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Original Article

Design, Development and *In Vitro* Characterization of Self Emulsifying Drug Delivery System for Irbesartan

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Abstract

The objectives of present investigations were to optimize concentration of oil, surfactant and cosurfactant by pseudoternary phase diagrams and to develop a stable formulation of self emulsifying drug delivery system (SEDDS) in order to enhance the dissolution rate of poorly soluble Irbesartan (IBS) by SEDDS. Pseudoternary phase diagrams were constructed to identify the self emulsifying region. Four self emulsifying formulations were prepared using mixture of Capryol 90 as oil, Tween 80 as surfactant and PEG 400 as cosurfactant in various proportions. Optimized liquid SEDDS formulations were converted into free flowing powder by spray drying technique and evaluated for drug content, infrared spectroscopy (FTIR), differential scanning colorimetry (DSC), powder X-ray diffraction (PXRD), Zeta potential analysis, Particle size analysis, scanning electron microscopy(SEM),*in vitro* dissolution study and *in vitro* diffusion study. The results suggested that considerable improvement in the dissolution rate of drug from optimized SEDDS formulation was attributed to decreased crystallinity, altered surface morphology and reduction in particle size. Optimal formulation of irbesartan SEDDS were successfully developed in this work. The study illustrated that potential use of SEDDS dispense lipid soluble drug by oral route.

Keywords: Bioavailability, Irbesartan, Poor water solubility, SEDDS, Spray drying, surfacnt.

1.Introduction

Oral ingestion is themost convenient and emp loyed route of drug delivery due to its ease of ad ministration, high patient compliance,cost effectiveness, least sterility constraints and flexibility in design of dosage form. As a result, many of generic drug companies are inclined more to produce bioequivalent oral drug products. However, major challenge with design of oral dosage forms lies with their poor bioavailability. Oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, pre systemic metabolism and suscepti bility to efflux mechanisms.The most frequent causes of low oral bioavailability is attributed to low solubility and low permeability.Approximately 40% of new chemical entities exhibit poor aqueous solubility in water, which leads to poor oral bioavailability, high intra-and inter-subject variability and lack of dose proportionality [1]. Thus it presents a major challenge to modern drug delivery system. Oral route is the easiest and most convenient way of non-invasive administration. Oral drug delivery systems being

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the most cost-effective have always lead the world wide drug delivery market. Oral route may be a problem for drug molecules which exhibit poor aqueous solubility [2]. To get absorbed from gastrointestinal tract; a drug has to be solublize, because, with some exceptions, passive diffusion of dissolved drug molecules from high to low drug concentration is driving force of drug absorption. Different physicochemical and physiological properties are the reasons for poor drug absorption, poor water solubility, low membrane permeability, carrier mediated drug efflux, drug metabolism, and pharmacological interactions [3]. Most of the new drug candidates in development today are sparingly soluble and associated with poor bioavailability (BCS class II). There were various formulation strategies reported to address these problems; these include use of surfactant(s), drug nanoparticles, solid dispersions, micronization [4], lipids, cogrinding as well as permeation enhancers and complexation with cyclodextrins have come up [5]. Majority of these approaches have resulted in limited success because of need for specialized equipments, complicated manufa cturing process, longer processing time and regu latory complexity [6]. Thus, it is realized that oral bioavailability of poor water soluble drugs may be enhanced when co-administered with meal rich in fat has led to increasing recent interest in the formulation of poorly water soluble drugs in lipids. More recently there has been much focus on the utility of self emulsifying drug delivery systems (SED DS) [7]. The unique properties of lipids viz., their physiochemical property, and biocompatibi lity proven ability to enhance oral bioavailability of poorly water soluble, lipophilic drugs through selective lymphatic uptake have made them very attractive candidates as carriers for oral formulations. With the above promises, emerging field of lipid-based oral drug delivery system (LBODDS) has attracted considerable attention. A great challenge in front of pharmaceutical scientist is to make poorly soluble molecules into orally administered medications with sufficient bioavailability. Lipids and lipophilic excipients typically increase solubilization capacity of small intestine (both directly and indirectly). The enormous scope of utility of lipid based formulations includes not only manufacturing and processing benefits such as formulation of high potent, low melting point drugs into conventional solid formulation but it also includes biopharmaceutical advantages like enhanced solubilization for poorly water soluble drugs, parenteral delivery of low soluble drugs etc. Lipid-based formulations can positively influence drug absorption in a number of ways including; increasing solubilization capacity, preventing drug precipitation on intestinal dilution, enhancing membrane permeability, inhibiting efflux transporters, reducing CYP enzymes, enhancing chylomicron production and lymphatic transport. Since in many cases dissolution step is rate limiting step, formulation design can be a useful approach to improve dissolution and thus oral bioavailability of such drug candidates will be increased. Self-emulsifying drug delivery systems (SEDDS) are among methods used to improve oral bioavailability of poorly soluble drugs by presenting and maintaining drug in a dissolved state, in small droplets of oil, all over its transit through gastrointestinal tract. Irbesartan (IBS) is slightly soluble in alcohol and methylene chloride and practically insoluble in water. Compounds with aqueous solubilities lower than 0.1mg/mL often represents dissolution rate limited absorption. Irbesartan is currently marketed as tablet (75, 150 and 300mg) presently available conventional formulation. The estimated bioavailability is greater than 60%, however plasma level do not increase proportionally with dose. The calculated biopharmaceutical parameter suggests that IBS has very low absorbable dose. Also volume of aqueous medium is required to dissolve highest dose, calculated using ratio of dose/solubility was 20L. Thus, theoretically IBS exhibits a solubility limited bioavailability and would be advantageous to enhance solubility and dissolution rate of irbesartan. To overcome this problem there is need to develop self micro emulsifying drug delivery system which improves oral bioavailability of Irbesartan.Hence, objectives of present investigation are (i) to optimize SEDDS by pseudoternary phase diagram, (ii) to formulate S-SEDDS by spray drying technique, (iii)to

Characterize prepared SEDDS, (iv)to investigate *invitro* release profile of SEDDS, and (v) to investigate *invitro* diffusion of SEDDS.

