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Enhancement Of Solubility And Oral Bioavailability Of Poorly Soluble Drug Valsartan By Novel Solid Self Emulsifying Drug Delivery System

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Abstract

The main objective of present work was to prepare a solid SEDDS for enhancement of oral bioavailability of Valsartan, poorly water soluble drug. The solubility of the drug was determined in various vehicles. A pseudo ternary phase diagram was constructed to identify the self-micro emulsification region. Further, the resultant formulations were investigated for clarity, phase separation, globule size, effect of pH and dilutions and freeze-thaw stability. The optimized SMEDDS (F4) formulation of Valsartan contained Capmul MCM (Oil), Kolliphor HS 15 (Surfactant) and PEG 400 (Co-surfactant). This optimized formulation was converted in to solid SEDDS by adding required quantity of Neusilin US2 as adsorbing agent used for in vitro dissolution and bioavailability assessment. The oral bioavailability of Valsartan from solid SEDDS was 1.6-fold higher compared to that of Valsartan suspension in rats, suggesting a significant increase ($p < 0.05$) in oral bioavailability of Valsartan from solid SEDDS.

Keywords: Valsartan, solid SEDDS, particle size, neusilin US2 enhanced oral bioavailability.

Introduction

Oral route has been the major route of drug delivery for the chronic treatment of human diseases. However, oral delivery of 50% of the drugs is hampered because of the high lipophilicity [1]. In drug discovery, about 40% of the new drug candidates display low solubility in water, which leads to poor bioavailability, high intra subject/inter subject variability and lack of dose proportionality. Therefore producing suitable formulations is very important to improve the solubility and bioavailability of such drugs [2]. Self-emulsifying systems are a useful means of improving the bioavailability of poorly water soluble drugs, particularly the self-micro emulsifying drug delivery systems are well known for their potential as alternative strategies for delivery of hydrophobic drugs [3]. SEDDS are isotropic mixtures of drug, oil/lipid, surfactant and/or co-surfactant, which form fine emulsion/lipid droplets on dilution with physiological fluid. The researchers now focused on solid SEDDS area were increasing. Solid SEDDS prepared by solidification of liquid or semisolid self emulsifying ingredients into powders, have gained popularity. These solid SEDDS were prepared by extrusion/spheronization method or wet granulation in a high shear mixer and adsorption to solid carriers involves addition of the liquid formulation onto carriers by mixing in a blender [4].

Hypertension is one of the most prevalent chronic adult illnesses today and cannot be cured, but can be controlled. The pharmacological treatment for control of hypertension utilizes various drug therapies such as single doses or associations of diuretics, beta-blockers, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor (AT1) antagonist (ARA) [5]. Valsartan is chemically 3-methyl-2-[pentanoyl-[[4-[2-(2H-tetrazoyl-5- yl) phenyl] phenyl] methyl] amino] butanoic acid is an orally active specific angiotensin II receptor blocker effective in lowering blood pressure in hypertensive patient. The aim of the present study is to formulate and evaluate a stable self micro emulsion and solid SEDDS of poorly water-soluble drug Valsartan to enhance the solubility and oral bioavailability.

Materials and methods

Materials

Valzaar 40mg conventional tablets were purchased from Torrent pharmaceuticals, Ahmadabad, India. Valsartan was generous gift from Hetero drugs limited, Hyderabad, India. Capmul MCM, Vitamin E TPGS, Capryol 90, Gelucire 44/14 and Castor oil were obtained from Granules India limited, Hyderabad. Lauroglycol, Captex 355 and Labrasol were obtained from Aurobindo Pharma limited, Hyderabad. Kolliphor RH 40 and Kolliphor HS 15 were gifted from BASF, Mumbai. All other chemicals used were of analytical grade.

Methods

Solubility studies

The solubility of Valsartan in various oils (Capmul MCM, Capryol 90, Castor oil, Captex 355 and Vitamin E TPGS), surfactants (Kolliphor HS 15, Kolliphor RH 40, Gelucire 44/14, labrasol, Lauroglycol) and co-surfactants (PEG 400 & 600, Propylene glycol) were determined by mixing excess amount of Valsartan with 2 ml of each of the individual components. The drug was added to a 5-ml capacity stoppered glass vial and mixed for 10 min with each component using a vortex mixer. The mixture vials were then kept at 37 ± 1.^{0}C in an isothermal shaker for 72 h until homogeneity. The homogenate samples were then centrifuged at 10,000 RPM for 20 min at 4 ^{0}C. The supernatant was removed by pipetting and the drug concentration was determined by UV-VIS spectrophotometer at 250 nm [6].

Construction of ternary phase diagram

Pseudo ternary phase diagram is used to map the optimal composition range for three key excipients according to the resulting droplet size following self emulsification, stability upon dilution and viscosity [7]. On the basis of the solubility studies of drug in oil, surfactants and co-surfactants were used for construction of phase diagram. Surfactant and co-surfactant (Smix) in each group were mixed in different weight ratio (1:1, 1:2, 2:1, 3:1). These Smix ratios are chosen in increasing concentration of surfactant with respect to co-surfactant and in increasing concentration of co-surfactant with respect to surfactant for detail study of the phase diagram for formulation of microemulsion. For each phase diagram, oil and specific Smix ratios are mixed thoroughly in different weight ratio from 1:9 to 9:1 (1:9, 2:8, 3:7, 4:6, 5:5, 6:4,7:3, 8:2, 9:1) in different glass vials. Pseudo-ternary phase diagram was developed using aqueous titration method. Slow titration with aqueous phase is done to each weight ratio of oil and Smix and visual observation is carried out for transparent and easily flowable o/w micro emulsion. The physical state of the micro emulsion was marked on a pseudo-three-component phase diagram with one axis representing oil, the other representing surfactant and the third representing co-surfactant at fixed weight ratios [8].

Transmittance

% Transmittance of Valsartan SEDDS was measured by U.V spectroscopy at wavelength of 400 to 500nm. A graph for %particle range vs. formulations was plotted [9].

