Development and Evaluation of Solid Self-Microemulsifying Drug Delivery System for Solubility Enhancement of Valsartan.

Aditi R. Beldar[1*], Sujit S. Kakade[2], Prashant H. Khade[2], Ashok V. Bhosale[3]

Riya R. Bhondve [1], Harshal M. Shinde[1], Ruchita A. Bhalerao[1]

[1]Research Scholar, Department of Pharmaceutics, PDEAs Shankarrao Ursal College of Pharmaceutical Sciences and Research Centre, Pune, Maharashtra, India.

[2] Assistant Professor, Department of Pharmaceutics, PDEAs Shankarrao Ursal College of Pharmaceutical Sciences and Research Centre, Pune, Maharashtra, India.

[3] Principal, Department of Pharmaceutics, PDEAs Shankarrao Ursal College of Pharmaceutical Sciences and Research Centre, Pune, Maharashtra, India.

Correspondence – Aditi R. Beldar

aditibeldar@gmail.com

ABSTRACT:

Valsartan is orally active, and specific angiotensin II antagonist acting on the AT1 receptor subtype (angiotensin receptor blocker). It is a lipophilic in nature and is feebly aqueous soluble drug with absolute bioavailability of 25%. The goal of the present study was to develop Solid self-micro emulsifying Drug Delivery System (S-SMEDDS) of valsartan to improve its oral bioavailability. The formulations were explored on the basis of solubility, FTIR study and excipient compatibility, emulsification efficiency, particle size and zeta potential. Solubility of valsartan was determined in various vehicles and maximum solubility was found in Castor oil as (oil), Tween 60 as (surfactant) and Kollisolv PG as (co-surfactant). These elements were used to design pseudo-ternary phase diagrams to identify the micro emulsion zone. Solid-SMEDDS were prepared by adsorption technique using Aerosil 200 (1% w/w) and were evaluated for micromeritic properties, scanning electron microscopy, X-ray diffraction, FTIR study and Drug content. The designed Solid-SMEDDS were further evaluated for stability study. Solid-SMEDDS may be considered as a better solid dosage form as solidified formulations are more ideal than liquid ones in terms of its stability. These results suggest the potential use of SMEDDS and solid-SMEDDS to improve the dissolution and hence oral bioavailability of poorly water-soluble drugs like valsartan through oral route.

KEYWORDS: Valsartan, Bioavailability, Lipophilicity, Microemulsion, L-SMEDDS, S-SMEDDS.

1. INTRODUCTION:

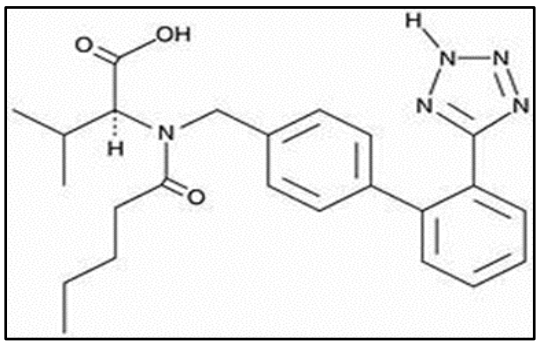
Self-microemulsifying drug delivery system (SMEDDS) are the newly emerging techniques for the enhancement of lipophilic drug delivery. Primary challenge of any oral formulation design program is to maintain drug solubility within G.I tract and particularly maximizing drug solubility within primary absorption site of the gut.[1] For lipophilic drug compounds which exhibit dissolution rate limited absorption self microemulsifying drug delivery systems (SMEDDS) can offer great step-up in rate and extent of absorption, leading to reproducible blood time profiles of BCS class II drugs in particular. [2]

According to Lipinski's rule of five for oral absorption trends, it predicts that poor permeation or poor absorption is more likely when there are more than 5-H bond donors, more than 10 H-bond acceptors, with molecular weight >500 and log P>5. [3]

SMEDDS are isotropic mixtures of oils, surfactants and co-surfactants, which form oil-in-water micro emulsion in aqueous media under gentle agitation. The finely divided oily droplets, with a droplet size less than 50 nm, provide a large surface area for drug release and absorption. The oily phase allows the drug to be present in its solubilised state, thereby avoiding the slow and rate-limiting dissolution process of a hydrophobic drug. [4] It can be prepared either in liquid form or encapsulated in hard or soft gelatine capsule. Nevertheless, it has some drawbacks also such as instability, leakage, precipitation of drug, and ageing of shells of the capsules.[5] to solve these above obstructions, the researchers have successfully developed solid SMEDDS using solid carriers and demonstrated their usefulness in dissolution and bioavailability. Recently the spray drying method for solidification of SMEF has been reported using different adsorbent materials for enhancement of solubility and bioavailability. [6]

Valsartan is a potent, orally active nonpeptide tetrazole derivative and selectively inhibits Angiotensin II Receptor type 1 which causes reduction in blood pressure and is used in treatment of hypertension. [7] It is a lipophilic drug and possesses moderate onset of action than other drugs of the same category. It is soluble in the neutral pH range. Valsartan is 3-methyll-2-[pentanoyl-[[4-[2-(2H-tetrazoyl-5-yl)phenyl]phenyl]methyl]amino]-butanoicacid (Structure 1) with empirical formula $C_{24}H_{29}N_5O_3$. Its molecular weight is 435.519g/mol.[8]Valsartan is a white coloured powder that is freely soluble in ethanol, methanol, and sparingly soluble in water. The partition coefficient of Valsartan is 0.033 (log P=1.499), suggesting that the compound is hydrophilic at physiological pH. The compound is stable under storage in dry conditions. Valsartan has bioavailability of about 25% due to its acidic nature. Being acidic in nature it is poorly soluble in the acidic environment of GIT and is absorbed from the upper part of GIT that is acidic in nature and where its solubility is low. [9]

Fig.1: Molecular Structure of Valsartan.



The main aim of the study was to develop valsartan SMEDDS to improve upon the solubility of the valsartan which will have some bearing on the bioavailability. The SMEDDS consists of an isotropic mixture of drug, lipid, surfactant, and typically a co-surfactant or co-solvent. When exposed to the fluids of the gastrointestinal (GI) tract, these precursor solutions spontaneously emulsify to form highly dispersed microemulsions. These dispersions commonly have been shown to enhance the oral bioavailability of lipophilic drugs. The ease of dispersion and the very small particle size of the resultant colloidal microemulsion have

historically been viewed as the principal reasons for their utility in the delivery of lipophilic drugs. [10]

2. MATERIALS AND METHODS:

2.1 MATERIALS:

Valsartan was purchased from Dhamtec Pharma ltd. Navi Mumbai. Tween 60, Etocas, Isopropyl myristate was a kind gift from Croda India Company pvt. Ltd, Navi Mumbai, Maharashtra. Kollisolv PG was kind gift from BASF India, Ltd. Navi Mumbai. Acrysol EL-135 and Acrysol K-150 was a kind gift received from Corel Pharma Chem Pvt. Ltd. Ahmedabad, Gujarat. All other chemicals used were of analytical reagent grade.

2.2 METHODS:

2.2.1 Solubility of the oil phase, surfactant and co-surfactant:

The solubility study was performed to select the suitable oil (O), surfactant (S), and co-surfactant (Co-S) that possesses high solubilizing capacity for valsartan Selection of the oil phase was based upon the maximum solubility of the drug. Different oils like Oleic acid, Etocas, long-chain triglycerides (Soyabean, Sunflower, Castor oil, and Coconut Oil) and Isopropyl Myristate. Surfactants like Tween 20, Tween 40, Tween60, Tween80, Span 20, Acrysol EL-135, and Acrysol K-150. Co-surfactants like Kollisolv PG, Polyethylene Glycol 200 and Polyethylene Glycol 400 were selected and their solubility was determined by shaking flask method.[11] The excess amount of drug was placed in 5.0 mL screw cap glass bottle having 2.0 mL of each oil, surfactant, and co-surfactant. The mixture vials were then kept at 25 ± 1.0 °C in an isothermal shaker for 72 hr. to reach equilibrium. The equilibrated samples were removed from shaker and centrifuged at 3000 rpm for 20 min. The supernatant was taken and filtered through a 0.45 µ m membrane filter. The concentration of Valsartan was determined in oils and water using UV Spectrophotometer at wavelength of 248 nm. [12] The data is shown in the Table 3.1, 3.2, 3.3 and Figure 3.1, 3.2 and 3.3.

2.3 Drug-Excipients Compatibility:

The Drug – Excipients Compatibility Studies were performed in order to confirm the drug-excipients compatibility. The study mainly include FT-IR study. Mixture of Drug+ Oil, Drug + Surfactant, and Drug + Co-Surfactant. [13]

2.4 Construction of Pseudo-ternary phase diagram:

On the basis of the solubility study of drug, oil, surfactants, co-surfactants and aqueous phase were used for construction of phase diagram. Oil, surfactant, and co-surfactant are grouped in four different combinations for phase studies. Surfactant and co-surfactant (Smix) in each group were mixed in different weight ratio (1:1, 1:2, 2:1, 3:1). [15] 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 micro emulsion. For each phase diagram, oil, and specific Smix ratio 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.[16] Different combination of oils and Smix were made so those maximum ratios were covered for the study to delineate the boundaries of phase precisely formed in the phase diagrams. 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 flow able o/w micro emulsion. The physical state of the micro emulsion was marked on a pseudo-three-component phase diagram with one axis Data of aqueous phase, the other Data of oil and the third Data of a mixture of surfactant and co-surfactant at fixed weight ratios (Smix ratio). [17] Each of these ratios was mixed with increasing percentage of oil, i.e., 10%, 20%, 30%, 40% up to 90% of oil to get phase diagram. To determine the effect of drug addition in SMEDDS, phase diagrams were also constructed in presence of drug. In order to prepare SMEDDS, selection of microemulsion region from phase diagram was based on the fact that solution remains clear even on infinite dilution. [18]

2.5 Selection of Formulation from Pseudo ternary Phase Diagram:

From each phase diagram, constructed, different formulations were selected from micro-emulsion. Selected formulations were subjected to different thermodynamic stability and Dispersibility tests. [19]

2.5.1 Thermodynamic stability studies: [20]

It was determined by carrying heating cooling cycle, centrifugation test and freeze thaw cycle.

a. Heating cooling cycle:

Six cycles between refrigerator temperatures 4°C and 45°C with storage at each temperature for not <48 hr. was studied. If SMEDDS stable at these temperatures was subjected to centrifugation test.

b. Centrifugation test:

Passed SMEDDS were centrifuged at 3500 rpm for 30 min using digital centrifuge (Remi motors Ltd). If SMEDDS did not show any phase separation was taken for freeze-thaw stress test.

c. Freeze-thaw cycle :

Three freeze-thaw cycles between −21°C and +25°C with storage at each temperature for not < 48 h was done for SMEDDS.