2. Materials and Methods

2.1. Materials

Irbesartan (IBS) was gift sample from Lupin Research Park Pune. India. IPM (SD Fine Chemicals, Mumbai), Labrafil, Capryol 90, Maisine 35-1, Transcutol (Gattefosse ,France), Captex 800, Captex 355, Capmul MCM NF, Captex 300(Abitec Corporation, USA), Cremophor ELP, Cremophor RH 40, Cremophor EL(Libraw Pharma, New Delhi) were received as gift samples. Ethanol, Olive, Tween 80, Span 20, Span 80, Ethyl Oleate, PEG 400, PEG 200, Maltodextrin were purchased from (Oasis Alcohol Pvt Ltd, Tasavade and Loba Chemi. Pvt. Ltd., Mumbai, India). All chemicals were of analytical grade.

2.2. Solubility Study of IBS in Different Solvents

Solubility studies were carried out in different solvents according to method reported by Higuchi and Connors [8]. An excess amount of IBS was placed in conical flask containing 10mL of different solvents (water, SGF, phosphate buffer pH5.8, phosphate buffer pH6.8, 0.1N HCl, acetate buffer pH4, citrate buffer). These flasks were sonicated for 30min. and kept at room temperature. After these mixtures were centrifuged at 2000 rpm for 10min. Content of each flask was filtered through a whatmann filter paper no.41. Filtrates were diluted with particular solvents. Amount of drug solublized was analyzed spectrophotometrically (SHIMADZU UV-1601, Japan) at 220nm for water, phosphate buffer pH5.8, phosphate buffer pH6.8, acetate buffer pH4, and citrate buffer respectively. 241.5nm for SGF and 244nm for 0.1N HCl. Solubility was determined in triplicate (n=3) [8].

2.3. Saturation Solubility Studies

In order to find out appropriate solvents with good solubilizing capacity for Irbesartan, saturation solubility of Irbesartan was investigated in various oils (Captex 355, IPM, Captex 800, Labrafil, Capryol 90, Olive, Ethyl oleate, Maisine35-1, Capmul MCM NF, Captex 300), surfactants (Span 80, Cremophor ELP, Tween 80, Cremophor RH40, Span 20, Cremophor EL) and cosurfactants (Transcutol PEG 400, PEG 200) by using shake flask method. In this study excess amount of IBS was added to each vial containing 2mL of vehicle. These vials were sealed. The mixture was vortexed using a cyclomixer (CM101, Remi Motors Ltd., Mumbai) for10 min in order to facilitate proper mixing of IBS with the vehicles. The mixtures were shaken for 72h in incubated orbital shaker (Remi Moters Ltd., Mumbai) maintained at 37±1˚C to attain equilibrium. Equilibrated samples were centrifuged at 2000rpm for 15 min, followed by filtration through membrane filter (0.45µm). Aliquots of supernatant were diluted with ethanol and drug content was quantified using an UV –visible double beam spectrophotometer. (Jasco V 630, Japan) against ethanol as blank at λ_{max} 244 nm. All measurements were done in triplicate.

2.4. Construction of Pseudoternary Phase Diagrams

Pseudo-ternary phase diagrams were constructed by drop wise addition of distilled water to homogenous liquid mixture of oil, surfactant, and co-surfactant, at ambient temperature by water titration method. Ratios of surfactant/co surfactant were prepared in specific manner, i.e.1:1, 2:1, 3:1 and 4:1 (w/w) which was labeled as Km values 1, 2, 3 and 4 respectively. At desired Km value (1:1, 2:1, 3:1, and 4:1) S_{mix} and oil were mixed at ratio of 1:1, 1.5:1, 2:1, 2.5:1, 3:1, 3.5:1, 4:1, 4.5:1 and 5:1 in pre-weighed test tube. To resultant mixtures, distilled water was added dropwise till first sign of turbidity in order to identify end

point. Phase diagrams were constructed from data gathered by the titration method. Phase diagrams were constructed to define the extent of the microemulsion regions i.e. proportion in which the three/four essential components must be mixed to form a transparent, clear, single phase, homogeneous and stable microemulsion.

2.5. Design of SEDDS Formulation

A series of SEDDS formulations were prepared using Capryol 90 as oil, Tween 80 and PEG 400 as S/CoS combination (Table 1).In all formulations, the level of irbesartan was kept constant. Briefly oil, surfactant and co-surfactant were accurately weighed and mixed by gentle stirring. Amount of irbesartan was dispersed into mixture of oil and S/Cos. Components were mixed by gentle stirring on magnetic stirrer until irbesartan was completely dissolved. Prepared liquid SEDDS formulations were spray dried by using spray dryer at inlet temperature 160˚C, outlet temperature 80˚C, aspirator speed70%, feed rate 10% and compressed air flow rate 2bar. Prepared solid SEDDS was collected and sealed into glass vial and stored at room temperature for further studies.

2.6. Drug Content Determination

For determination of drug content, prepared SEDDS formulations (10mg) were diluted with SGF (pH1.2) without enzyme and finally volume was made up to 100mL with the same. Amount of drug present was analyzed spectrophotometrically (SHIMADZU UV-1601, Japan) at 241.5 nm after sufficient dilutions with SGF without enzyme (pH1.2)

2.7. Particle Size Determination

Solid SEDDS formulations (10 mg) were diluted with 10 mL double distilled water in a beaker with constant stirring on a magnetic stirrer. The average droplet size, size distribution, and polydispersity index of microemulsion from solid SEDDS were assessed by lesser light scattering technique using Malvern Master Sizer (PSS-Nicomp, Santa Barbara, Calif., USA).