Emulsification time

A predetermined volume of mixture (0.2 ml) was added to 300 ml of water in a glass beaker and temperature was maintained at 37^{0}C using a magnetic stirrer. The tendency of formation of emulsion was observed. If the droplet spreads easily in water was judged as 'good' and judged as 'bad' when there was milky or no emulsion or presence of oil droplets [10].

Development of SEDDS formulations

Weigh accurately 40mg of Valsartan and transferred in to a glass vial. To this Capmul MCM oil was added and warmed on water bath. To this oily mixture, Kolliphor HS 15 (surfactant) and Poly ethylene glycol 400 (Co-surfactant) mixtures was added. Then the components were mixed by gentle stirring and vortex mixing at 37 ºC until Valsartan was completely dissolved. Then the mixture was sealed in glass vial and stored at room temperature until used [11]. The composition was given in the Table 1.

Table 1: Formulation trials of liquid SEDDS

Smix (Surfactant: co-surfactant)	Oil: Smix	Formulation code	Valsartan (mg)	Oil (Capmul MCM) (ml)	Surfactant (Kolliphor HS 15) (ml)	Co-surfactant (PEG-400) (ml)
3:1	1:9	F1	40	0.02	0.135	0.045
	1:7	F2	40	0.025	0.131	0.043
	1:6	F3	40	0.028	0.128	0.042
	1:5	F4	40	0.033	0.124	0.041
	1:4	F5	40	0.04	0.12	0.04
2:1	1:9	F6	40	0.02	0.12	0.06
	1:8	F7	40	0.022	0.118	0.059
	1:7	F8	40	0.025	0.116	0.058
	1:6	F9	40	0.028	0.114	0.057

Freeze thawing

Freeze thawing was employed to evaluate the stability of formulations. The formulations were subjected to 3 to 4 freeze-thaw cycles, which included freezing at – 4 C for 24 hours followed by thawing at 40 C for 24 hours. Centrifugation was performed at 3000 rpm for 5 minutes. The formulations were then observed for phase separation. Only formulations that were stable to phase separation were selected for further studies [12].

Determination of drug content

Accurately measured dose of Valsartan formulation (0.2ml) equivalent to 40mg was taken in volumetric flask and the volume is made to 100ml with phosphate buffer pH 6.8. Suitable dilutions were made and absorbance was measured at λ_{max} 250 nm against blank by UV-VIS spectroscopy.

$$\% \text{ Drug content} = \frac{\text{Actual amount of drug in SEDDS}}{\text{Theoretical amount of drug in SEDDS}} \times 100$$

In Vitro dissolution studies of SEDDS

The dissolution test was performed using USP type 2 dissolution apparatus (paddle method) with 900 ml of pH 6.8 phosphate buffer containing various concentrations of Valsartan at 37 ^{0}C with a paddle speed of 50 rpm. The liquid SEDDS containing 40 mg of Valsartan was filled into hard gelatine capsules (Capsule No. 00), samples were collected at appropriate time intervals 2, 5, 10, 15, 20, 25, 30, 45 & 60min. 5 ml of the sample was withdrawn and replaced with same volume of dissolution medium and the concentration of Valsartan was measured at 250nm by UV-VIS spectroscopy [13].

Oil adsorption study

Microcrystalline cellulose, colloidal silicon dioxide, Neusilin US2, dicalcium phosphate and tricalcium phosphate were used as adsorbents. They were added separately to the optimized liquid SEDDS formulation i.e F4 under stirring. Neusilin US2 showed higher oil adsorption capacity when compared to microcrystalline cellulose and colloidal silicon dioxide (shown in the figure 23) [14].

Conversion of SEDDS to solid SEDDS

The optimized liquid SEDDS formulation (F4) based on droplet size and dissolution study was converted into free flowing powder by adsorption onto solid carriers. The composition was shown in Table 2. The solid carrier used for adsorption comprised of materials that provided a high surface area with good disintegration characteristics. 200 mg of Neusilin US2 (Magnesium aluminum silicate) was used as a solid carrier. It can adsorb at high levels up to 70% (w/w). The conversion process involved addition of liquid formulation onto carriers under continuous mixing. The powder was dried and filled directly into capsules [15].

Table 2: Composition of Valsartan SEDDS and solid SEDDS

S. No	Components (%wt/wt)	F4 Liquid SEDDS (mg)	Solid SEDDS(mg)
1	Valsartan	40	40
2	Capmul MCM	52.78	52.78
3	Kolliphor HS 15	205	205
4	PEG-400	71.41	71.41
5	Neusilin US2	-	200

Determination of drug content of solid SEDDS

Accurately weighed dose of Valsartan solid SEDDS was taken in volumetric flask and make the volume upto 100ml with phosphate buffer pH 6.8. Suitable dilutions were made and absorbance was measured at λ_{max} 250 nm against blank. The amount of drug present in one dose of solid SEDDS formulation was determined by using UV-VIS spectroscopy.

Dissolution studies of solid SEDDS

The release of drug from solid SEDDS formulations and pure drug was determined using a US Pharmacopoeia Type II dissolution apparatus (Here same conditions and media applied as used for SEDDS. The dissolution media is phosphate buffer pH 6.8 (900ml), and temperature of the dissolution medium was maintained at 37^0C operated at 50 rpm. 10ml sample was withdrawn at predetermined intervals 2, 5, 10, 15, 20, 30, 45 and 60 min and filtered through 0.45-µm pore size membrane filters. The concentrations were assayed spectrophotometrically at 250nm.

Characterization of SEDDS

Drug-Excipient compatibility studies by FTIR

The IR spectra of pure drug, excipients and optimized formulations were recorded using FT-IR (Shimadzu 8400-S) with diffuse reflectance principle. Sample preparation involved, drying of potassium bromide (KBr), drug and excipients in the oven to get rid of any moisture content then mixing the sample with KBr by triturating in glass mortar. Finally preparing of pellet and placing in the sample holder. The spectrum was scanned over a frequency range 4000 – 400 cm^{-1}. [16]

Differential scanning calorimetry (DSC)

Differential Scanning Calorimetry (DSC) studies were carried out using DSC 60, having TA60 software, Shimadzu, Japan. Accurately weighed samples were placed on aluminium plate, sealed with aluminium lids and heated at a constant rate of 5ºC /min, over a temperature range of 0 to 250ºC [17].