2.5.2 Dispersibility Studies: [21]

The dispersibility test of SMEDDS was carried out to assess to compatibility to disperse into emulsion and the size of resulting globules to categorize them as SMEDDS. It was carried by using a standard USP Paddle type dissolution test apparatus, formulation was added to 500 ml of water at 37±0.5°C and the paddle was rotated at 50 rpm. On titration with water the SMEDDS formulation forms a mixture which was of different type. Depending upon which the in vitro performance of formulation can be assessed.

Grade	Dispersibility and Appearance
A	Rapidly forming (Within 1 min) microemulsion having a clear or bluish appearance
B	Rapidly forming, slightly clear emulsion having a bluish white appearance
C	Fine milky emulsion that formed within 2 min

D	Dull, greyish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2min)

Those formulations that passed the thermodynamic stability and also Dispersibility test in Grade A, and Grade B was selected for further studies.[22]

2.6 Preparation of SMEDDS:

A series of microemulsions of SMEDDS were prepared with varying ratios of oil, surfactant, and co-surfactant. Formulations 1, 2, and 3 were prepared using Castor oil as oil, Tween 60 as surfactant, and Kollisolv PG as co-surfactant. In all the formulations, the level of Valsartan was kept constant (i.e. 20mg). The amount of SMEDDS should be such that it should solubilize the drug (single dose) completely.[23] The Valsartan (20 mg) was added in the mixture. Then the components were mixed by gentle stirring and mixing, and heated at 37˚C.The mixture was stored at room temperature until used. So, prepared SMEDDS was the concentrate of oil, surfactant, co-surfactant and drug. The composition of formulations is given in Table 1, 2 and 3.[24]

Table No. 2.1: Composition of Formulation 1

Formulation 1 (1:1)	Valsartan (mg)	Castor Oil (w/w)	Tween 60 (w/w)	Kollisolv PG (w/w)
M1	20	40	30	30
M2	20	30	35	35
M3	20	20	40	40
M4	20	10	45	45

Table No. 2.2: Composition of Formulation 2

Formulation 2 (2:1)	Valsartan (mg)	Castor Oil (w/w)	Tween 60 (w/w)	Kollisolv PG (w/w)
M1	20	40	40	20
M2	20	30	46.10	23.30
M3	20	20	53.3	26.7
M4	20	10	60	30

2.7 Physicochemical characterization of self-microemulsifying drug delivery system:

a) Appearance:

The prepared microemulsion was inspected visually for clarity, colour and presence of any particulate matter.

b) FT-IR Study

In this study FTIR instrument was used. FTIR spectra for the drug and the excipients of the optimized formulations were obtained.[25]

c) Drug content:

Self-microemulsifying drug delivery system containing valsartan 10 mg was added in 10 mL methanol and mixed well with shaking and was sonicated for 10-15 min. Further was centrifuged and supernatant was further was further diluted with suitable quantity of fresh methanol and drug content was determined using UV-spectrophotometer at λmax 248 nm. [26]

d) Robustness to dilution:

Robustness to dilution was studied by diluting SMEDDS to 50, 100 and 1000 times with water, 0. 1 N HCl and phosphate buffer pH 6.8. The diluted SMEDDS were stored for 12 h and observed for any signs of phase separation or drug precipitation. [27]

e) Self-Emulsification Time:

The emulsification time of SMEDDS was determined according to USP 22, dissolution apparatus each formulation added drop wise to 500ml purified water at 37°C. Gentle agitation was provided by a standard stainless steel dissolution paddle rotating at 50 rpm. Emulsification time was assessed visually. [28]

f) Viscosity:

The viscosities were measured to determine rheological properties of formulations. Brookfield viscometer at 30˚C used to serve this purpose. [29]

g) Refractive index :

Refractive indices of the prepared micro emulsions were determined at 25°C by Abbe's refractometer by placing one drop of micro emulsion on the slide. [30]

h) % Transmittance:

The percent transmittance of various formulations was measured at 248 nm using UV spectrophotometer keeping water as a blank.[31]

i) Cloud Point Measurement:

The formulated SMEDDS was diluted with 50ml water in a beaker which was placed on a water bath with gradually increasing temperature until the diluted formulation turned cloudy. It mainly insists about the stability of microemulsion at the temperature of body. [32]

j) Particle Size Determination:

Particle size of the prepared microemulsion was determined using Dynamic Light Scattering (DLS) method. For DLS particle sizing, the sample needs to be crystal clear to very slightly hazy. If the solution is white or too hazy, it should be diluted further before attempting a DLS size measurement. When the solution is ready for analysis and transfer it in the cuvette, care should be taken to avoid bubbles which are formed on the walls of the cuvette. Slowly tilting or tapping the cuvette on a hard surface may help also. Once the solution was homogenous and ready for DLS measurement, the cuvette containing the solution was placed in the instrument. The instrument was run and solution was analysed for particle size. [33]

k) Zeta Potential:

Zeta Potential of the prepared microemulsion was determined using Light Scattering method. For Zeta Potential determination, the sample needs to be crystal clear. When the solution is ready for analysis and transfer it in the cuvette, care should be taken to avoid bubbles which are formed on the walls of the cuvette. Slowly tilting or tapping the cuvette on a hard surface may also help to remove the bubble formed. Then the electrode was dipped inside the cuvette containing sample solution. Care should be taken to avoid bubbles in between the electrodes.

The cuvette containing the solution was be placed in the instrument. The instrument was run and solution was analysed for Zeta Potential.[33]

l) Polydispersity Index (PI) :

Polydispersity Index (PI) of the prepared microemulsion was determined using Dynamic Light Scattering (DLS) method. For DLS method, the sample needs to be crystal clear to very slightly hazy. If the solution is white or too hazy, it should be diluted further before attempting a DLS size measurement. When the solution was ready for analysis and transfer it in the cuvette, care should be taken to avoid bubbles which are formed on the walls of the cuvette. Slowly tilting or tapping the cuvette on a hard surface may also help to remove the bubbles formed. Once the solution was homogenous and ready for DLS measurement, the cuvette containing the solution was be placed in the instrument. The instrument was run and solution was analysed for Polydispersity Index .[33]

m) *in vitro* Dissolution Studies:

In vitro dissolution study of was performed by using USP Dissolution Apparatus II. The dissolution vessel was fitted with 900 mL dissolution media 0.1 N HCl and 6.8 buffer and kept at 37 ± 0.5∘ C with a rotating speed of 50 rpm. The aliquot of 5.0 mL was withdrawn at 5, 15, 30, and 60 min and filtered through 0.45 μm Whatman membrane filter. The volume withdrawn was replaced each time by fresh dissolution media. [34]

2.8 Preparation of Solid SMEDD:

The optimized liquid self microemulsifying formulation was transformed into free flowing granules using Aerosil 200 colloidal porous carriers as adsorbent. The L-SMEDDS and Aerosil 200 were taken in ratio 1:1 w/w to optimize the drug loading on colloidal silica. The mixture was further dried to obtain the free flowing powder.

2.9 Evaluation of Solid SMEDDS Formulations:

1. **Micromeritics Properties:**

Prepared solid-SMEDDS was evaluated for micromeritics properties such as angle of repose, bulk and tapped density, compressibility index and Hausner ratio (HR).[35]

2. **Scanning electron microscopy:**

Scanning electron microscopy (SEM) for Valsartan and prepared solid-SMEDDS was taken using scanning electron microscope (Philips, XL-30) at accelerating voltage at 3-5 kV to study surface topography. [36]

3. ***in vitro releas*e studies :**

Dissolution study was carried out using USP Type II apparatus (Paddle method) at 50 rpm, and at 37°C ± 0.5°C. The dissolution medium was 0.1 N HCl and 6.8 pH Phosphate Buffer and. Prepared solid-SMEDDS with equivalent amount of drug 20 mg were placed in 900 ml of dissolution medium respectively. A sample of 5 ml were withdrawn at regular time interval of 5, 15, 30, and 60, and filtered using 0.45 µm filter. An equal volume of respective dissolution medium was added to maintain sink conditions. Drug content from sample was analysed using UV-spectrophotometer at 248 nm.[37]

4. **X-ray diffraction study:**

The X-ray diffraction (X-RD) of Valsartan were obtained using X-RD instrument Bruker AXS, D8 Advance with Ni-filtered Cu radiation, at a voltage of 45 kV and current of 40 mA. The scanning speed was 2°/min between 5θ and 50θ. [38]

5. **Drug content:**

S-SMEDDS equivalent to 20mg was diluted in suitable quantity of methanol. The sample was mixed thoroughly to dissolve drug in methanol by stirring. Drug content in the solvent extract is filtered through 0.45 um membrane filter. Drug content analysed by suitable analytical method against the standard solvent solution of drug. [39]

6. **Fourier transform-infrared spectroscopy :**

In this study FTIR instrument was used. FTIR Spectra was determined of Solid SMEDD.

2.10 Stability Study:

Stability studies for solid-SMEDDS were studied at different temperature conditions according to ICH guidelines at room temperature i.e. 25°C ± 2°C/60% ± 5% relative humidity (RH). The samples were withdrawn at different time intervals as 0, 30, 60, 90 days. Formulation was evaluated for Appearance, equivalent to 20 mg of the drug was dissolved in methanol, diluted approximately and estimated for the drug content spectrophotometrically at 248 nm using methanol as blank. Effect of storage conditions on drug release was also studied.[41]

3. RESULT AND DISCUSSIONS:

3.1. Screening of Excipients:

3.1.1 Solubility Study:

Table 3.1: Data for solubility of Valsartan in various oil phase

Sr No	Oil Phase	Solubility (mg/ml)
1	Oleic Acid	11.38
2	Castor oil	12.35
3	Isopropyl myristate	11.33
4	Soyabean Oil	5.15
5	Coconut Oil	3.79
6	Etocas	11.71
7	Sunflower Oil	3.98

SMEDDS of Valsartan, it should possess good solubility in the oil, surfactants and co-surfactants of system. The solubility of Valsartan in various oils, surfactants and co-surfactants was investigated. Valsartan had significantly higher solubility in castor oil (12.35 mg/ml) than, Sunflower oil, Coconut oil, soyabean oil, etocas, isopropyl myristate, oleic acid. Among surfactants and co-surfactants, tween 60 (12.38 mg/ml) and Kollisolv PG (12.378mg/ml)

respectively showed highest solubilities .Therefore, castor oil was screened as oil phase , Tween 60 as surfactant and Kollisolv PG as co-surfactant based on solubility studies. Table 3.1, 3.2, 3.2 respectively and it is represented graphically in Figure 3.1, 3.2, 3.3.