2.8. Measurement Of Zeta Potential

Measurement of Zeta potential is also a prerequisite to know the stability of microemulsion. Zeta potential is a measure of surface charge of particles and thus it imparts the colloidal stability due to particle-particle repulsion, as particle aggregation is less to occur for charged particles (a high Zeta potential). So, the prediction of Zeta potential also allows the prediction of stability of colloidal dispersion. The zeta potential of the Microemulsion droplet surface was determined by electrophoretic mobility in an apparatus such as a Malvern

Table 1. Composition of selected formulations.

Sr. no.	Formulation	Drug (mg)/10 gm	%Composition (w/w)		
			Oil	S_{mix}	Water
1	ME1	500	12	53	35
2	ME2	500	10	50	40
3	ME3	500	7	43	50
4	ME4	500	4	40	56

Master Zetasizer (PSS-Nicomp, Santa Barbara, Calif., USA) equipped with suitable software and calibrated with the supplied standard. Three consecutive measurements are performed at 25 ºC using a constant cell drive of 150 mV. The electrophoretic mobility is converted into zeta potential values through the Smoluchowsky equation, using the dielectric constants and viscosity of dispersion medium.

2.9. Infrared (IR) Spectroscopy

FTIR studies were done to assess whether any possible interaction among drug, oil, surfactant, co-surfactant and maltodextrin. This was done by FTIR Spectrophotometer (Jasco-410, Japan), infrared spectrums of pure drug, mixture of ingredients of the formulation, and also formulated batches were recorded in wavelength region of 4000 to 400 cm^{-1}. From overlain spectrum analysis compatibility of ingredients in formulations was determined. The procedure consist of a sample in excess was dispersed in potassium bromide nearly at ratio 1:100, mixed well and then mixture kept into sample holder for analysis.

2.10. Powder X- ray Diffraction Studies

To obtain the changes in the crystallinity of the components of formulation prepared, the PXRD study was carried out by using X ray diffractometer (D2 Phaser, Bruker). For this the sample of pure drug, prepared batch and maltodextrin was taken and irradiated with monochromatised CuKa radiation and analyzed between 10˚ - 80˚ (2θ).

2.11. Differential Scanning Colorimetry

Thermograms of pure drug, solid SEDDS batches and physical mixtures were obtained using Differential Scanning Colorimetry (TA Instruments SDT-2960, USA) equipped with an intracooler. Indium standard was used to calibrate the DSC temperature and enthalpy scale. The samples were heated in hermetically sealed aluminum pans under nitrogen flow rate 100 mL/min at a scanning rate of 10˚C/min from 30˚C to 300˚C. Empty aluminum pan was used as reference.

2.12. Scanning Electron Microscopy

The surface characteristics of pure drug, maltodextrin as excipients and prepared solid-SEDDS were studied by SEM (JEOL, JSM 50 A, Tokyo, Japan) at 2000x. The samples were mount on double-sided adhesive tape that has previously been secured on copper stubs and then analyzed. The accelerating voltage was 15kV.

2.13. In-vitro Dissolution Study

To determine the dissolution profile of irbesartan alone and prepared solid –SEDDS were carried out using dissolution apparatus (DBK- Dissolution rate test apparatus USP type II).Dissolution studies were carried out using 900mL SGF (pH1.2) without enzyme) at 37± 0.5˚C at 50rpm. 25 mg of pure irbesartan and its equivalent amount solid SEDDS were added to 900mL SGF. 5mL samples were withdrawn after 5,10,15,30,45,60,90,120 min and replaced each time with 5 mL fresh SGF. The solutions were immediately filtered through membrane filter (0.45 µm). After that from filter ed sample 1mL sample was withdrawn and diluted upto 10mL with SGF (pH1.2) without en zyme. Concentration of IBS was determined spe ctrophotometrically at 241.5nm.All measurements were carried out in triplicate.

2.14. In-vitro Diffusion Study

Permeability study of irbesartan alone and prepared solid –SEDDS were carried out using dialysis membrane (Himedia lab. Pvt. Ltd., Mumbai). 25mg of pure irbesartan and its equivalent amount solid SEDDS were diluted in 2 mL of SGF pH1.2 (without enzyme) and individually filled in to hollow activated dialysis membrane bag with both ends tied with thread.

These bags were placed with aid of stand in beaker containing 200mL Phosphate buffer of pH 7.4. Temperature was maintained at 37± 0.5˚C and rotation speed was 50rpm with magnetic stirrer. 5mL samples were withdrawn at regular intervals (0.5, 1, 2, 3 4, 5, 6, 7, 8, 9 hours) and replaced each time with 5mL fresh phosphate buffer pH7.4 to maintain a constant volume and sink condition. The solutions were immediately filtered through 0.45µm membrane filter. From filtrate 1mL sample was withdrawn and diluted upto 10mL with phosphate buffer pH 7.4 concentration of irbesartan wasdetermined spectrophotometricall y at 220nm. All measurements were carried out in triplicate.

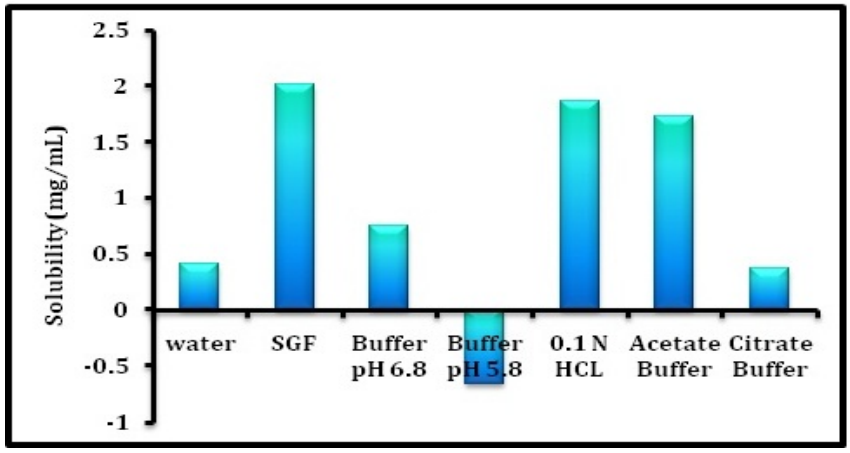

Figure 1. Solubility of IBS in various solvents.