Determination of droplet size

The droplet size of the micro emulsions is determined by photon correlation spectroscopy (which analyses the fluctuations in light scattering due to Brownian motion of the particles) using a Zetasizer able to measure sizes between 2 nm and 5000 nm. Light scattering is monitored at 25 C at a 90 angle.

Determination of zeta potential

The emulsion stability is directly related to the magnitude of the surface charge. The zeta potential of the diluted SEDDS formulation was measured using a zeta meter system. Zeta-potential of the resulting micro emulsion was determined using a Malvern Zetasizer [18].

Micromeritic properties of Solid SEDDS

Prepared S-SEDDS was evaluated for micromeritic properties such as angle of repose, bulk and tapped density, compressibility index and Hausner's ratio [19].

Drug entrapment efficiency of solid SEDDS

The quantities of the drugs theoretically contained in the SEDDS were compared with the quantity actually obtained, from the drug content studies i.e. the quantity loaded into the SEDDS formulated [20].

Scanning electron microscopy

The surface and shape characteristics of pellets were determined by scanning electron microscopy (SEM) (HITACHI, S-3700N). Photographs were taken and recorded at suitable magnification.

Stability studies

The SEDDS formulations were put into empty hard gelatin capsules and subjected to stability studies at 25 C/60% relative humidity (RH), 30 C/65% RH, and 40 C/75% RH. Samples were charged in stability chambers (Thermolab, Mumbai, India) with humidity and temperature control. They were withdrawn at specified Accelerated conditions and 3months for long-term conditions. Drug content of the capsules was analyzed using a previously developed and validated stability-indicating UV method.

In vivo bioavailability studies

Twelve healthy Wister rats weighing 250 ± 20 g were used for this study. The protocol of animal study was approved by the institutional animal ethics committee. The Wister Rats were divided in to two groups at random and each group contains six animals. First group was administered with pure Valsartan made suspension with 0.5% methocel and second group was administered with solid SEDDS diluted in 0.5% methocel by oral route at an equivalent dose of 40 mg/kg body weight. About 500 µl of blood was withdrawn from retro orbital plexus at different time intervals such as 0.25, 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 8.00 & 24.00h. Blood samples were transferred into eppendorf tubes containing heparin in order to prevent blood clotting. The samples were centrifuged immediately at 4000 rpm and the plasma was stored in light-protected container at -20 ^{0}C till analysis. The concentration of Valsartan from plasma was measured by using reversed phase HPLC. The chromatographic system consisted of a C18 chromatographic column, Phenomenex (150 mm 4.6 mm ID) and a mobile phase consisting of acetonitrile-phosphate buffer (0.05 M) with pH 2.8 in the proportion of (40/60, v/v) at a flow rate 0.8 ml/min and the wavelength detection was 250 nm [21]. Plasma

samples (250 µl) were transferred into a test tube to which internal standard (Hydrochlorothiazide 50µl) and 1 ml of acetic acid was added and vortexed for 3 min. To this, 1ml of chloroform was added and vortexed. The samples were centrifuged at 10,000 rpm for 10 min. The organic phase was transferred into another test tube and the solvent was evaporated to dryness. The residue was redissolved in 200 µl of mobile phase, of which 20 µl of the supernatant was injected for analysis [22].

Pharmacokinetic analysis

The pharmacokinetic parameters employed to evaluate were maximum plasma concentration (C_{max}), time to attain C_{max} i.e., T_{max} and $t_{½}$ values, area under plasma concentration–time curve from zero to the last sampling time (AUC_{0-t}), area under plasma concentration–time curve from zero to infinity ($AUC_{0-\infty}$). AUC_{0-t} was calculated by the linear trapezoidal rule and $AUC_{0-\infty}$ from the following formula.

$AUC_{0-\infty} = AUC_{0-t} + C_t / K_E$

Results and Discussion

Solubility studies

The Valsartan pure drug solubility of was found to be 34.91 mg/ml. The solubility of the Valsartan drug was tested in different oils phases and maximum solubility was found in Capmul MCM as 50.62 mg/ml (Figure 1). The solubility of the drug was tested in different surfactants and co-surfactants, maximum solubility was found in Kolliphor HS-15 as 76.32 mg/ml (Figure 2) and 52.26 mg/ml was in PEG-400 respectively (Figure 3). Capmul MCS, Kolliphor HS-15 and PEG-400 were used for the formulation of valsartan SEDDS.