Table 3.2: Data for solubility of Valsartan in various surfactants

Sr No	Surfactants	Solubility (mg/ml)
1	Cremophor RH 40	10.13
2	Tween 20	10.92
3	Tween 60	12.38
4	Tween 80	11.22
5	Span 20	11.88
6	Acrysol K-150	9.934
7	Acrysol EL-135	9.625

Table 3.3: Data for solubility of Valsartan in various co-surfactants

Sr. No.	Co-Surfactants	Solubility (mg/ml)
1.	Kollisolv PG	12.37
2	Polyethylene Glycol 200	9.52
3	Polyethylene Glycol 400	10.08

Figure 3.1: Solubility of Valsartan in Various Oil Phases

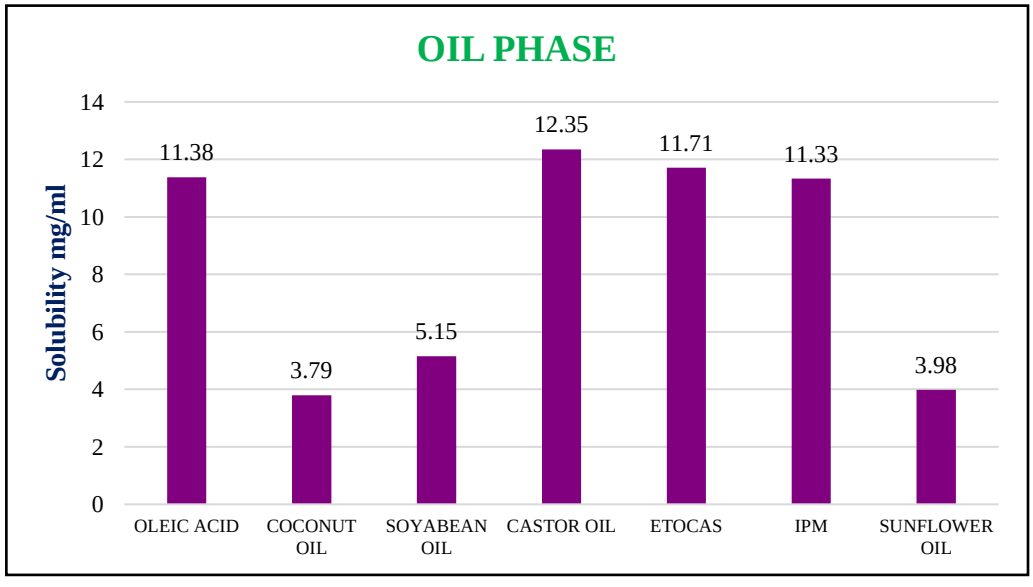


Figure 3.2: Data for solubility of Valsartan in various surfactant

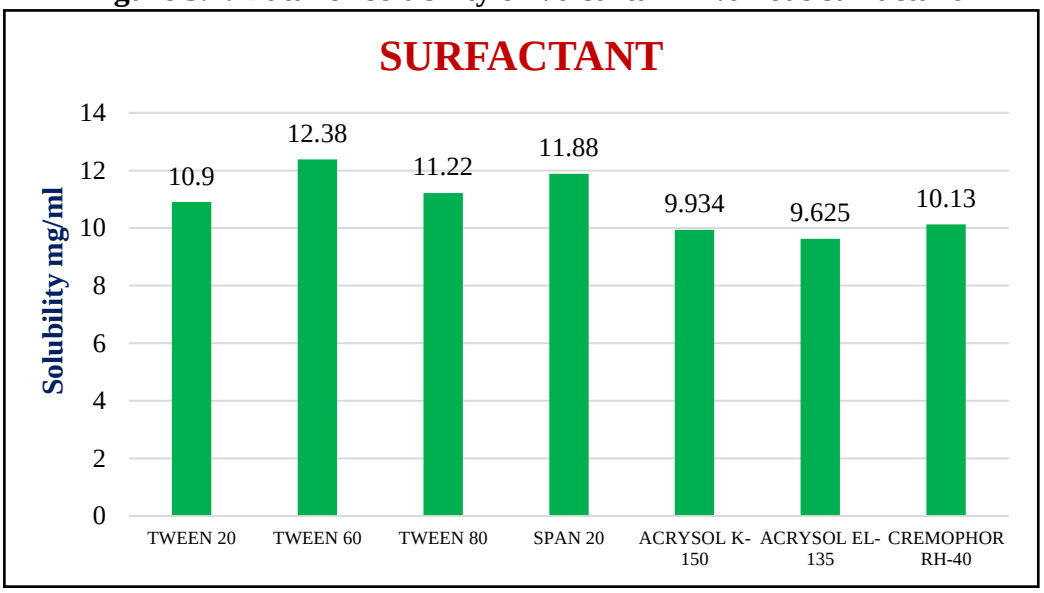
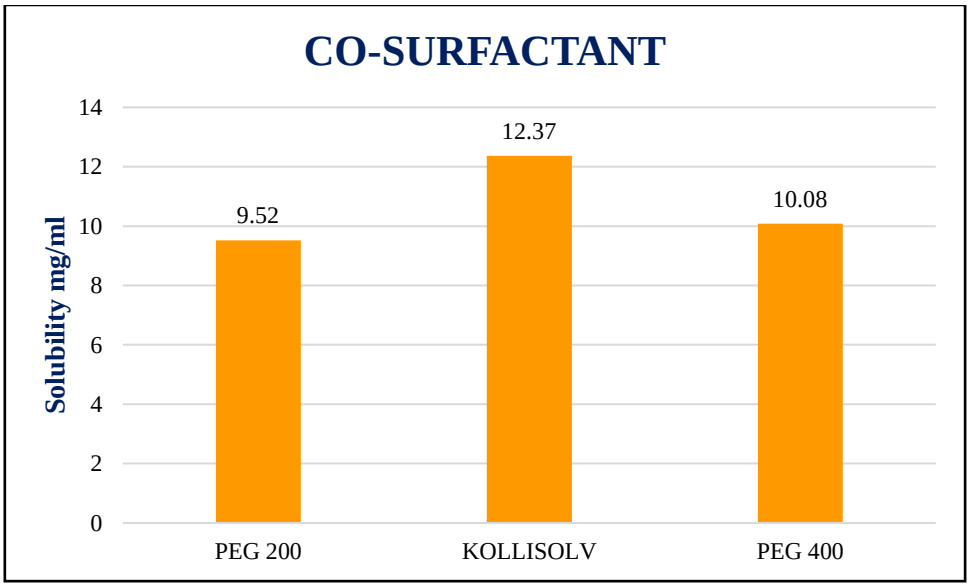


Figure 3.3: Data for solubility of Valsartan in various co-surfactants



Based on the results of Solubility screening, one distinct system was selected which was: Castor Oil as oily phase, Tween 60 as surfactant, Kollisolv PG as co-surfactant for further studies.

3.2 Drug – Excipients Compatibility Study:

The scanning range was 400 to 4000 cm-1 and resolution was $1cm^{-1}$. The major peaks in recorded spectra were compared with standard spectra given in figure below. So it can be concluded that the spectra of pure drug valsartan and the combination of drug with additives,

that all the characteristic peaks of valsartan were present in the combination spectrum, thus indicating compatibility of the drug and additives.

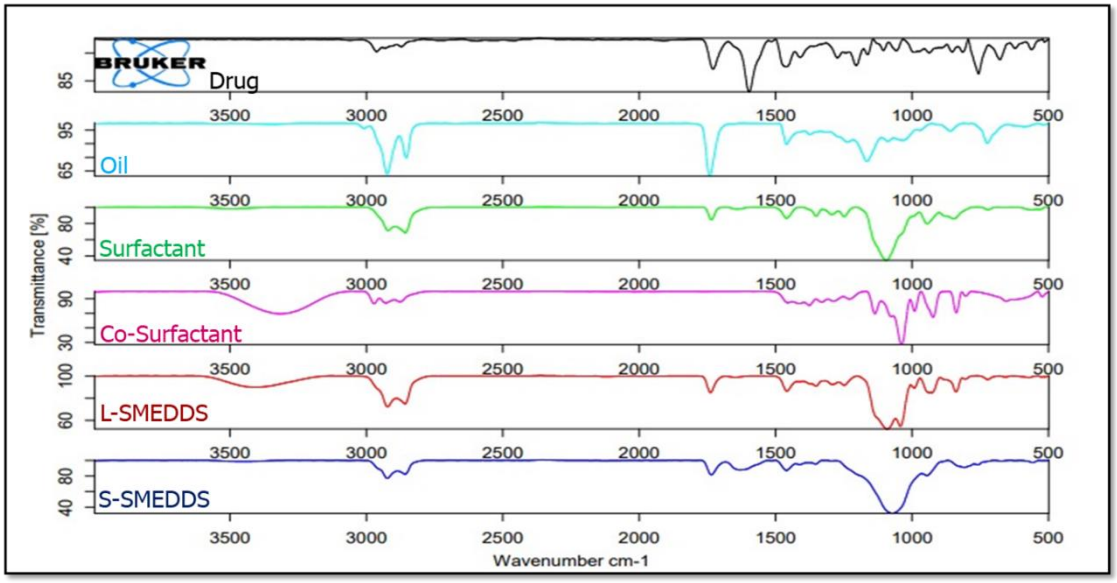
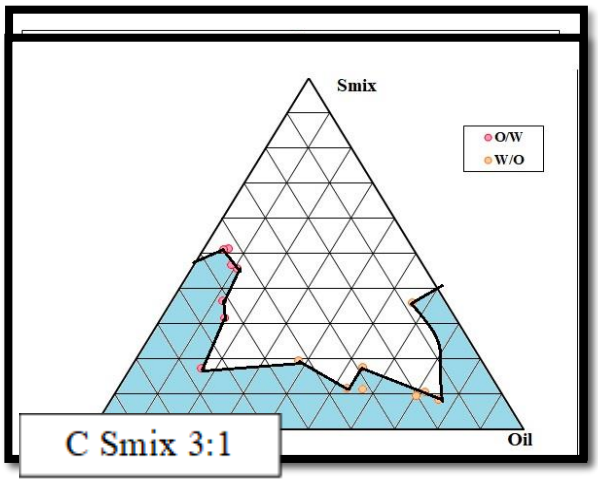
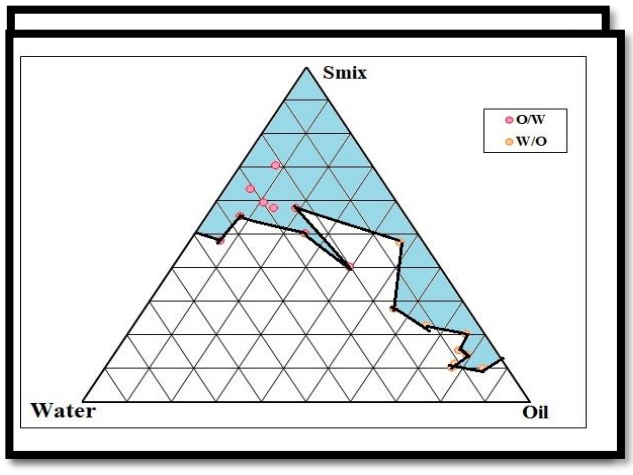