3. Results and Discussion

3.1. Solubility Study of IBS In Different Solvents [9]

Selection of suitable media plays a significant role in *in vitro* dissolution study of SEDDS formulation, to achieve maximum drug release with desirable pharmacokinetic profile. Solubility of Irbesartan in different media is given in Figure 1. Solubility of Irbesartan was high in SGF without enzyme compared to other solvents. So the *invitro* dissolution studies were carried out in SGF (pH 1.2) without enzyme.

3.2. Saturation Solubility Studies [10, 11]

The self emulsifying formulation consists of one or more surfactant and drug dissolved in oil. The pre-concentrate mixture should be clear, monophasic liquid at room temperature and should have good solvent properties to allow presentation of drug in solution. The objective of solubility study is to identify oil and surfactants with good solubilizing capacity for irbesartan. The concentration of irbesartan in various excipients was determined by UV spectrophotometer at room temperature and results are shown in following figure 2, 3 and 4. The surfactants used in SEDDS formulations are known to improve the bioavailability by various mechanisms. Moreover, the addition of cosurfactants has been shown to increase the extent of the microemulsion region. Oil was selected on the basis of good solubilizing capacity for irbesartan as well as ease of emulsification. From solubility data, Capryol 90 as oil, Tween 80 as surfactant and PEG 400 as cosurfactant were selected for irbesartan SEDDS formulation.

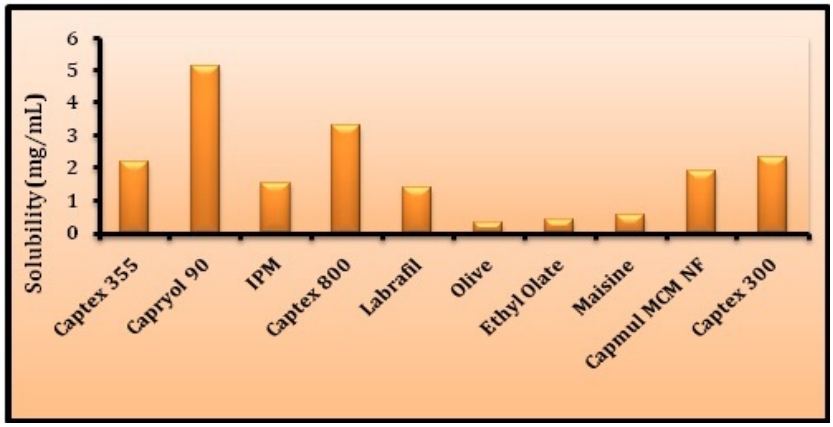

Figure 2. Solubility of IBS in various Oils.

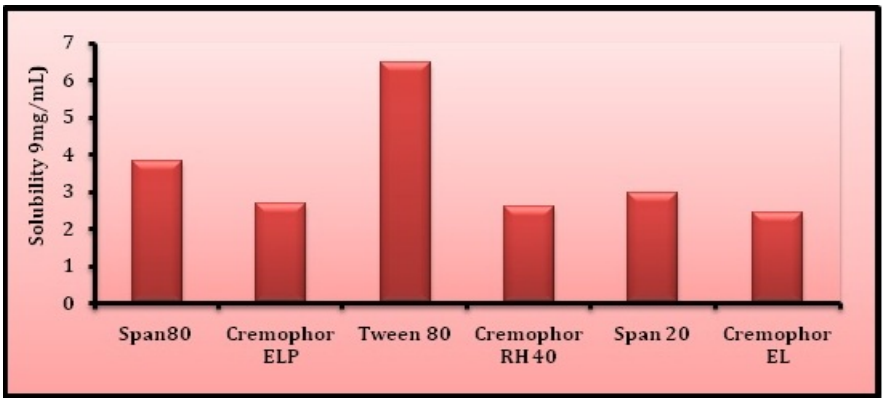

Figure 3. Solubility of IBS in various surfactants.

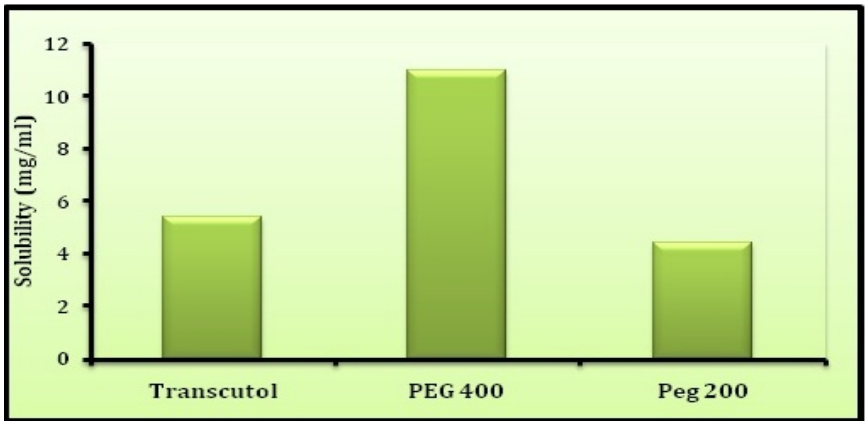

Figure 4. Solubility of IBS in various co-surfactants.