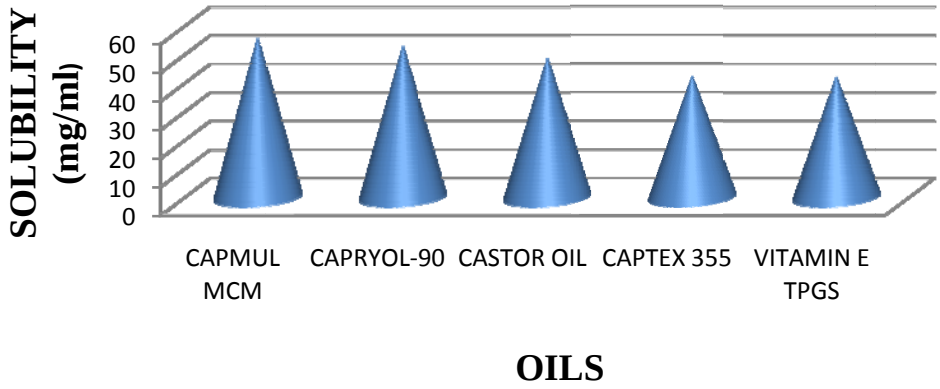

Figure 1: Solubility studies of Valsartan in oils

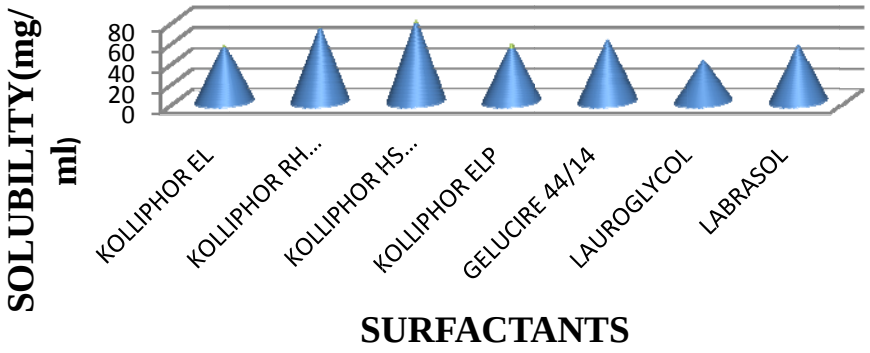

Figure 2: Solubility studies of Valsartan in surfactants

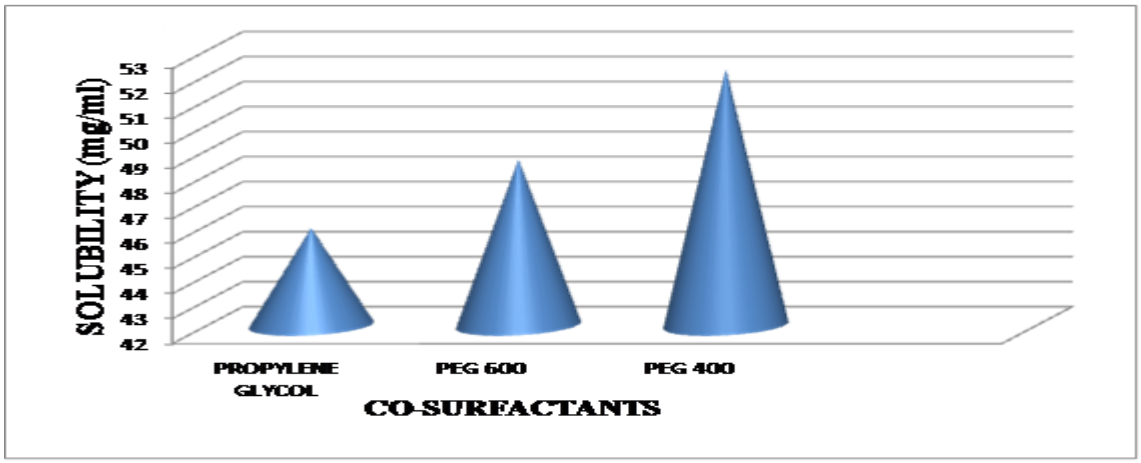

Figure 3: Solubility studies of Valsartan in Co-surfactants

Construction of ternary phase diagram

From the above chosen oils, surfactants and co-surfactants were taken in different ratios (Table 1) for the construction of ternary phase diagrams to know the emulsion and micro-emulsion domains such that at particular concentration of oil, surfactant and co-solvent ratios, a stable self-emulsifying formulation is formed. The Self emulsification process is affected on the concentration of Kolliphor HS-15 and PEG-400 and their ratio. The phase diagram representing that series I (3:1) and series II (2:1) showed a narrow microemulsifying domain (Figure 4). So the concentration of oil, surfactant and co-surfactant was selected in these domains for the study. From the phase diagrams, it was observed that self emulsifying region increased with increasing concentrations of surfactant or combination of surfactant and co-surfactant. Efficiency of self-emulsification was good when the surfactant concentration was increased.

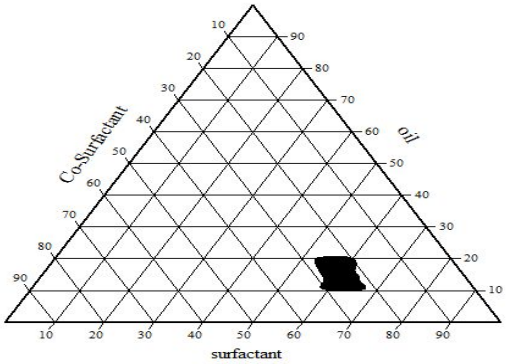

Figure 4: Ternary phase diagram of Capmul MCM, Kolliphor HS 15 and PEG 400

Visual observation and % Transmittance

The clarity of microemulsions was checked by transparency, measured in terms of transmittance (%T). SEDDS forms o/w microemulsion since water is external phase. Some Formulations have % transmittance value greater than 99%.These results indicate the high clarity of microemulsion. In case of other systems %T values were about 97% suggesting less clarity of microemulsions. This may be due to greater particle size of the formulation. Due to higher particle size, oil globules may reduce the transparency of microemulsion and thereby values of %T. The results of %T are as shown in Table 3.

From this liquid mixtures of Capmul MCM, Kolliphor HS 15 and PEG 400 of 1:9, 1:7 1:6 1:5 1:4 oil: Smix ratios belongs to 3:1 Smix and 1:9, 1:8 1:7, 1:6 oil: Smix ratios belongs to 2:1 Smix shown highest % transmittance i.e. above 90%, therefore these ratios are suggested for high clarity of microemulsoin. In case of other ratios gave turbid solutions which are not suggesting for microemulsion formulation. The results are tabulated in Table 3.

Table 3: Visual observation and %Transmittance of different formulations

Smix (surfactant: Co-surfactant)	Oil: Smix	Visual observation	%Transmittance
3:1	1:9	Transparent	99.56
	1:8	Slightly clear	89.99
	1:7	Transparent	99.50
	1:6	Transparent	92.24
	1:5	Transparent	99.89
	1:4	Transparent	97.12
	1:3	Turbid	70.02
	1:2	Turbid	57.52
	1:1	Turbid	20.99
	6:1	Turbid	18.78
	7:1	Turbid	10.34
	8:1	Turbid	15.89
	9:1	Turbid	45.78
2:1	1:9	Transparent	96.98
	1:8	Transparent	96.22
	1:7	Transparent	97.09
	1:6	Transparent	95.53
	1:5	Slightly clear	87.99
	1:4	Slightly clear	88.84
	1:3	Slightly clear	54.89
	1:2	Slightly clear	48.97
	1:1	Turbid	28.72
	3:1	Turbid	14.99
	2:1	Turbid	25.52

Emulsification time

The tendency of formation of emulsion was observed with this method. If the droplet spreads easily in water was judged as 'good' and judged as 'bad' when there was milky or no emulsion or presence of oil droplets. Formulation F4 has % transmittance value greater than 99% (shown in table 3).These results indicate the high clarity of microemulsion. In case of other systems %T values were less than 99% suggesting less clarity of microemulsion. This may be due to greater particle size of the formulation. Due to higher particle size, oil globules may reduce the transparency of microemulsion and thereby values of %T. The results of %T are as shown in Table 4.

