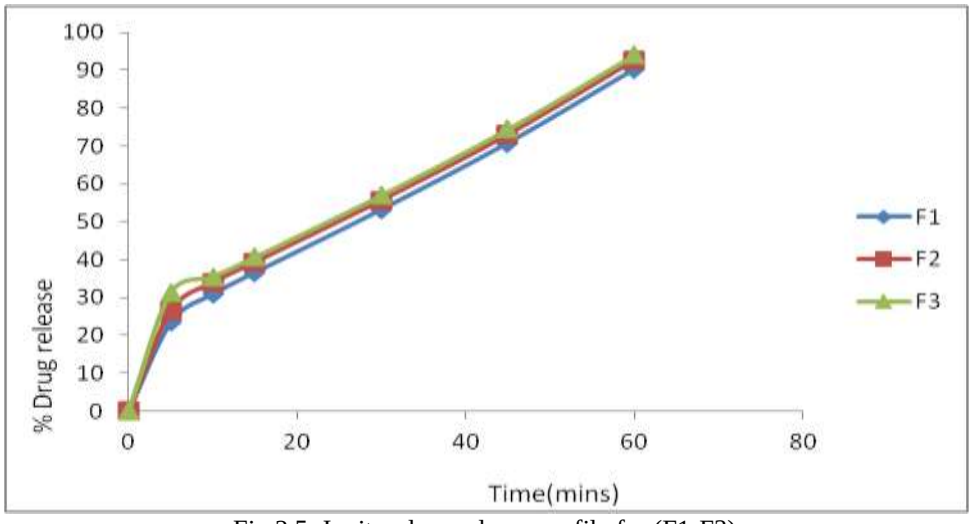


Fig 2.5: Invitro drug release profile for (F1-F3)

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

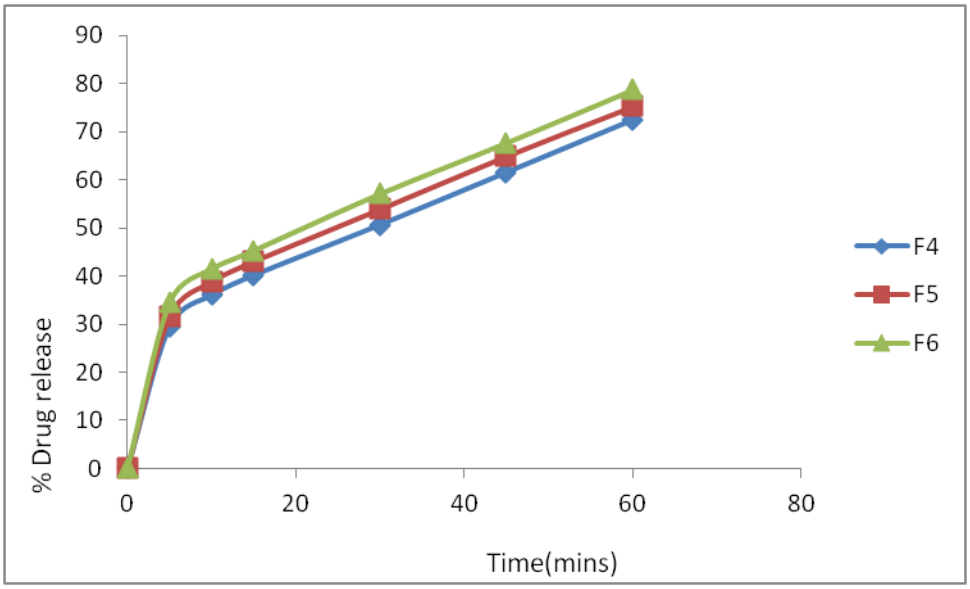


Fig: Invitro drug release profile for (F4-F6)