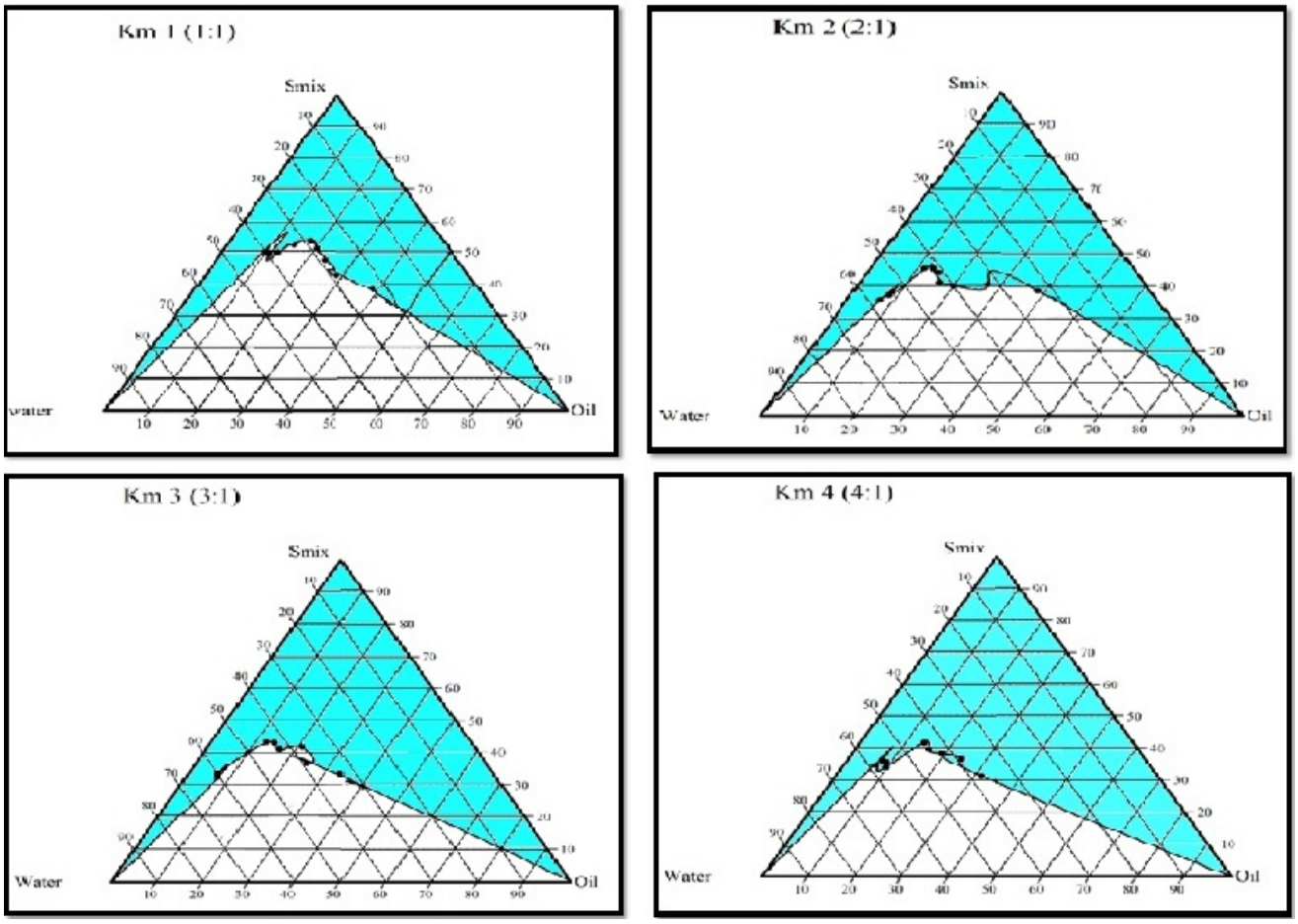

Figure 5. Pseudoternary phase diagram of capryol 90: tween80: PEG 400: water at Km1, Km2, km3, Km4.

3.3. Pseudoternary Phase Diagrams

Pseudo-ternary phase diagrams were constricted to identify the microemulsion region and optimize the concentration of the selected vehicles. For development of a SEDDS formulation, optimum ratios of excipients concentrations established by means of phase diagram studies provided the area of the microemulsion region. It is useful to determine area in order to ensure successful aqueous dilution without 'breaking' the microemulsions [12]. Based on results of solubility studies oil, surfactant and co-surfactant were selected for microemulsion formulation. Nine different potential combination of surfactant mixture to oil at different K_m values (1, 2, 3 and 4) (figure 5) were used for the phase diagram study of IBS SEDDS. No distinct conversion of water-in-oil (w/o) to oil-in-water (o/w) was observed. The boundary layer of o/w microemulsion was determined in each phase diagram. Components used for construction of pseudoternary phase diagram are Capryol 90 (oil phase), TWEEN 80 (surfactant), PEG 400 (co-surfactant) and distilled water (aqueous phase). The phase diagram at K_m value 4 showed better microemulsion existence region than Km 1, 2 and value at 3 didn't showed further increase in microemulsion existence region.

3.4. Design Of SEDDS Formulation

The four formulations were selected from phase diagram at K_m value 4, named as ME1, ME2, ME3 and ME4 Quantitative unit compositions of selected formulation of SEDDS are presented (Table1).

3.5. Drug Content Determination

Drug content of irbesartan solid SEDDS batches was determined by UV spectroscopy method to evaluate uniformity of formulation. The drug content of different irbesartan solid SEDDS batches was given in Table 2.