Figure 3.4: FT-IR Spectra of Overlay for compatibility study.

3.3 Construction of Pseudo ternary phase diagram:

The consideration for screening formulation of SMEDDS usually involves: the formulation composition should be simple, safe, and compatible; it should possess good solubility; a large efficient self-microemulsification region which should be found in the pseudo-ternary phase diagram, and have efficient droplet size after forming microemulsion. Thus, pseudo-ternary phase diagrams were constructed to identify the self-microemulsifying regions with maximum drug loading and to optimize the concentration of oil, surfactant and co-surfactant in the SMEDDS formulations and to obtain transparent and stable O/W micro-emulsions .The shaded areas in the pseudo-ternary phase-diagrams shown in fig 3.9 represented the existence field of stable, clear and transparent O/W microemulsions containing Castor oil as oil and with the Tween 60: Kollisolv PG fixed mixing ratio, respectively. For any selected composition of





D Smix 1:2

surfactant and co-surfactant ratio from self-microemulsifying region of ternary phase diagram (shaded) the addition of great volumes of continuous phase allowed the clear system.

Figure 3.5: Phase diagram of Castor oil (oil), Smix (Tween 60 and Kollisolv PG) were water system having different Smix ratio.

3.4 Selection of Formulation from Pseudo ternary Phase Diagram:

After the construction of Pseudo ternary phase diagram 1.1, 2:1 and 3.1 Smix ratios, maximum area was selected and also which indicate that the area covers the maximum number of formulation. The phase diagram of selected formulation is shown in Fig 3.9. The Smix ratios 1:2 and 3:1 was discarded due to smaller microemulsion region and excess of surfactant concentration which cause GIT irritation. Hence it was discarded. Ratio 1:1 and 2:1 were taken for further studies.

3.4.1 Thermodynamic stability studies:

Microemulsions are thermodynamically stable systems and are formed at a particular concentration of oil, surfactant and water, with no phase separation, creaming or cracking. It is the thermostability which differentiates microemulsion from emulsions that have kinetic stability and will eventually phase separate .Thus, the selected formulations were subjected to different thermodynamic stability testing by using heating cooling cycle, centrifugation and freeze thaw cycle stress tests. Those formulations, which passed thermodynamic stability tests, were taken for dispersibility test. (Table 3.8, and 3.9). Thus it was concluded that the efficiency of surfactant and co-surfactant mixture was unaffected after exposing to extreme conditions.

3.4.2 Dispersibility test:

When infinite dilution is done to microemulsion formulation, there is every possibility of phase separation, leading to precipitation of a poorly soluble drug as microemulsions are formed at a particular concentration of oil, surfactant and water. For oral microemulsions the process of dilution by the GI fluids will result in the gradual desorption of surfactant located at the globule interface. The process is thermodynamically driven by the requirement of the surfactant to maintain an aqueous phase concentration equivalent to its CMC. In the present study, we used distilled water as a dispersion medium because it is well reported that there is no significant difference in the microemulsions prepared using non-ionic surfactants, dispersed in either water or simulated gastric or intestinal fluid. Formulations in Group I (Table 3.8) and Group II (Table 3.9) that passed dispersibility test in Grade A, B and C were taken for further study, as Grade A and B formulations will remain as microemulsions when dispersed in GIT. Formulation falling in Grade C could be recommended for self microemulsifying drug delivery formulation.

So from the study, total four formulations were selected for further study two from each group i.e. M3 and M4 from Group I and M3 and M4 from Group II.

Table 3.4 - Data for Thermodynamic stability test and Dispersibility test of different formulations selected from Group I

Group I Smix 1:1	Observations based on the preparation, thermodynamic stability studies and dispersibility tests				Inference
Formulation	**Heating Cooling**	**Centrifugation Test**	**Freeze Thaw**	**Dispersibility**	
M1	X	X	X	D	Rejected
M2	✓	X	X	C	Rejected
M3	✓	✓	✓	A	Selected
M4	✓	✓	✓	A	Selected

Table 3.5 - Data for Thermodynamic stability test and Dispersibility test of different formulations selected from Group II

Group II Smix 2:1	Observations based on the preparation, thermodynamic stability studies and dispersibility tests				Inference
Formulation	**Heating Cooling**	**Centrifugation Test**	**Freeze Thaw**	**Dispersibility**	
M1	✓	X	X	B	Rejected
M2	✓	✓	X	C	Rejected
M3	✓	✓	✓	A	Selected
M4	✓	✓	✓	B	Selected

3.5. Preparation of Liquid SMEDDS Formulations:

Formulations selected in section 3.8 and 3.9 were prepared as per the composition reported in Table 2.1 and 2.2 and found to be thermodynamically stable.

3.6. Evaluation of Liquid SMEDDS Formulations:

a. Appearance:

Appearance of the prepared microemulsion was inspected visually and all the batches of Valsartan were Clear, Colourless, and free from any particulate matters.

b. FTIR Spectra:

The scanning range was 400 to 4000 cm-1 and resolution was $1cm^{-1}$. So it can be concluded that the spectra of pure drug valsartan and the Liquid SMEDDS spectrum, that all the characteristic peaks of valsartan were present in the Liquid SMEDDS spectrum.

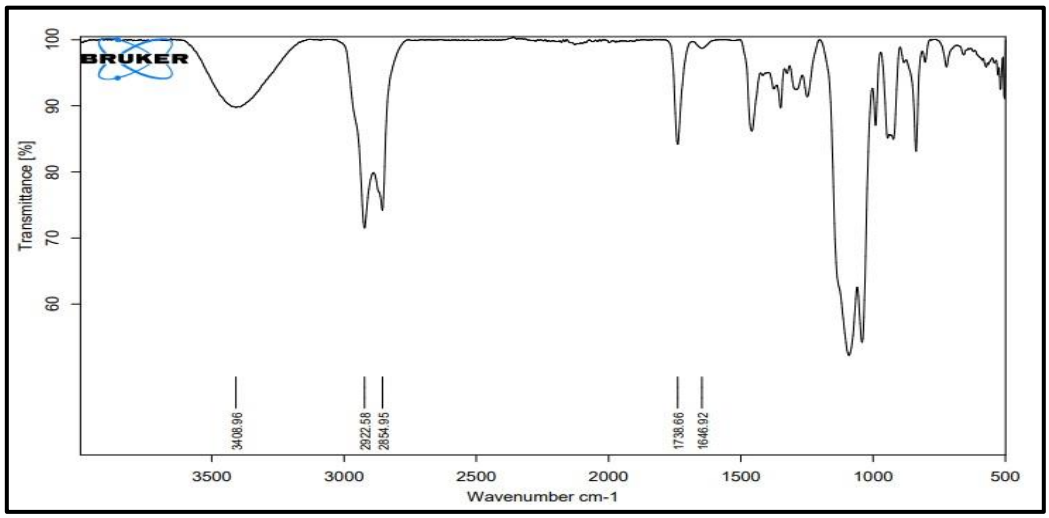


Fig 3.6: FTIR Spectra of Optimized Liquid SMEEDS

c. Drug content:

The drug content at 250 nm was found to be in the range of in the selected batch of Group I formulation M3 and M4 as well as Group II formulations M3 and M4. The data is shown in the table no. 3.6

Formulation Code	Group I	Group II
M3	91.01±0.01	97.77±0.16
M4	94.08±0.22	97.48±0.08

Table 3.6: Drug Content of Selected formulation.

d. Robustness to dilution:

After diluting SMEDDS to 50, 100 and 1000 times with water, 0.1 N HCl and buffer pH 6.8 and storing for 12 h, it was observed that there was no sign of phase separation or drug precipitation in formulations.

Formulation	Drug Precipitation or Phase Separation		
Group I	**Water**	**0.1 N HCl**	**6.8 pH buffer**
M3	-	-	-
M4	-	-	-
Group II			
M3	-	-	-
M4	-	-	-

Table 3.7: Data of the Robustness to dilution.

e. Self-Emulsification Time:

The emulsification time of liquid SMEDDS are presented in Table 3. Among the tested formulations, formulations of Group I`s M4 and Group II `s both formulation M3 and M4 showed shortest emulsification time than Group I`s M3.

Formulation Code	Group I	Group II
M3	Within 2 min	Within 1 min
M4	Within 1 min	Within 1 min

Table 3.8: Data of self-emulsification time.

f. Viscosity:

Formulation Code	Group I	Group II
M3	13.20±1.3 cps	18.00±1.2 cps
M4	14.40±1.2 cps	19.20±1.6 cps

All formulations of Group I and Group II were found to have rather low viscosities, ranging from to cps. The viscosity of the micro emulsion increased with increasing concentration of the surfactant.