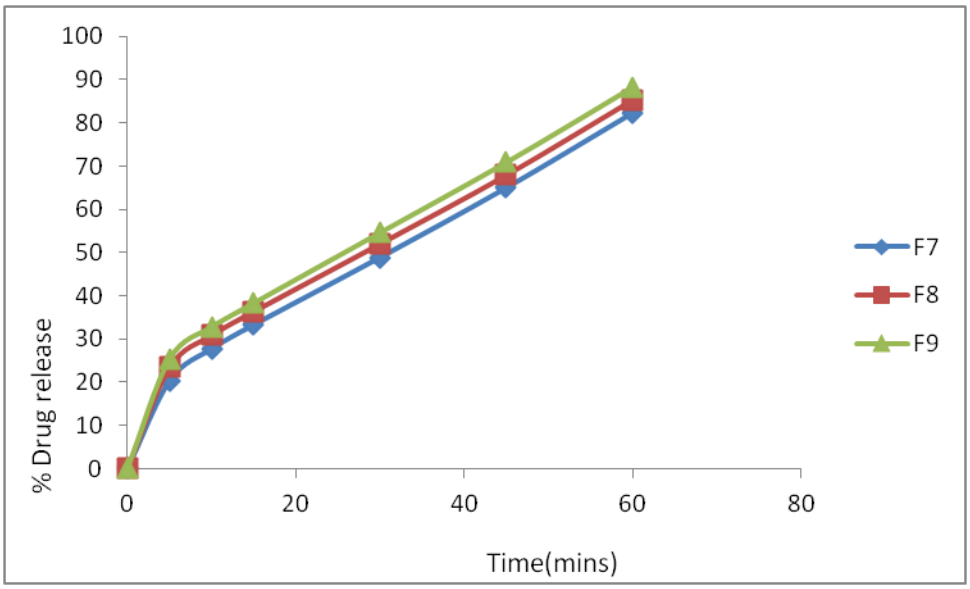


Fig: Invitro drug release profile for (F7-F9)

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

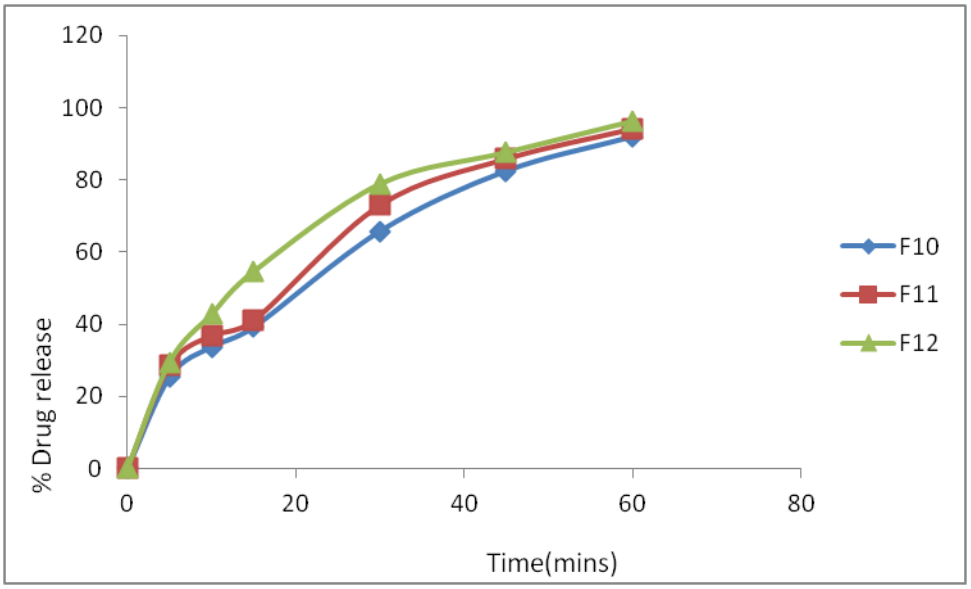


Fig: Invitro drug release profile for (F10-F12)

Finally, by comparing all the formulations (F1-F12) formulation F12 containing Ambrisentan: PEG 6000 (1:3) shows better results at the end of 60 min with drugrelease of 96.28%, hence it was selected as the best formulation among all the formulations.

In-vitro drug release kinetics studies for best formulation F12 by fusion method Zero order release kinetics studies:

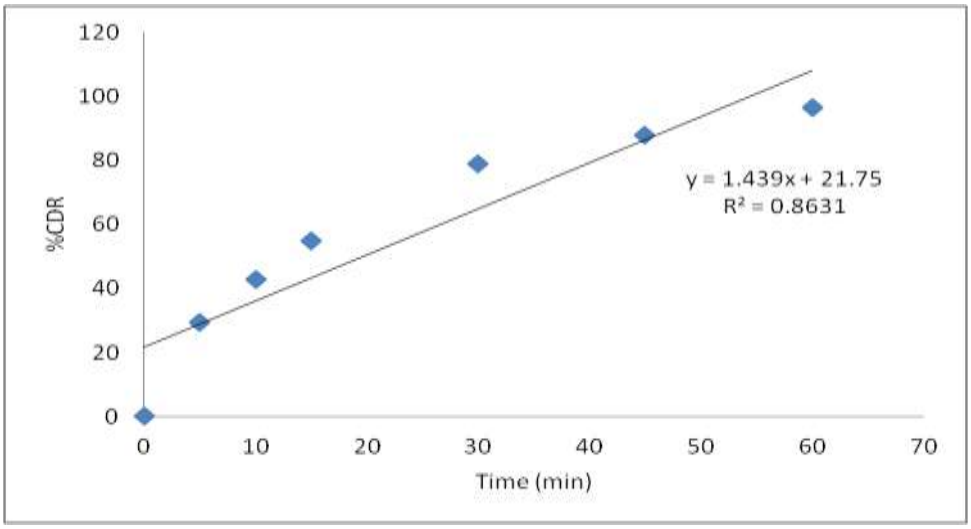


Fig:2.6 Zero order release profile for best formulation (F12)

First order release kinetics studies:

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

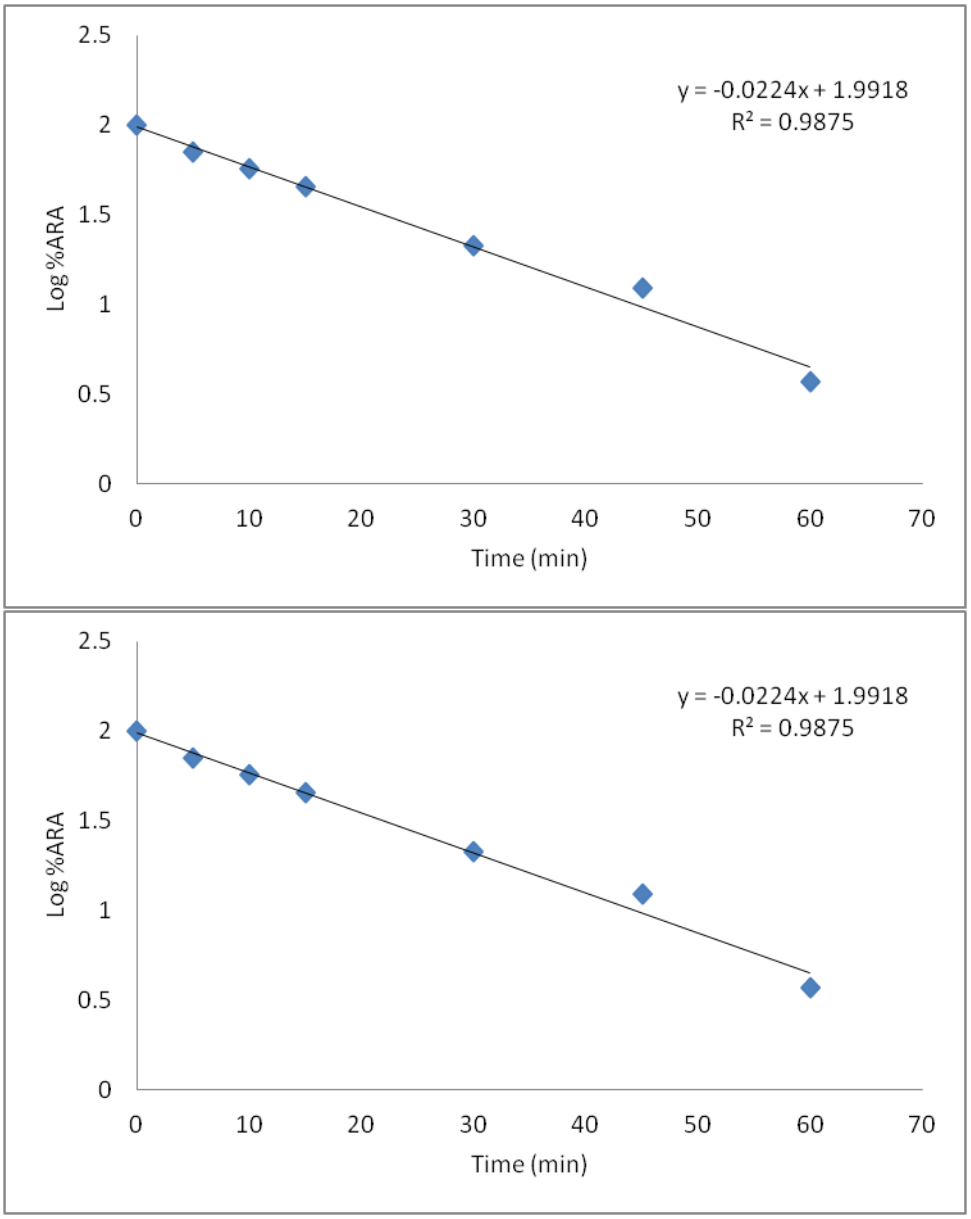


Fig: 2.7 First order release profile for best formulation (F12)