3.6. Particle Size Determination

There is a relationship between droplet size and concentration of the surfactant being used. In some cases, increasing the surfactant concentration could lead to droplets with smaller mean droplet size. In this case, it could be explained by stabilization of oil droplets as a result of localization of the surfactant molecules at the oil–water interface. On the other hand, in some cases, the mean droplet size may increase with increasing surfactant concentrations. This phenomenon could be attributed to the interfacial disruption elicited by enhanced water penetration into the oil droplets mediated by the increased surfactant concentration and leading to ejection of oil droplets into the aqueous phase [13] The droplet size of the emulsion is the crucial factor in the self-emulsification performance because it determines the rate and extent of drug release as well as drug absorption. Moreover, it has been reported that the smaller is the particle size, the larger is the interfacial surface area which may lead to more rapid absorption and improve the bioavailability. Polydispersity index (PDI) for all formulations have been summarized in (Table 3).These results show that particle size of SEDDS ME1, ME2, ME3,and ME4 were more than 100nm and with less PDI. Polydispersity is the ratio of standard deviation to the mean droplet size. This signifies the uniformity of droplet size within the formulation. The higher the value of polydispersity, the lower is the uniformity of the droplet size in the formulation [14]. Here the PDI values of SEDDS ME1, ME2, ME3, and ME4 are 0.100, 0.182, 0.125 and 0.105 respectively, which indicate the uniformity of droplet size within the formulation. If PDI value more than 1 it indicates that nonuniformity of particles in emulsion. A less solubility of drug in solvents may be reason behind this. This leads to precipitation of drug and thereby to an increase in particle size [15]. SEDDS with increased particle size causes agglomeration of globules and suffers with instability of system which show that low uniformity in particle size of formulation to have remarkable effect on droplet size and self emulsification nature of liquid SEDDS. Formulations were having particle size between 100-300 nm which fulfill criteria of SEDDS and low PDI shows uniformity of particles. Therefore, formulation batches are considered for further *in vitro* studies.

Table 2. Drug content of solid SEDDS batches.

Batch	Drug Content (%)
ME1	99.91±0.96
ME2	98.38±0.88
ME3	67.07±0.85
ME4	95.73±0.98

3.7. Zeta Potential Analysis

Electrostatic forces of micro emulsion droplets are critical for assessing the stability of the SEDDS formulation. An increase in the electrostatic repulsive forces between micro emulsion droplets prevents coalescence of microemulsion droplet and a decrease of electrostatic repulsive forces resulting in

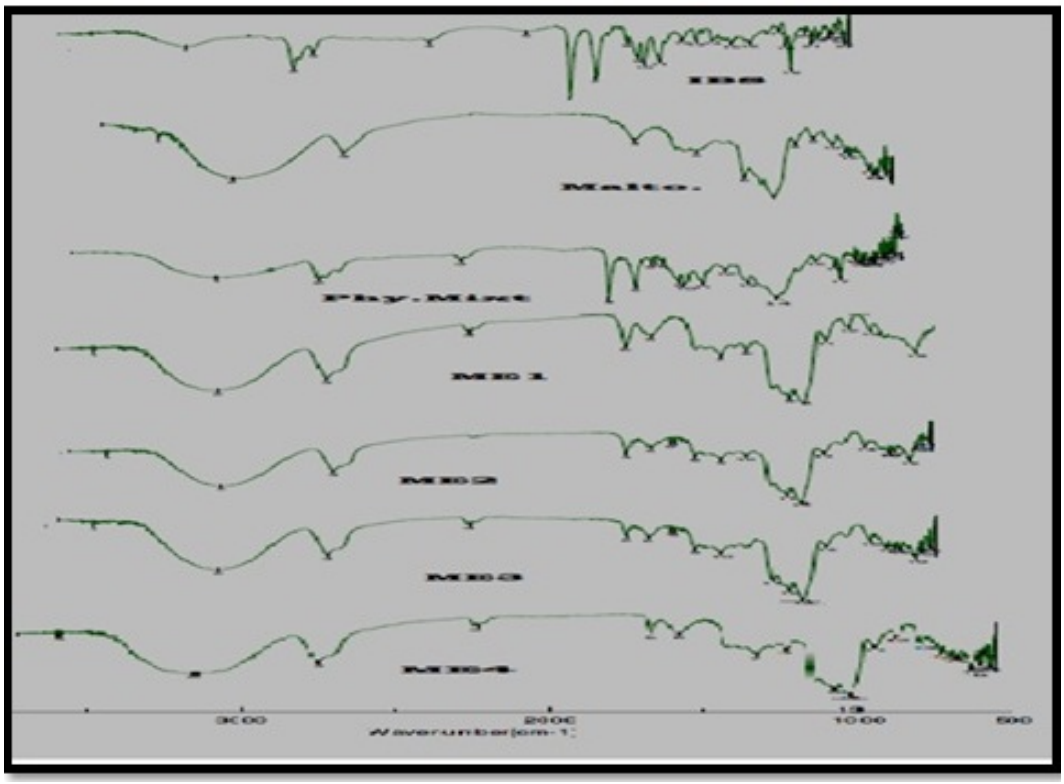

Figure 6. Overlain of IR spectra of IBS, maltodextrin, physical mixture and formulations.

phase separation. The surfactant (Tween 80) and co surfactant (PEG 400) used in this study are nonionic which do not contribute any charge to the micro emulsion particle. Dixit A.R et al reported stable SEDDS using same excipients. This indicates that negative charge particle do not affect the stability of emulsion [14, 16]. The zeta potential value of all microemulsion batches were found to be in between -12 to -35 (Table 4) The negative sign indicates that free fatty acids presents in oil droplet. So, considering these results it can be concluded that SEDDS with S/Cos ratio 1:4 generates maximum microemulsion region and forms rapid microemulsion with lesser particle size, low PDI and low zeta potential.

3.8. Infrared (IR) Spectroscopy

The possible interaction between drug and excipients as SEDDS formulations were studied by FTIR spectroscopy as shown in follo wing figures. The pure irbesartan showed peaks at 1733.69cm^{-1}, 1617.98cm^{-1}, 1300-1400cm^{-1}, 757.89cm^{-1} due to presence of C=O, conjugation with double bond, C-N stretch, and C-H bending vibration of aromatic ring respectively. It was observed that all important peaks due to functional group of drug were presented in SEDDS formulations with some ne w intense peaks indicating the presence of OH. These peaks were observed in range of 3300-3450 cm^{-1} in SEDDS formulations [17, 18]. So fundamental peaks of the irbesartan are retained in the spray dried batches, and the FTIR of the physical mixture and that of treated batches are almost identical. The fundamental peaks retained in all batches are shown in figure 6. These results showed that there was no chemical interaction or changes during spray drying of liquid microemulsion and irbesartan was stable in all spray dried formulation. The intensity of the peaks was reduced in formulation batch.