Table 3.9: Data of Viscosity of Group I and Group II.

g. Refractive Index (RI):

The refractive index was carried out by Abbe refractometer was found to be in the range of 1.45 to 1.49 of Group I to Group II formulations along with the plain formulation which is closely related to the RI of water.

Formulation Code	Group I	Group II
M3	1.4971	1.4591
M4	1.4886	1. 4692

Table 3.10: Data of Refractive Index of Group I and Group II.

h. % Transmittance:

Formulation Code	Group I	Group II
M3	93.28±0.04	98.40±0.01

M4	94.77±0.01	97.76±0.01

The percent transmission was found to be in the range of 98.23 % to 99.37 % for formulations of Group I and Group II along with the plain formulation which confirms good transparent nature of formulations.

Table 3.11: Data of % Transmittance of Group I and Group II.

i) **Cloud Point Measurement:**

Cloud point of prepared SMEDDS formulations Group I and Group II was found to be higher than 70°C, which indicates that micro emulsion will be stable at physiological temperature without risk of phase separation.

Formulation	Particle Size (nm)	Zeta Potential
Group I		
M3	219	-40.78
M4	217	-41.95
Group II		
M3	191	-45.60
M4	215	-43.60

Table3.12: Data of Cloud Point of Group I and Group II.

j) Particle Size Determination:

Particle Size Determination Particle size of the prepared Valsartan microemulsion was determined using Dynamic Light Scattering (DLS) method. Particle size determination results for all the prepared batches of Valsartan microemulsion are presented in the Table 3.13 and all the Graph obtained are reported in the Figure 3.7

Table 3.13: Data of Particle Size and Zeta Potential values of Group I and Group II

k) Zeta Potential:

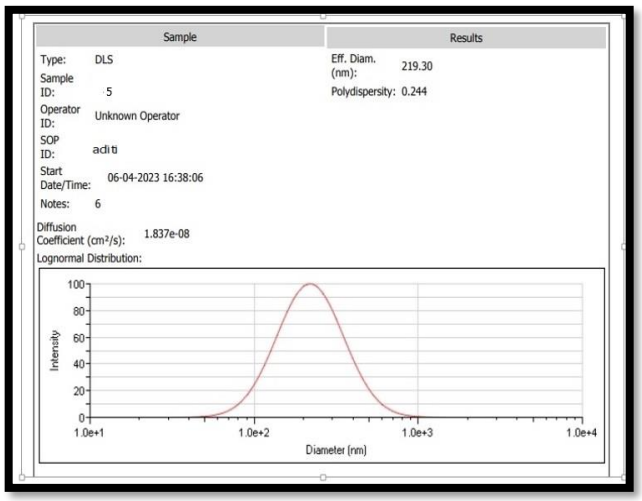
Zeta Potential of the prepared Valsartan microemulsion was determined using Light Scattering method. Zeta Potential results for all the prepared batches of Valsartan microemulsion are presented in the Table 3.13 and all the Graph obtained are reported in the Figure 3.8

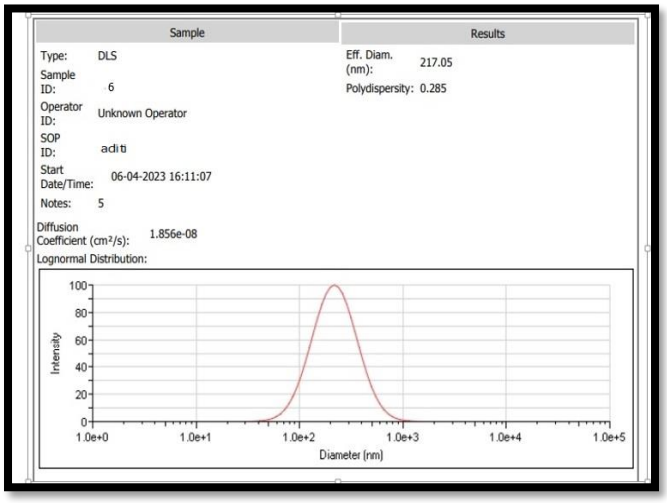
l) Polydispersity Index (PI):

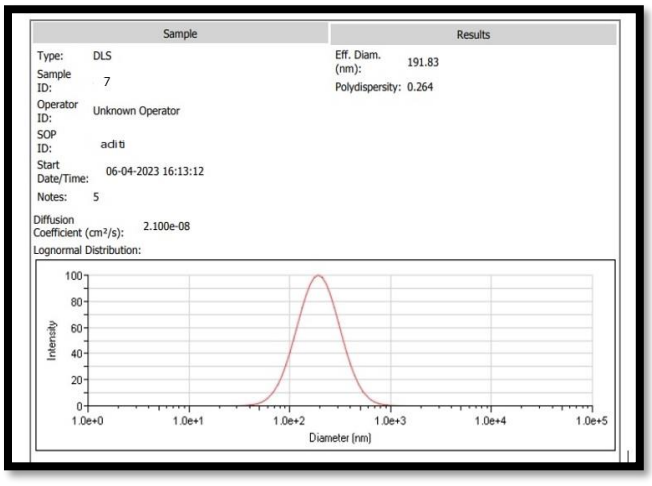
Polydispersity Index (PI) of the prepared microemulsion was determined using Dynamic Light Scattering (DLS) method. Result of Polydispersity Index (PI) is reported in the Table 3.14 and Figure 3.7

Formulation Code	Polydispersity Index
Group I	
M3	0.244
M4	0.285
Group II	
M3	0.264
M4	0.276

Table 3.14: Polydispersity Index of Group I & Group II







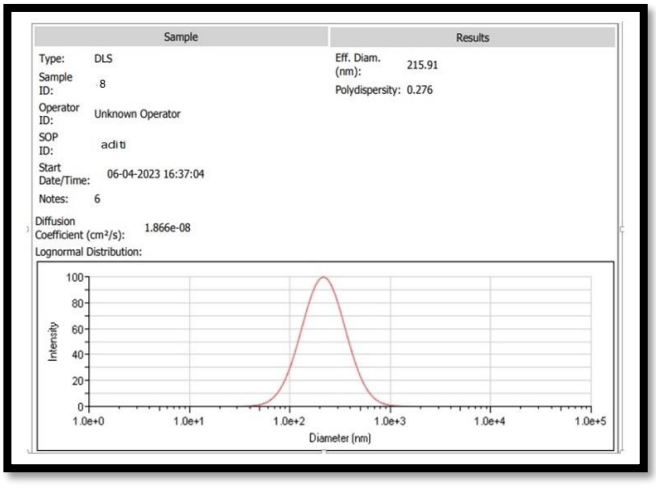


Figure 3.7: Particle Size Analysis of all the Formulation.

Where, Sample 5 and Sample 6 indicate Group I M3 and M4 respectively whereas Sample 7 and Sample 8 indicate Group II M3 and M4 respectively.

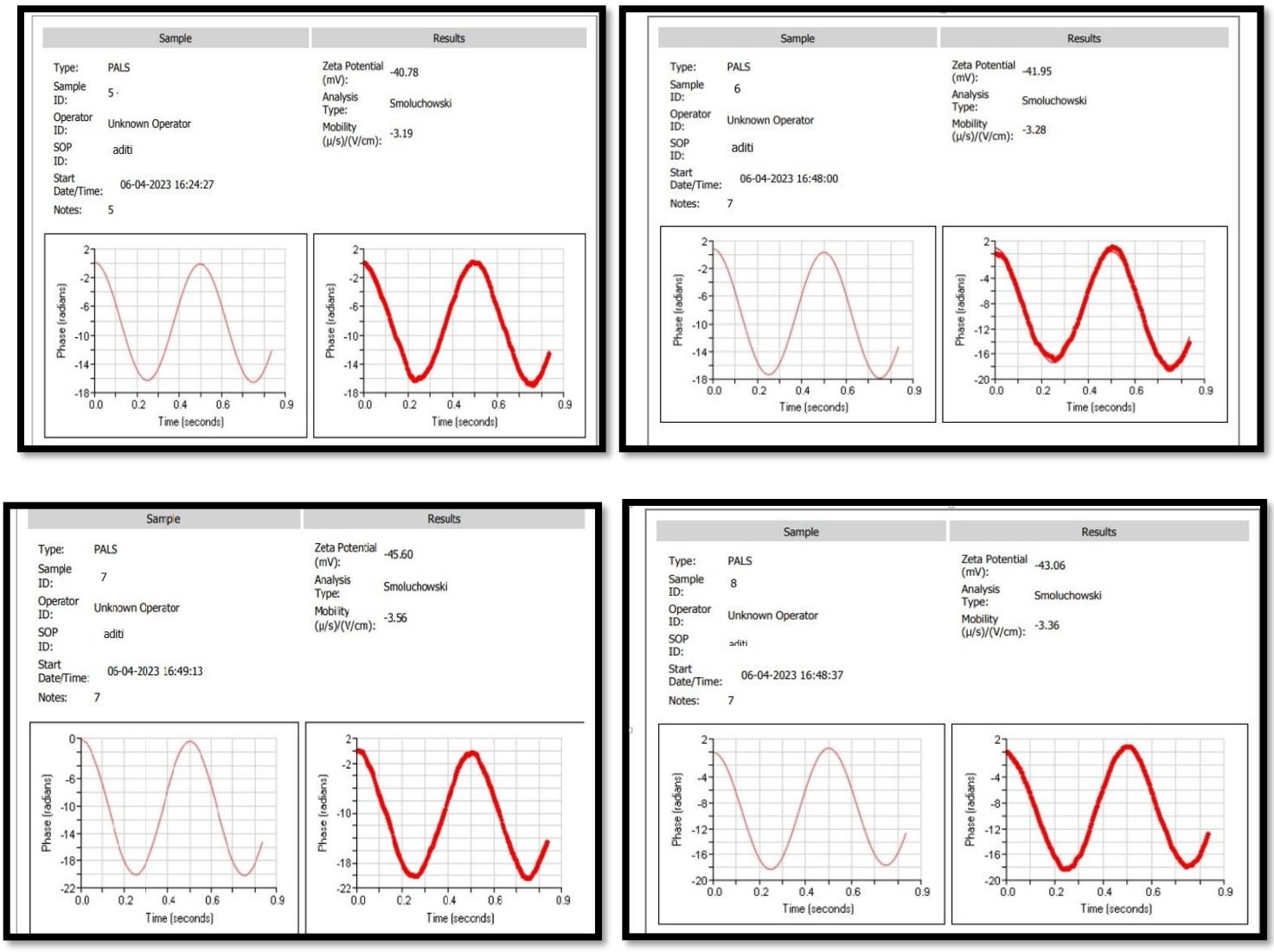


Figure3.8: Data of Zeta Potential of Group I & Group II

Where, Sample 5 and Sample 6 indicate Group I M3 and M4 respectively whereas Sample 7 and Sample 8 indicate Group II M3 and M4 respectively.

m) *in-vitro* drug release:

The in-vitro drug release study for the batches for Valsartan drug and microemulsion was carried out using paddle method (USP apparatus II). Data for in-vitro drug release study is presented in the following Table and the graphical representation of Percentage Drug Release vs. Time graph is shown in the Figure and. The release study was carried out in both 0.1N HCl and 6.8 pH phosphate buffer. The data showed that release of valsartan was faster in phosphate

buffer of pH 6.8 than other media. The pH-dependent solubility of drug can be responsible for higher release.