Table 4: Emulsification time of SEDDS Formulations

Smix (Surfactant: co-surfactant)	Oil:Smix	Time (min)	Visual observation	Grade
3:1	1:9	<1	Clear fibres, clear solution	A
	1:7	<1	Clear fibres, clear solution	A
	1:6	<1	Very Slight fibres, clear solution	A/B
	1:5	<1	Clear fibres, clear solution	A
	1:4	<1	Slight fibres, clear solution	A/B
2:1	1:9	<1	Very Slight fibres, clear solution	A/B
	1:8	<1	Slight fibres, clear solution	A/B
	1:7	<1	Slight fibres, clear solution	A/B
	1:6	<1	Very Slight fibres, clear solution	A/B

Preparation of Valsartan SEDDS

SEDDS of Valsartan were prepared by using Capmul MCM (Oil), Kolliphor HS 15 (Surfactant) and PEG 400 (Co-surfactant). In the present investigation 9 formulations were prepared and their complete composition is shown in Table 1. All the prepared SEDDS were found to be clear.

Freeze thaw method

In thermodynamic stability study, no phase separation and no change of temperature variations on prepared formulations were observed. There was no change in the visual description of samples after centrifugation freeze-thaw cycles.

Drug content of SEDDS

Actual drug content of all 9 formulations are shown in Table 5. The drug content of the prepared SEDDS was found to be in the range of 91.50 – 98.11 %. Maximum % drug content i.e. 98.11% was found in the formulation F4.

Table 5: % Assay of different formulations

Formulation Code	Assay (%)
F1	96.43
F2	96.16
F3	91.50
F4	98.11
F5	94.84
F6	93.76
F7	94.98
F8	92.64
F9	95.31

In Vitro Dissolution Studies of SEDDS

The results of in vitro dissolution comparisons of SEDDS formulations are summarized in Table 6. The faster and highest drug dissolution from SEDDS may be attributed to the fact that in this formulation, the drug is a solubilized form and upon exposure to dissolution medium results in small droplet that can dissolve rapidly in the dissolution medium. The release from SEDDS formulation F4 was highest (97.34) faster than other SEDDS formulations and pure drug substance indicating influence of droplet size on the rate of drug dissolution.

Table 6: Dissolution profiles of various formulations

Time (min)	Dissolution media – Phosphate buffer pH 6.8 (% drug release) Formulation Code									
	Pure drug	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0	0
2	2.29	28.19	14.78	42.01	39.53	25.12	21.76	19.92	29.7	15.33
5	10.10	57.71	66.80	56.75	78.10	46.37	50.18	42.42	42.2	45.96
10	17.90	69.19	74.47	66.62	85.68	52.97	63.91	53.81	63.9	68.05
15	21.12	71.72	79.39	74.63	90.50	61.66	68.52	59.91	71.8	70.76
20	23.41	78.82	82.48	79.92	92.61	75.54	72.39	67.66	79.9	81.82
25	30.70	83.37	87.58	82.79	95.28	80.05	79.86	79.95	81.1	85.27
30	35.81	90.50	91.62	86.34	96.33	87.06	83.84	81.65	84.8	89.07
45	37.19	91.21	91.99	86.88	96.33	87.34	84.31	82.20	85.0	89.43
60	43.60	91.43	92.04	87.11	97.34	87.61	84.56	82.66	85.3	89.71

Selection of optimized formulation

When compared to % transmittance, emulsification test and in vitro drug release studies for all formulations, F4 formulation was found to be best and optimized formulation and further characterized for other studies.