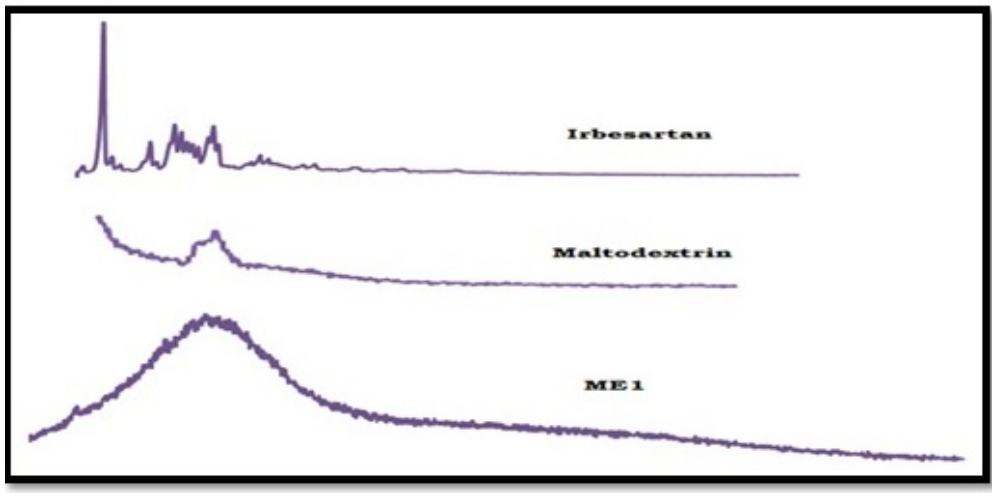

Figure 7. Overlain of PXRD of IBS, maltodextrin and ME1.

3.9. Powder X- ray Diffraction Studies

In the powder X-ray diffraction studies, the diffractograms of the representative batches were taken to find out the effect on the crystallinity of the drug and excipients. The PXRD of plain irbesartan showed peak of crystallinity at 12.55˚ (2θ) with peak intensity of 23011 indicating its crystalline nature. The relative degree of crystallinity values of irbesartan SEDDS at specific angle is 0.065 for ME1. It indicates decrease in crystallinity of irbesartan in SEDDS formulation and complete amorphonization of drug along with excipients were observed (Figure7).

Table 4. Zeta potential of solid SEDDS formulation.

Sr.No	Batch No	Mean Zeta Potential (mV)
1	ME1	-35.11
2	ME2	-12.91
3	ME3	-28.33
4	ME4	-23.55

3.10. Differential Scanning Colorimetry

DSC curves of pure drug and spray dried formulation batches are shown in figure 8. Pure IBS shows sharp endothermic peak at about 188ºC, which may be melting point of drug followed by exothermic peak at 250ºC. This exothermic peak might convert the drug into more stable but less soluble form. The peak of formulation was broad, less sharp than drug. SEDDS formulation also shows exothermic peak at about 250ºC. By correlating PXRD and DSC results, the sharpness of peaks as well as number of sharp peak present in IBS was found to be significantly diminished in case of SEDDS formulations. Decrease in melting point than pure IBS which may due to existence of drug in formulation was totally different from other than crystalline form.

3.11. Scanning Electron Microscopy

SEM images of pure irbesartan, maltodextrin and solid SEDDS of batch ME1 are shown in figure 9. The pure irbesartan was characterized by crystals of larger size irregular shape. According to SEM images, the solid SMEDDS formulation surface was found to be smooth regular. These particles were found almost in spherical shape. Thus modification in shape indicates that change in morphology of SEDDS formulation as compared to pure IBS. This spherical and smooth surface may show

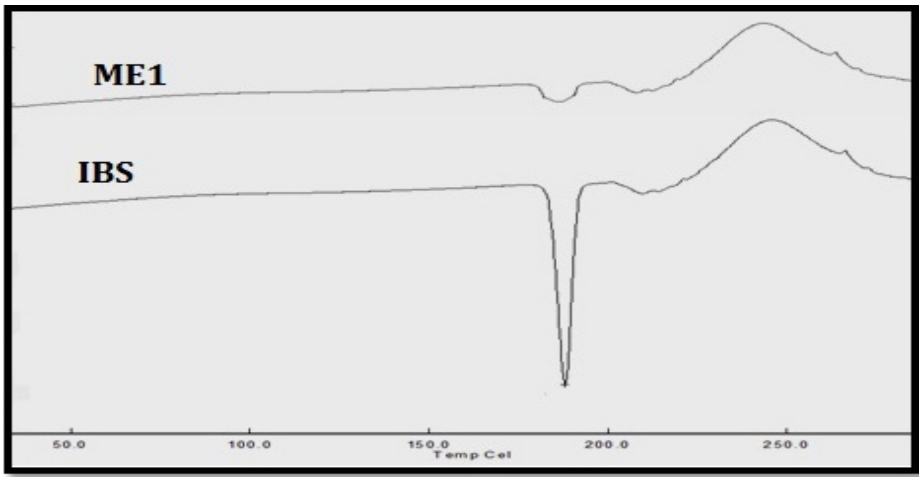

Figure 8. Overlain of DSC curves of ME1 and pure IBS.

improved solubility and dissolution rate as compared to pure IBS.

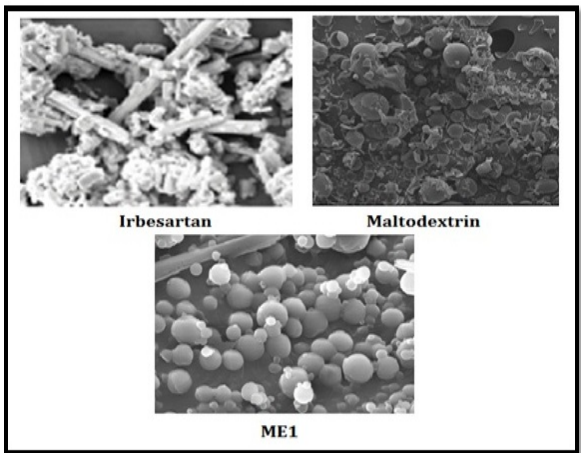

Figure 9. Scanning electron microscopy of SEDDS.