- ***in-vitro* drug release in 0.1 N HCl :**

Time	% Drug Release		
(min)	Valsartan	SMEDDS(1:1)	SMEDDS(2:1)
0	0	0	0
5	15.1±1.2	17.53±0.89	22.71±0.94
15	20.25±1.04	22.19±2.5	24.69±0.32
30	23.7±1.05	24.12±0.75	26.56±0.26
45	25.96±1.1	28.99±0.23	29.65±0.51
60	29.93±1.02	30.91±1.2	31.89±0.47
75	31.85±1.02	32.90±0.68	33.89±1.3
90	32.79±1.05	34.93±1.01	36.14±2.2
105	34.16±1.01	36.64±1.06	39.61±1.2
120	35.6±1.02	37.57±1.22	41.37±0.79

Table 3.15: Dissolution data for Liquid SMEDDS in 0.1N HCl

- ***in-vitro* drug release in 6.8 pH Phosphate Buffer:**

Formulation	Percent Drug Release				
	0 min	5 min	15 min	30 min	60 min
Valsartan	**0**	26.26±1.02	28.37±1.28	32.06±1.17	42.39±2.1
M4(Group I)	**0**	76.34±1.4	78.75±1.02	81.56±1.08	83.79±2.0
M3 (Group II)	**0**	84.48±1.2	86.26±1.09	90.23±1.10	92.33±2.1

Table 3.16: Dissolution data for Liquid SMEDDS in 6.8 pH buffer

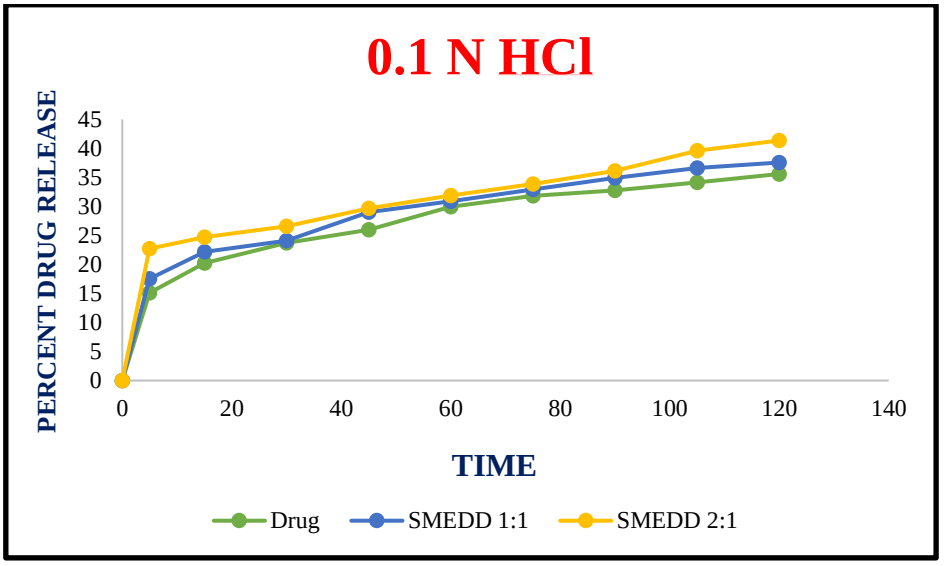


Figure 3.9: In- vitro drug release profile of Liquid SMEDDS and Valsartan (API), M4 (Group I), M3 (Group II) in 0.1N HCl.

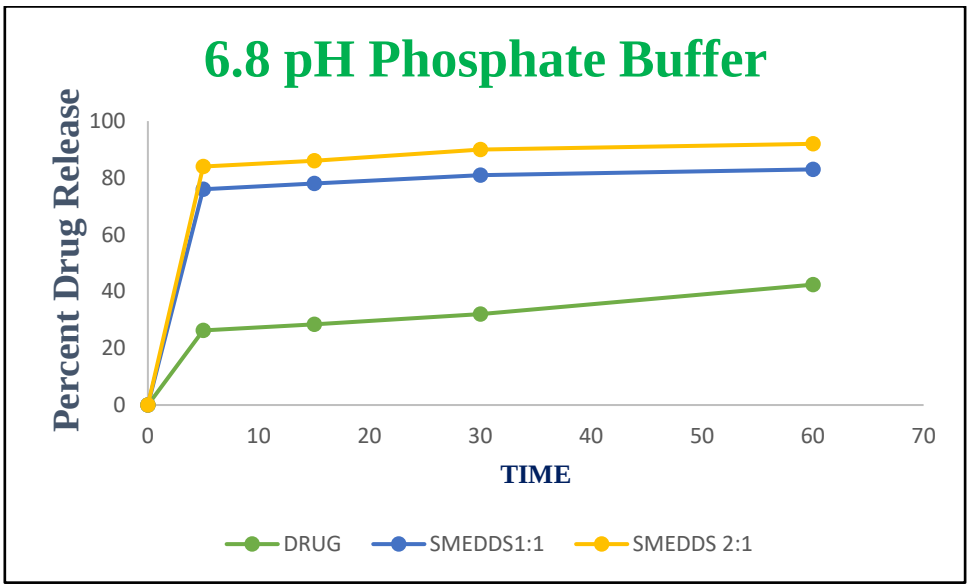


Figure3.10: - In- vitro drug release profile of Liquid SMEDDS and Valsartan (API), M4 (Group I), M3 (Group II) in 6.8 pH phosphate buffer.

3.7. Preparation of Solid SMEDDS:

Solid SMEDDS were prepared as per the composition reported

3.8. Evaluation of Solid SMEDDS Formulations:

1. Micromeritics properties:

The formulation indicated angle of repose < 30 which showed that they had excellent flow properties. Bulk density and tapped density was evaluated to study Carr's index and Hausner`s Ratio. Results indicated in the table 3.17.

Formulation Code	Angle of repose	Bulk density	Tapped density	Carr`s index	Hausner`s ratio
S1	25.64°	0.47m/ml	0.54gm/ml	12.96%	1.12

Table 3.17 : Micromeritic properties of Solid SMEDD.

2. Scanning electron microscopy:

Solid-SMEDDS appeared as smooth surfaced particles, indicating that the liquid SMEDDS is adsorbed onto the Aerosil 200 with a lesser amount of aggregation which showed effective particle size reduction of SOLID SMEDDS as compared to the drug. It is indicated in figure 3.11.

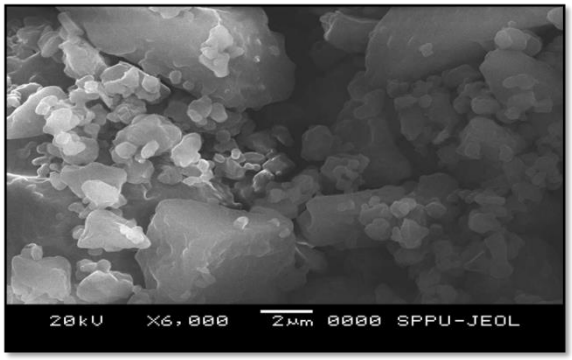


Fig 1: SEM of Valsartan

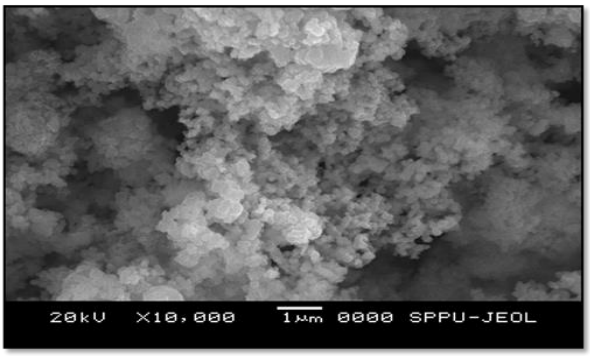


Fig 2: SEM of Solid SMEDDS

Figure 3.11: Scanning Electron Microscopy of Valsartan and Solid SMEDDS.

3. *in-vitro releas*e studies:

The release study of SOLID SMEDDS was carried out in both 0.1N HCl and 6.8 pH phosphate buffer. The data showed that release of valsartan was faster in phosphate buffer of pH 6.8 than other media. Data for in-vitro drug release study is presented in the following Table 3.18 and 3.19 and the graphical representation of Percentage Drug Release vs. Time graph is shown in the Figure 3.12 and 3.13.

- **in-vitro drug release 0.1 N HCl:**

Time (min)	% Drug Release of Solid SMEDD
0	0
5	20.505±0.76
15	23.225±1.02
30	25.948±1.05
45	29.409±1.1
60	30.668±1.02
75	32.664±1.03
90	34.661±1.02
105	36.661±0.49
120	39.644±1.03

Table 3.18: Dissolution data for Solid SMEDDS in 0.1N HCl.