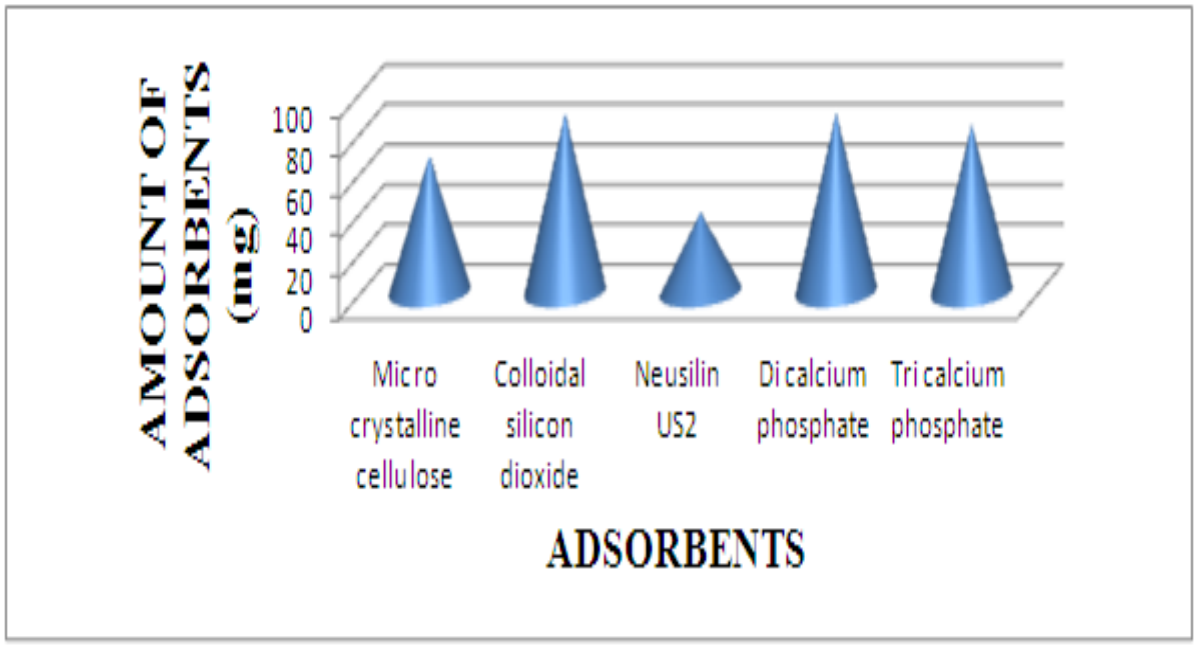

Figure 5: Adsorption studies of Valsartan with different adsorbents

Oil adsorption study

Oil adsorption study was performed for Valsartan by using different adsorbents and results are depicted in Figure 5. Neusilin US2 showed higher oil adsorption capacity when compared to other adsorbents. From oil adsorption study Neusilin US2 was used for the preparation of Solid SEDDS from optimized SEDDS formulation (F4).

Conversion of SEDDS to Solid SEDDS

On the basis of faster and complete dissolution rate, formulation F4 was selected as optimized formulation and this formulation was converted in to solid SEDDS by adding required quantity of Neusilin US2 as adsorbing agent.

Micromeretic properties of Valsartan solid SEDDS

The micromeretic properties angle of repose, LBD, TBD, Carr's index and Hausner's ratio of the solid SEDDS was found to be 28.31, 0.22, 0.25, 13.30 and 1.16 respectively, which shows good flow properties of the powdered blend.

Drug content of solid SEDDS

The drug content of solid SEDDS was carried out. The % assay of the solid SEDDS was found to be 98.31%.

Drug entrapment efficiency

The dug entrapment efficiency of solid SEDDS was carried out. The results of drug entrapment efficiency of solid SEDDS formulation was found to be 92.57%

Dissolution Studies of Valsartan pure drug Solid and Liquid SEDDS and Innovator product (Valzaar 40mg)

The release of Valsartan from solid, liquid SEDDS formulations, pure drug and innovator product - Valsartan 40mg tablets (Valzaar 40mg) was determined. The concentrations were assayed spectrophotometrically at 250nm. Comparative dissolution profiles of solid and liquid SEDDS formulation (F4) with pure drug and innovator product are summarized in Table 7. Solid and liquid SEDDS have shown better release profiles when compared with the pure drug and the innovator product.

Table 7: Comparative results of drug release from SEDDS, Solid SEDDS, Pure drug and Innovator product (Valzaar 40mg)

Time (mins)	Dissolution media - Phosphate buffer pH 6.8 (% Drug release)			
	Pure Drug	Innovator product (Valzaar 40mg)	Liquid SEDDS (F6)	Solid SEDDS
0	0	0	0	0
2	2.29	28.19	39.53	59.83
5	10.10	46.23	78.10	67.48
10	17.90	57.90	85.68	79.46
15	21.12	64.32	90.50	83.02
20	23.41	69.33	92.61	90.00
25	30.70	73.82	95.28	94.65
30	35.81	77.21	96.33	97.57
45	37.19	81.43	96.33	97.61
60	43.60	87.69	95.34	97.89

Particle size analysis for SEDDS

Droplet size of Valsartan emulsion decreased with reducing the oil content in SEDDS (Figure 6). The smaller the droplet size, the larger the interfacial surface area will be provided for drug absorption. The size of F4 was found to be below range of 71.1 nm which indicated that formulation F6 was SEDDS. The Polydispersity index of the optimized Valsartan formulation (F4) was found to be 0.064.

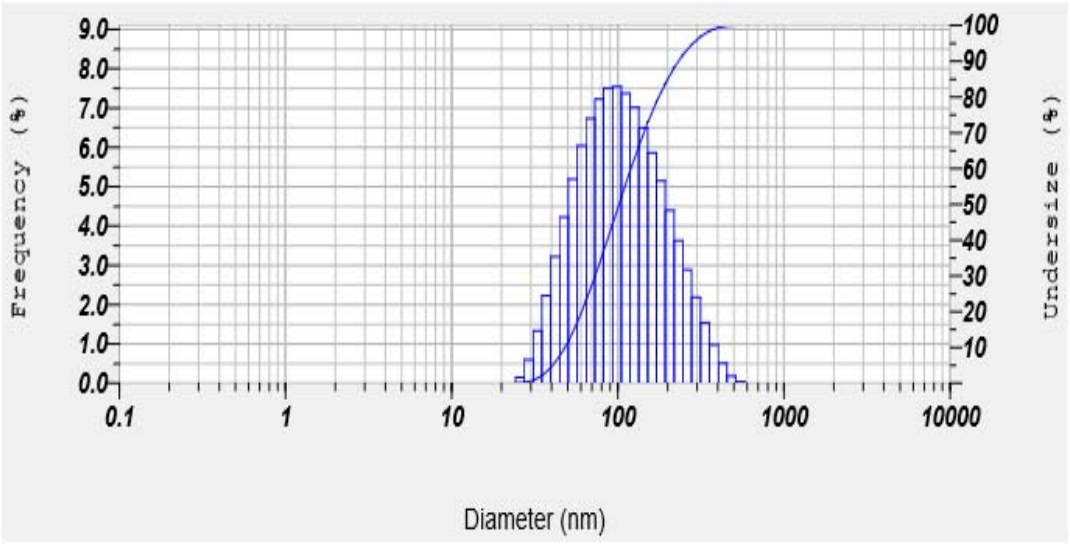

Figure 6: Particle size analysis of optimized formulation

Zeta potential

The optimized formulation F4 was shown very low polydispersive index and low viscosity.