3.12. In-vitro Dissolution Study

In the self-micro emulsifying system, the free energy required to form an emulsion was very low, thereby allowing spontaneous formation of an interface between the oil droplets and water. It is suggested that the oil/surfactant/co surfactant and water phases effectively swell decrease the oil droplet size and eventually increase the release rate. The *in vitro* dissolution comparison of solid SEDDS formulation in dissolution media SGF pH 1.2 without enzyme shown in figure10 Drug releases from solid SEDDS formulations were found to be significantly higher as compared to pure irbesartan. Result revealed that Irbesartan SEDDS showed more than 90% release in 120 min. It could be suggested that the solid SEDDS formulation resulted in spontaneous formation of a microemulsion with a small droplet size, which permitted a faster rate of drug release into the aqueous phase, than that of pure irbesartan. Thus, this greater availability of dissolved IBS from the solid SEDDS formulations could lead to higher absorption and higher oral bioavailability. From figure 10 it clearly observed that solid SEDDS formulations shows more than 90% drug release in 120 min in SGF where as pure irbesartan showed <65% drug release in SGF. This observation shows that the formulation of solid SEDDS of irbesartan shows better dissolution than pure irbesartan.

3.13. In-vitro Diffusion Study

In the diffusion study of pure irbesartan and solid SEDDS formulation ME1, it was observed that ME1 formulation showed faster diffusion of drug i.e.95.18% in 9 h which is shown in figure11**.** The reason was small droplet size of formulation than the pure drug. The factors affecting drug release may be **(a)** SEDDS with reduced particle size provides more surface area

to release drug from solvents and thereby increases drug release rate and **(b)** oil phase of

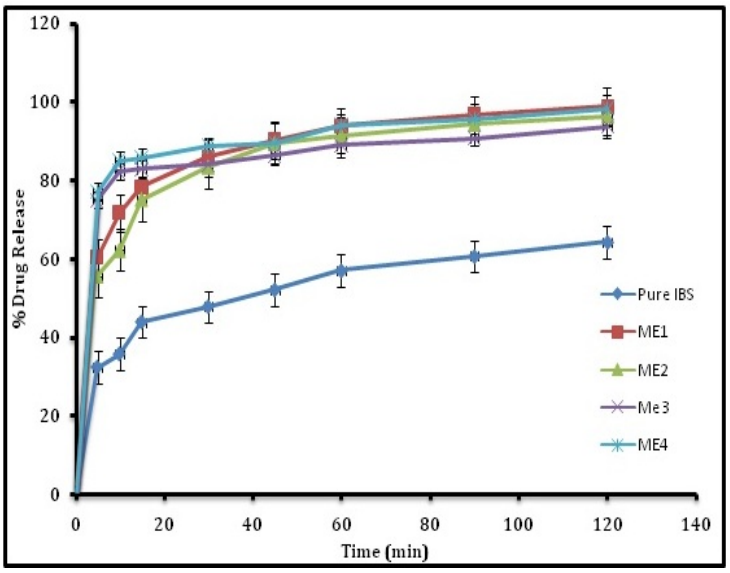

Figure 10. *In-vitro* release profile of solid SEDDS formulations and IBS in SGF.

SEDDS may act as carrier molecules which itself does not diffuse through the barrier but allow drug molecules to get diffused form membrane of dialysis bag. Although exact mechanism is not known, it is confirmed that any of these factors affect the bioavailability of drug. Flux (J) is the amount of permeant crossing the membrane per time [19]. *Pure IBS showed flux of 0.055 mg/cm^2/hr whereas ME1 showed 0.122 mg/cm^2/hr.* These results revealed that that formulation ME1 showed greater drug diffusion as compared to pure IBS.

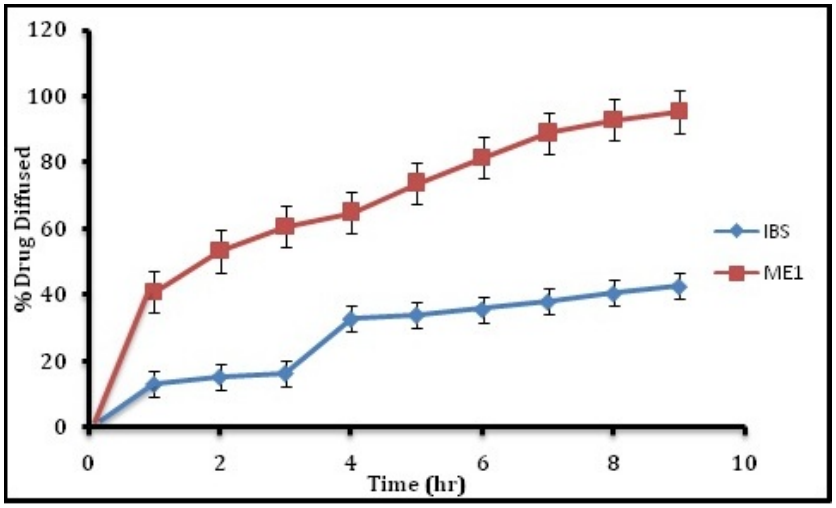

Figure 11. *In-vitro* diffusion study profile of solid SEDDS formulation and IBS in phosphate buffer (pH 7.4).

4. Conclusion

In the present investigation, an attempt has been made to formulate and evaluate self emulsifying drug delivery system of Irbesartan. It is practically insoluble in water and having low oral bioavailability. In the present investigation, optimal formulation of irbesartan liquid SEDDS and solid SEDDS were successfully developed. Thus, this study illustrated that potential use of SEDDS dispenses lipid soluble irbesartan by oral route.

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