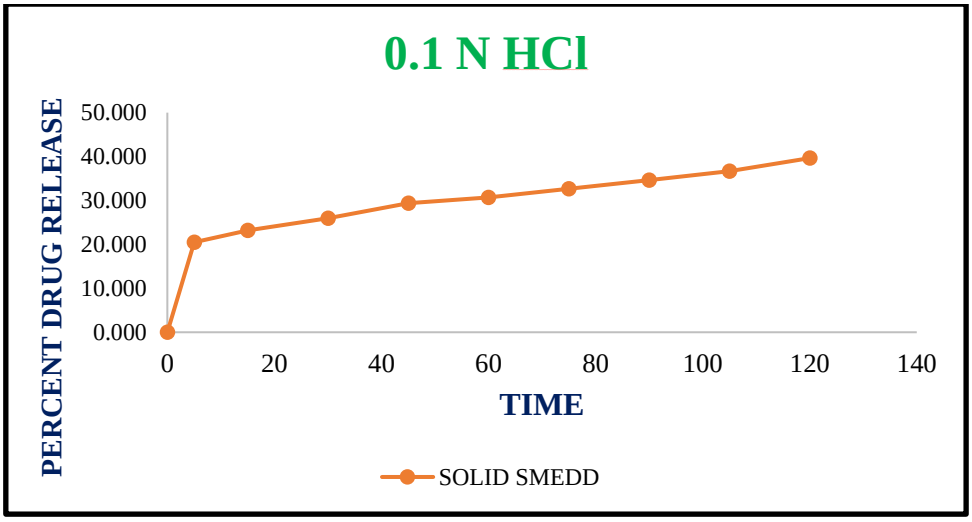


Figure 3.12: - In- vitro drug release profile of Solid SMEDDS in 0.1N HCl.

- **in-vitro drug release 6.8 pH phosphate buffer:**

Formulation	Percent Drug Release				
S1	0 min	5 min	15 min	30 min	60 min
	0	83.82 ±1.02	85.99 ±1.05	88.99 ±2.1	91.58 ±1.02

Table 3.19: Dissolution data for Solid SMEDDS in 6.8 pH phosphate buffer

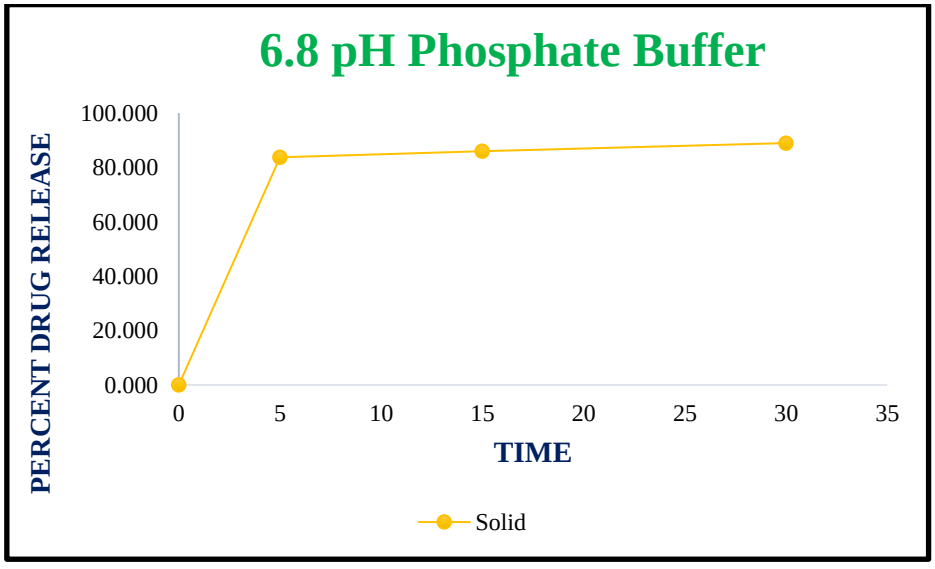
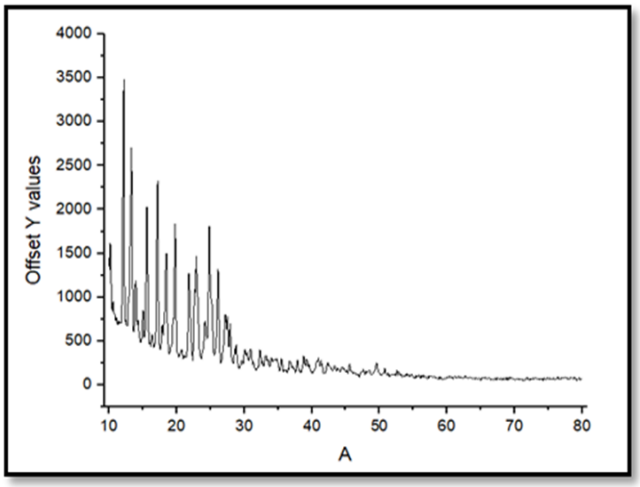


Figure 3.13: In- vitro drug release profile of Solid SMEDDS in 6.8 pH phosphate buffer.

4. X-ray diffraction study:

The diffraction pattern of valsartan revealed several sharp high-intensity peaks at diffraction angles 2θ suggesting that the drug existed as crystalline material. There were few

characteristic peaks of valsartan with a considerable reduction in the peak intensity. This diminished peak suggests conversion of the drug into an amorphous form. This marked reduction in peak intensities provides may increase dissolution rates of Solid-SMEDDS preparation. It is indicated in figure 3.14.



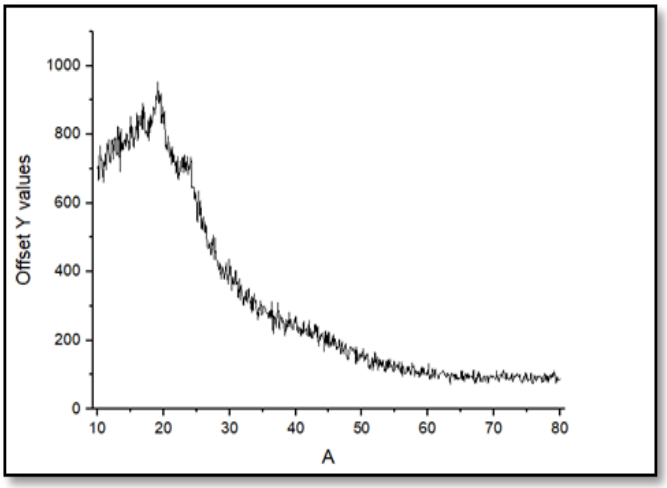


Fig: X-ray Diffraction of Valsartan

Fig: X-ray Diffraction of Solid SMEDDS

Figure 3.14: X ray diffraction of Valsartan and Solid SMEDDS

5. Drug Content:

The drug content of Solid SMEDDS formulation was found at 248 nm. The data is shown in the Table no 3.20

Formulation Code	Drug Content
S1	97.73±1.05

Table 3.20: Drug Content of Solid SMEDDS formulation.

6. FTIR Spectra:

The scanning range was 400 to 4000 cm-1 and resolution was 1cm^{-1}. So it can be concluded that the spectra of pure drug valsartan and the Solid SMEDDS spectrum, that all the characteristic peaks of valsartan were present in the Solid SMEDDS spectrum.

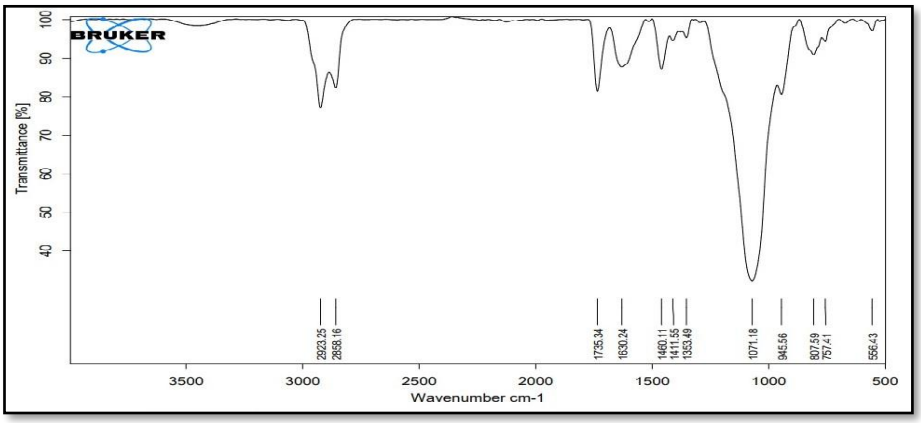


Figure3.15: FT-IR Spectra of Solid SMEDDS.

7. Stability study:

The results of stability studies depicted that the solid-SMEDDS formulation remained clear even after a period of 3 months at temperature 25°C ± 2°C & 60% ± 5%. All the formulations were found to be consistent with respect to their drug content and appeared clear on reconstitution.

Temperature& Humidity	Month	Appearance	Drug Content
25±2°& 60% ± 5%	0	Clear	97.73±1.5
25±2°& 60% ± 5%	1	Clear	97.56±1.2
25±2°& 60% ± 5%	2	Clear	97.49±2.5
25±2°& 60% ± 5%	3	Clear	97.37±2.1

Table 3.21: Stability Study of S-SMEDDS

CONCLUSION:

In the present study, Valsartan an antihypertensive drug who has low aqueous solubility was formulated in the form of Self-Microemulsifying Drug Delivery System (SMEDDS) to increase its solubility which will result in enhancement in Dissolution Rate and Bioavailability of the drug. Firstly the solubility was checked in various oil, surfactant and co-surfactant. Liquid SMEDDS were formulated from which the optimized micro emulsion formulation M3 containing Castor oil as oil, Tween 60 as surfactant, and Kollisolv PG as co-surfactant and distilled water was a transparent, clear and low viscosity system, with particle size 191 nm. The optimized formulation was converted into solid by adsorption on a Solid Carrier (Aerosil 200). The *in-vitro* release of drug was checked in both the medium 0.1N HCl and 6.8 pH Phosphate buffer. It was found out that valsartan has more solubility in the 6.8 pH phosphate buffer. Optimized SMEDDS showed good in vitro release which is increased more than 90%. Solid-SMEDDS were preferred over SMEDDS in terms of stable dosage form. It can be concluded that valsartan solid-SMEDDS offer more predictable and more extensive drug release/absorption than the corresponding conventional formulations. The results from the study showed the utility of solid-SMEDDS to enhance solubility and bioavailability of sparingly soluble compounds like valsartan, which can be helpful to reduce dose and related side effects of the drug. The present research work successfully illustrates the prospective advantage of Solid-SMEDDS for the delivery of poor aqueous soluble compounds.