The zeta potential of the optimized Valsartan formulation was found to be very low i.e., -40.6Mv. Hence, the formulation rapidly formed emulsion and remained stable for longer time (Figure 7)

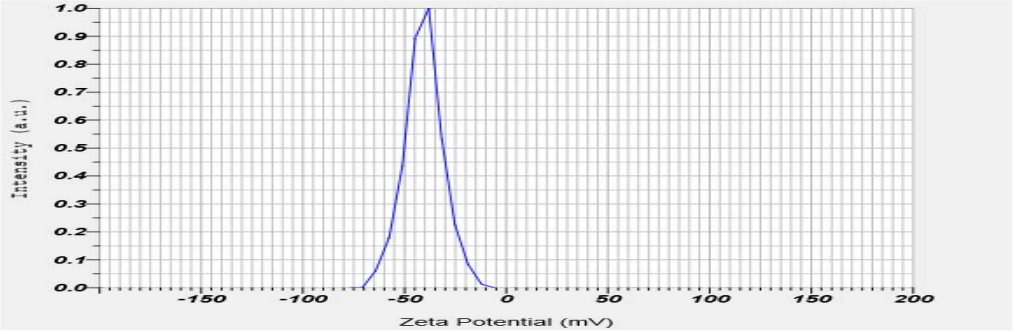

Figure 7: Zeta potential of the optimized formulation

Drug excipient compatibility studies

FTIR Studies

The FTIR spectra of pure Valsartan displayed bands at 3419.9 cm^{-1} due to N-H stretch, at 2962.76 cm^{-1} due to C=N stretching, at 1732.13 cm^{-1} due to Carboxylate stretching. The spectra also showed bands at 1631.83 cm^{-1} due to C=O bending at 1107.18 due to C-N bonding (Figure 8). The FTIR spectrum of Valsartan SEDDS exhibited characteristic bands consistent with the molecular structure of Valsartan which indicated that no chemical interaction occurred between the drug and excipients used in the formulation (Figure 9).

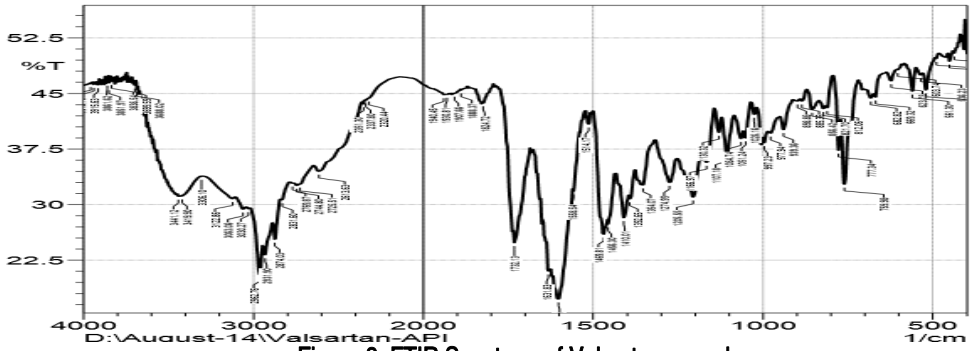

Figure 8: FTIR Spectrum of Valsartan pure drug

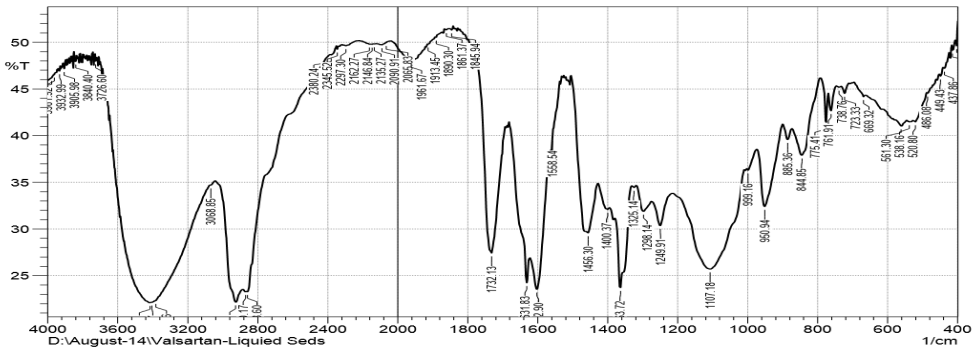

Figure 9: FTIR Spectrum of optimized formulation of Valsartan liquid SEDDS

Drug excipient interactions by DSC studies

Differential Scanning Calorimetry (DSC) was performed on pure drug, excipients and optimized formulation. DSC results revealed that the pure drug Valsartan showed a melting point at 116ºC, and optimized SEDDS formulation at 119 ºC. There was no considerable change observed in melting endotherm of drug in optimized formulation. It indicates that there was no interaction between drug and other excipients used in the formulation (Figure 10).

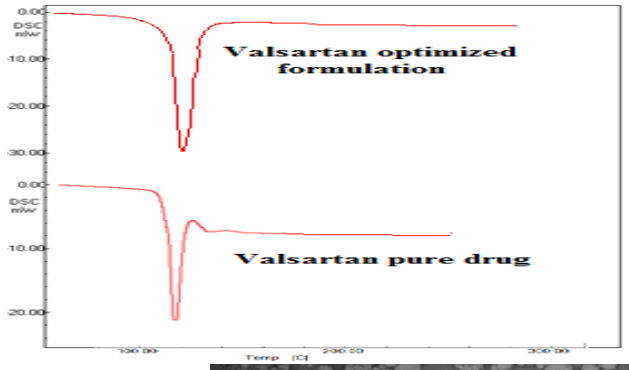

Figure 10: DSC thermograms of pure drug and optimized SEDDS (F4) formulation

Scanning electron microscopy

Micrographs of Solid SEDDS shows Liquid SEDDS adsorbed onto the surface of Neusilin US2 particles. Since the formulation process involved facilitating adsorption through physical mixing, partially covered Neusilin US2 is also visible in the field of vision. Crystalline structures characteristic of Valsartan are not seen in solid SEDDS micrographs suggesting that the drug is present in a completely dissolved state in the Solid SEDDS. Figure 11(i) & (ii) represents the morphology of solid SEDDS. This indicates that solid SEDDS appeared as spherical particles having an even and a smooth surface.