X. DISCUSSION:

By comparing the release kinetics studies of best formulation with zero order and first order we can say that the best formulation follows first order release kinetics studies having R^2 value 0.8637 were as zero order release kinetics studies having R^2 value 0.987, hence we can say that the best formulation follows first order release kinetics.

XI. SUMMARY AND CONCLUSSION

SUMMARY:

The therapeutic efficacy of a drug product intended to be administered by the oral route depend so its absorption by the gastro–intestinal tract. It is well established that dissolution is frequently the rate-limiting step in the gastro intestinal absorption of a drug from a solid dosage form. Poorly soluble drugs have been shown to be unpredictable and are slowly absorbed as compared with drugs with higher solubility. Consequently, these drugs present great challenges to further development into bioavailable dosage forms. Hence it is important to enhance the aqueous solubility, dissolution rate and bioavailability of these drugs from its oral solid dosage forms.

Ambrisentan is rapidly absorbed after oral administration, with time to reach peak

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1221-1263 www.ijprajournal.com ISSN: 2249-7781

concentrations (T max) within 5ms but possess oral bioavailability (90 %). The poor oral bioavailability is attributed to its low aqueous solubility, crystalline nature, and high hepatic first-pass metabolism. Furthermore, the bioavailability of Ambrisentan is highly variable due to its instability in the acidic milieu of the stomach. Therefore, a favourable formulation which can enhance solubility and dissolution rate of this model drug through solid dispersion technique using PEG 4000, Ethyl cellulose, PVP K30, PEG 6000.

The brief introduction about solid dispersions were explained in the introduction part. Furthermore, in this chapter introduction on dissolution rate and various approaches to improve the solubility; particularly on solid dispersion technology was elaborated. The aim and objective were also discussed.

Drug profile and excipient profiles were included with complete drug description of Ambrisentan and outlined their usage, contraindication and side effects.

Literature survey related to preparation and past research work on solid dispersions with various drugs and also by different methods.

Methodology as well as materials used and experimental methods employed in the present investigation were explained in detail. Later introduction regarding all the evaluation parameters and method of preparation of solid dispersions of Ambrisentan by melt extrusion method was explained. Solid dispersions of Ambrisentan were prepared with polymers in different ratios of drug and carrier (1:1, 1:2 &1:3).

Results of prepared solid dispersions of Ambrisentan by physical mixture method, and Fusion method were discussed which includes solubility, melting point determination, drug content uniformity, entrapment efficiency and invitro dissolution studies. Characterization in solid state was done by various analytical techniques such as FT-IR studies.

Finally, by comparing all the formulations (F1-F12), formulation (F12) containing Ambrisentan + PEG 6000 (1:3) shows better results by physical mixture method at the end of 60 min with drug release of 98.32%, hence it was selected as the best formulation. By comparing the release kinetics studies of best formulation of Ambrisentan with zero order and first order we can say that the best formulation follows Zero order release kinetics studies having R^2 value 0.863 were as firstorder release kinetics studies having R^2 value 0.987.

CONCLUSION

PEG 4000, Ethyl cellulose, PVP K30 and PEG 6000was used in the preparation of solid dispersions by physical mixture method. By observing the dissolution studies shows good results for Ambrisentan with PEG 6000(1:3) shows good results. And all the prepared solid dispersions were evaluated and results was explained in above mentioned data.

The following conclusions are drawn from above interpretations:

From the Solubility studies in various buffers we can say that 7.4pH buffer solution has more solubility when compared to other buffer solutions for Ambrisentan.

The melting point of Ambrisentan was found to be 165-168°C which was determined by capillary method.

Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug and optimized formulation (drug + excipients) which indicates there are no physical changes.

All the formulations of Ambrisentan were prepared by melt extrusion method

All the prepared solid dispersions were evaluated for percentage yield, drug content and entrapment efficiency and saturation solubilty.

The invitro dissolution studies of Ambrisentan was performed including the release kinetics studies, which shows that solubility of Ambrisentan was increased by using PEG 6000 in 1:3 ratio.

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