ACKNOWLEDGEMENT:

The authors would like to acknowledge PDEA`s Shankarrao Ursal College of Pharmaceutical Sciences and Research Centre, Pune, Maharashtra, India for offering all vital help to accomplish this work efficaciously.

REFERENCE:

1. Johanna Mercke Odeberg, Peter Kaufmann, Karl-Gunnar Kroon *et al*. Lipid drug delivery and rational formulation design for lipophilic drugs with low oral bioavailability, applied to cyclosporine.Int.J.Pharm. 20; 2003:375-382.

2. Sandeep Kalepu, Mohanvarma Manthina, Veerabhadraswamy Padavala. Oral lipid –based drug delivery systems – an overview. Acta Parmaceutica Sinica B. 3(6);2013: 361-372

3. Date AA, Nagersenkar MS. "Design and evaluation of self-nanoemulsifying drug delivery system(SNEDDS) for cefpodo ximeproxetil". Int. J. Pharm. 329;2007:166-172.

4. Aditi R. Beldar, Sujit S. Kakade, Ashok V. Bhosale , Self-Micro-emulsifying Drug Delivery System: A Promising Technique to Enhance the Solubility of Lipophilic Drugs" Published in International Journal of Trend in Scientific Research and Development (ijtsrd), ISSN: 2456-6470, Volume-7 | Issue-3, June 2023, pp.133-144

5. Bhondve Riya R, Kakade Sujit S, Bhosale Ashok V "A Review on Solid Self Micro-emulsifying Drug Delivery System: A Method for Enhancement of Oral Bioavailability" Published in International Journal of Trend in Scientific Research and Development (ijtsrd), ISSN: 2456- 6470, Volume-7 | Issue-3, June 2023, pp.145-155.

6. S. Nazzal and M. A. Khan, "Controlled release of a self-emulsifying formulation from a tablet dosage form: stability assessment and optimization of some processing parameters," International Journal of Pharmaceutics, vol. 315, no. 1-2, pp. 110– 121, 2006.

7. P. Balakrishnan, B.-J. Lee, D. H. Oh et al., "Enhanced oral bioavailability of Coenzyme Q10 by self-emulsifying drug delivery systems," International Journal of Pharmaceutics, vol. 374, no. 1-2, pp. 66–72, 2009.

8. Flesch G., Muller Ph., Lloyd P. Absolute bioavailability and pharmacokinetics of valsartan, an angiotenin II receptor antagonist in man. Eur J Clin Pharmcol 1997; 52: 115-120.

9. Saydam, Takka. Bioavailability File: Valsartan. FABAD J Pharm Sci 2007; 32:185-196.

10. Demiralay EC., Cubuka B., Ozkanb SA., Alsancaka G. Combined effect of polarity and pH on the chromatographic behavior of some angiotensin II receptor antagonists and optimization of their determination in pharmaceutical dosage forms. J Pharm Biomed Anal 2010; 53: 475-482.

11. Jayaraj AA, Keirns JJ. Lipid-based delivery systems for improving the bioavailability and lymphatic transport of a poorly water soluble LTB4 inhibitor. J Pharm Sci.1998;87: 164–9.

12. Shailesh T. Prajapati Harsh A, Joshi Chhaganbhai N. Patel. (2013)., Preparation and Characterization of Self-Micro emulsifying Drug Delivery System of Olmesartan medoxomil for Bioavailability Improvement., Journal of Pharmaceutics. 2013; 2: 01-09.

13.Sheikh S, Shakeel F, Talegaonkar S, Ahmad FJ, Khar RK and Ali M(2007). Development and bioavailability assessment of ramipril nanoemulsion formulation. Eur J Pharm Biopharm, 66, 227–243.

14. Kang BK, Lee JS, ChonSK, Jeong SY, Yuk SH, Khang G, Lee HB, Cho SH.(2004) Development of selfmicroemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs. International Journal ofPharmaceutics, 274: 65-73.

15. Atef E, Belmonte AA. Formulation and in-vitro and in-vivo characterization of a Phenytoin self-emulsifying drug delivery system. Eur J Pharm Sci 2008; 35:257-263.

16. Hosmer J, Reed R, Bentley MV, Nornoo A, Lopes LB. Microemulsions containing medium-chain glycerides as transdermal delivery systems for hydrophilic and hydrophobic drugs. Aaps Pharmscitech. 2009 Jun;10:589-96.

17. More HN, Hazare AA. Practical Pharmaceutics (Physical pharmacy). 1st ed. Kolhapur: Manas Prakashan; 2004. p. 86-105.

18. Gupta A.K, Mishra D.K and Mahajan S.C. Preparation and in-vitro evaluation of self-emulsifying drug delivery system of antihypertensive drug, Valsartan.2011;2 (3): 633-639.

19. Singh SK, Vuddanda PR, Singh S, Srivastava AK. A comparison between use of spray and freeze drying techniques for preparation of solid self-microemulsifying formulation of valsartan and in vitro and in vivo evaluation. BioMed research international. 2013 Jan 1;2013.

20. Shahu SG, Wadetwar RN, Dixit GR. Development of microemulsion for solubility enhancement of poorly water soluble drug valsartan. Int. J. Pharm. Sci. Rev. Res. 2013;22(2):246-51.

21. Patel KB, Patel B. Enhancement of oral bioavailability of valsartan by using solid self-emulsifying drug delivery system. International Journal of Universal Pharmacy and BioSciences. 2014; 3(3):141-56.

22. Mahajan HD, Shaikh T., Bhaviskar D. Design and development of self-emulsifying drug delivery system. IJPS 2011: 3 163-166.

23. Khoo SM, Humberstone AJ, Porter CJH, Edwards GA., Charman WN.(1998) Formulation design and bioavailability assessment of lipidic self-emulsifying formulations of halofantrine. International Journal of Pharmaceutics, 167, 155-164.

24. Srinivas C, Sagar SV, Enhancing the Bioavailability of Simvastatin Using Micro emulsion Drug Delivery System, Asian Journal of Pharmaceutical and Clinical Research, 5, 2012, 134-139.

25. Shweta Gupta, Sandip Chavhan, Kruthika K Sawanth. Self nanoemusifying drug delivery systems for adefovir-dipivoxil: Design, characterization, in vitro and ex vivo evaluation. Colloids and Surfaces A: Physiochem Eng Aspects. 392; 2011:145-155.

26. K. Khedekar, and S. Mittal, "Self-emulsifying drug delivery system: A review, "International Journal of Pharmaceutical Science and Research, vol. 4, no. 12, pp. 4494-4497, 2013.

27. Ghosh PK, Majithiya RJ, Umrethia ML, Murthy RSR, Design and Development of Microemulsion Drug Delivery System of Acyclovir for Improvement of Oral Bioavailability, American Association of Pharmaceutical Scientists, 7, 2006, E1- E6

28. Madhav S, Gupta D, A Review On Micro emulsion Based System, International Journal of Pharmaceutical Sciences and Research, 2, 2011, 1888-1899.

29. Shin DJ, Chae BR, Goo YT, Yoon HY, Kim CH, Sohn SI, Oh D, Lee A, Song SH, Choi YW. Improved dissolution and Oral bioavailability of valsartan using a solidified Supersaturable self-microemulsifying drug delivery system containing Gelucire® 44/14. Pharmaceutics. 2019 Jan 31;11(2):58.

30. Prashant H. Khade , Gururaj Shahabade , Sachin V.Kotwal , Priyanka D. Borude , Jyoti B.Darkunde, Harshal M.Shinde, Self-Emulsifying Drug Delivery System (SEDDS) for Enhancement of Solubility and Photostability of Amlodipine Besilate, doi: 10.31838/ecb/2023.12.si4.168

31. Dixit AR, Rajput SJ, Patel SG. Preparation and bioavailability assessment of SMEDDS containing valsartan. AAPS pharmscitech. 2010 Mar;11:314-21.

32. Ponnaganti H, Abbulu K. Enhanced dissolution of repaglinide: SMEDDS formulation and in-vitro evaluation. Research Journal of Pharmacy and Technology. 2014;7(11):1246-52.

33. Harshal M. Shinde , Prashant H. Khade , Ashok V. Bhosale, Aditi R. Beldar , Riya R. Bhondve , Rajratna D. Gaikwad, Preparation, Evaluation and Optimization of Nanosuspension of Poorly Water-Soluble Rosuvastatin Calcium**,** doi: 10.48047/ecb/2023.12.si6.177

34. Jaiswal P, Aggarwal G, Harikumar SL, Singh K. Development of self-microemulsifying drug delivery system and solid-self-microemulsifying drug delivery system of R. International journal of pharmaceutical investigation. 2014 Oct;4(4):195.

35. Taha E I, Saidam S A, Samy A M, Khan M A. Preparation and in-vitro characterization of a eutectic based semisolid self nanoemulsified drug delivery system of all trans-retinol acetate. Int J Pharm 2004; 285: 247-263.

36. Rai S, Yasir M. Cinnarizine loaded lipid based system: preparation, optimization and in-vitro evaluation. IOSR Journal of Pharmacy. 2012 Sep;2(5):47-56.

37. Bhagwat DA, Souza JI. Formulation and evaluation of solid self micro emulsifying drug delivery system using aerosil 200 as solid carrier. International current pharmaceutical journal. 2012 Nov 1;1(12):414-9.

38. Bhattacharya S, Prajapati BG. Formulation approach of self-emulsifying drug delivery system. Int J Pharm Formula 2015;6(1):1-6.

39. Anand S. Formulation & development of Self-Micro Emulsifying Drug Delivery System (SMEDDS) for oral bioavailability enhancement of a low soluble anti-diabetic drug: gliclazide.

40. Albekery MA, Alharbi KT, Alarifi S, Ahmad D, Omer ME, Massadeh S, Yassin AE. Optimization of a nanostructured lipid carriers system for enhancing the biopharmaceutical properties of valsartan. Digest journal of Nanomaterials and Biostructures. 2017 Apr 1;12(2):381-9.

41. Poudel BK, Marasini N, Tran TH, Choi HG, Yong CS, Kim JO. Formulation, characterization and optimization of valsartan self-microemulsifying drug delivery system

using statistical design of experiment. Chemical and pharmaceutical bulletin. 2012 Nov 1;60(11):1409-18.