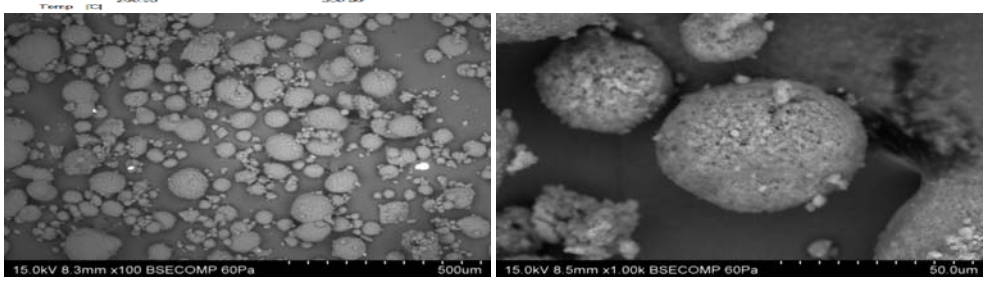

Figure 11(i) & (ii): Scanning Electron Microscopy of Solid SEDDS

Stability studies

The Valsartan SEDDS are put into hard gelatin capsules as the final dosage form. The developed formulation was subjected to stability studies to evaluate its stability and the integrity of the dosage form. There was no significant change in the drug content, drug release. It was also seen that the formulation was compatible with the hard gelatin capsule shells, as there was no sign of capsule shell deformation. There was no significant change in the appearance, or microemulsifying property. Thus, these studies confirmed that the formulation was stable and its compatibility with hard gelatin capsules.

Bioavailability studies

Table 8: Pharmacokinetic Parameters of Valsartan solid SEDDS formulation and pure drug (n = 6)

Pharmacokinetic Parameters	Valsartan Pure drug	Valsartan - solid SEDDS
C_{max} (µg/ml)	0.416	0.928
AUC_{0-t} (µg h/ml)	3.62	5.94
AUC_{0-inf} (µg h/ml)	3.85	6.05
T_{max} (h)	2.70	3.18
$t_{1/2}$ (h)	5.32	6.52

K_{el} (h^{-1})	0.264	0.161

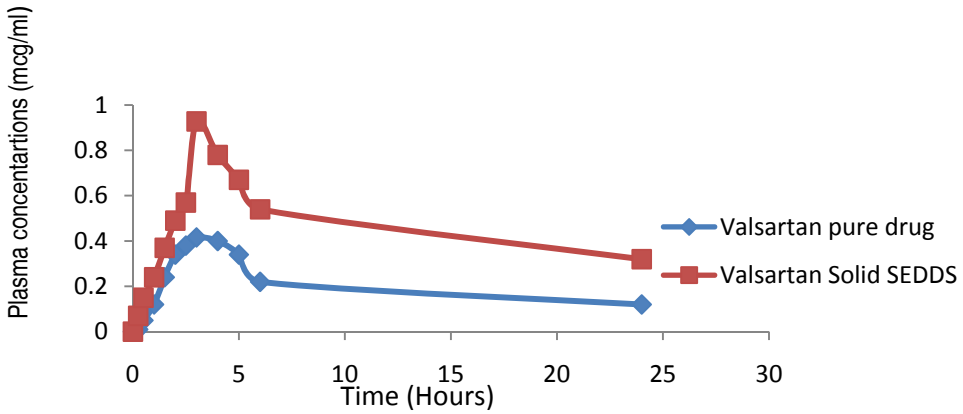

Figure 12: Plasma concentration profiles of Valsartan solid SEDDS and pure drug

Pharmacokinetic studies were carried out in healthy Wister rats for test formulation and reference pure drug and the results were depicted in Table 8. The comparison of plasma drug concentration of test formulation and reference pure drug was shown in Figure 12. As can be seen from the above table C_{max} of the solid SEDDS 0.928 µg/ ml was significant ($p<0.05$) as compared to the pure drug suspension formulation 0.416 µg/ ml. T_{max} of both solid SEDDS formulation and pure drug suspension was 3.18 and 2.70 h, respectively. AUC is an important parameter in evaluating bioavailability of drug from dosage form, as it represents the total integrated area under the blood concentration time profile and represents the total amount of drug reaching the systemic circulation after oral administration. AUC_{0-} infinity for solid SEDDS formulation was higher 6.05 µg h/ml than the pure drug suspension formulation 3.85 µg h/ml. The relative bioavailability of the solid SMEDDS formulation was 1.6-fold higher compared to the pure suspension. Therefore, drug delivery using solid SMEDDS is a promising approach for the effective absorption and rapid onset of action after oral administration of this drug and for improvement of its oral bioavailability.

Summary and conclusion

Systematic efforts were made to prepare nine formulations of valsartan SEDDS by using different polymers like Capmul MCM, Castor oil, Capryol -90, Vitamin E TPGS, Kolliphor HS 15, Kolliphor RH 40, Kolliphor ELP, Gelucire 44/14, Kolliphor EL Labrasol, Lauroglycol, PEG 400, PEG 600, Propylene glycol. From this study it was concluded that, prepared liquid SEDDS was thermodynamically stable with good self emulsification efficiency and having globule size in nanometric range which may be physiologically stable. On the basis of different evaluation parameters F4 was found to be optimized formulatin. Study also concluded that, S-SEDDS of Valsartan prepared with optimized SEDDS (F4) using adsorbing agent Neusilin US2 by adsorption technique have good flow property and drug content. SSEDDS formed clear micro emulsion with micrometric size. Results of SEM demonstrate that spherical S-SEDDS can be obtained without agglomeration. In-vitro drug release of S-SEDDS was much higher than that of pure Valsartan, SEDDS and marketed formulation. Hence it was concluded that S-SEDDS can be efficiently formulated by adsorption technique using Neusilin US2 as solid carrier to enhance dissolution rate of poorly soluble drug such as Valsartan. The oral bioavailability study of Valsartan solid SMEDDS showed improvement by a factor of 1.6 compared to the suspension in rats. Thus solid SMEDDS may be used for improvement of oral bioavailability of drugs with poor water solubility and low oral bioavailability.

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