RESEARCH ARTICLE

Design of a novel type IV lipid-based delivery system for improved delivery of drugs with low partition coefficient

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Abstract
Context: The physicochemical properties of drugs such as partition coefficient play a major role in the development of lipid-based drug delivery systems. The major obstacle lies in encapsulation of a drug with low partition coefficient into these systems.
Objective: The objective of this study was to design and optimize a novel lipid-based delivery system with higher loading, improved pharmacokinetics consequently enhancing the oral bioavailability of drugs with low partition coefficient like valsartan.
Materials and methods: The optimized formulation consists of Capryol 90, Cremophor RH 40, and Transcutol HP. Pseudo ternary phase diagrams were used to optimize the components and their concentrations in the formulation. Dissolution studies of the selected formulations were compared with plain drug and marketed product at three pH conditions (pH 1.2, 4.5 and 6.8). Pharmacokinetic parameters of optimized formulations were determined in Wistar rats and compared with that of plain drug.
Results and discussion: The optimized formulation with a mean particle size of 50 nm showed significant improvement ($p < 0.05$) in dissolution rate with pH independence compared to plain drug and marketed product. The in vivo studies in Wistar rats revealed about 2.30- and 1.68-fold increase in the oral bioavailability and $C_{\text{max}}$ of valsartan from lipid-based formulation compared to plain drug.
Conclusion: The engineered formulation strategy by type IV lipid-based formulations can be successfully exploited to improve the dissolution rate and oral deliverability of drugs like valsartan.

Keywords
Bioavailability, pH-depended solubility, poorly soluble, self nanoemulsifying delivery

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Introduction
The oral route of administration is still the preferred route for drug delivery, especially for treatments requiring multiple dosing, because of patient compliance, low invasive nature and ease of administration. Most of the drugs show poor physicochemical and biopharmaceutical properties, which limits their oral bioavailability. There are various advanced technologies that have provided a platform for development of such drugs by oral route, which includes salt formation, particle size reduction, hydrotropic solubilization, complexation, micellar solubilization, pH modification, dispersions, nanoemulsion, controlled precipitation spherical crystallization and various lipid based technologies (Leuner & Dressman, 2000; Mallick et al., 2007; Patel et al., 2014).

Lipid-based formulations enhances the bioavailability of poorly soluble drugs either by increased solubility or by enhancing drug absorption (Kalepu et al., 2013). The main advantage of lipid-based formulation is that the drug remains in solution or in dissolved state in small oil droplets, throughout its period in the gastrointestinal tract (GIT) (Pouton, 2000). Colin W. Pouton introduced lipid classification system for identifying the performance of lipid-based systems based on the composition of formulations (Pouton, 2000). Initially, four categories were discussed in the classification (Type I, II, IIIA and IIIB). Later, in the year 2006, type IV formulations were added to the existing lipid formulation classification system by Pouton (2006). Type IV formulations are extremely hydrophilic and contain water-insoluble and water-soluble surfactant along with hydrophilic co-solvent. Drugs that are insoluble or sparingly soluble in oils due to low partition coefficient can easily loaded into this type of formulations.

Self-emulsifying drug delivery systems (SEDDS) are newer lipid-based technology that has attracted much interest after the commercial success of Neoral® (cyclosporine A), Norvir® (ritonavir) and Fortovase® (saquinavir) (Kanika Sarpal et al., 2010). SEDDS are isotropic mixtures of oils (natural or synthetic) and surfactants along with co-solvents or co-surfactants. SEDDS are thermodynamically stable and spontaneously form oil-in-water emulsion upon contact with
GI fluids with droplet size ranging from nanometers to micrometers (Porter et al., 2008). Self nano-emulsifying drug delivery systems (SNEDDS) are the SEDDS formulations in which globule size is in nano size range (less than 100 nm) (Singh et al., 2009). The physicochemical properties of drug-like partition coefficient (log P) plays a major role in the formulation of SNEDDS. Generally, drugs with log P ≥4 are more suitable for SNEDDS as drug loading can be maximum (Thi et al., 2009).

Valsartan, an orally active non-peptide is mostly preferred in the treatment of mild to moderate essential hypertension due to its lower incidence of dry cough compared to other angiotensin-converting enzyme inhibitors (Markham & Goa, 1997). It is also used to treat congestive heart failure (Mazayev et al., 1998). However, valsartan belongs to biopharmaceutics classification system class II with low solubility (<100 μg/mL). The solubility of valsartan is also pH dependant with low solubility at lower pH. The drug is rapidly absorbed from the upper part of GIT and shows oral bioavailability of about 23% (Cappello et al., 2006). Furthermore, the presence of food decreases its absorption by 40% (Burnier & Brunner, 2000). In addition, partition coefficient of valsartan is 0.033 (log P = 1.499) (Saydam & Takka, 2007). As a result, valsartan exhibits inter- and intra-subject variability in absorption resulting in poor oral bioavailability and pharmacokinetics (Yamada et al., 1990). Formulations that can improve valsartan solubility or dissolution at lower pH will improve its pharmacokinetics and bioavailability. Literature cites various techniques to enhance the dissolution of valsartan that include solid dispersions (Yan et al., 2012), crystal engineering (Blagden et al., 2007), ball milling (Sonoda et al., 2008), use of mesoporous silica carriers (Ahuja & Pathak, 2009), complexation (Nalawade et al., 2009), self-microemulsifying drug delivery systems (SMEDDS) (Dixit et al., 2010) and lipidoloid compacts (Chella Naveen et al., 2012). So far, to the best of our knowledge, no technique has been reported that gives pH-independent dissolution for valsartan. Dixit et al. prepared SMEDDS containing valsartan and estimated the bioavailability in rats. However, the authors reported low drug loading (∼5%) that results in increased dose to be administered, which in turn lead to higher surfactant concentration per dose. Higher surfactant concentrations (≥60%) may cause gastric irritation (Nielsen et al., 2008; Singh et al., 2009; Tang et al., 2008) hence, generally not recommended. Similarly, the authors failed to show significant improvement in dissolution at lower pH (pH 1.2 and 4.5), which is required for valsartan as the drug is predominantly absorbed at its absorption window.

To address all the above-mentioned issues, the objective of this investigation was to prepare type IV lipid-based formulations with improved drug loading and reduced surfactant concentration per dose. The second objective was to improve the dissolution rate and oral bioavailability of poorly soluble drugs with low partition coefficient. All the ingredients used in the formulation were either approved in pharmacopoeia or present in FDA-inactive ingredient database (Kanika Sarpal et al., 2010). The concentrations were also well below the limits mentioned in US FDA-inactive ingredient data base or their LD50 values (FDA).

Materials
Valsartan was kindly gifted by Aurobindo Pharmaceuticals (Hyderabad, India). Capryol 90, Labrafil M2125CS and Transcutol HP (highly purified diethylene glycol monoethyl ether) were obtained as gift samples from Gattefosse India Pvt. Ltd. (Mumbai, India). Polyethylene glycol 200, 400 and 600, propylene glycol, Tween 20 and Tween 80 were purchased from SD Fine-Chem Ltd. (Mumbai, India). All other excipients, reagents and chemicals used were of analytical grade. HPLC-grade acetonitrile was procured from Merck Millipore (Mumbai, India). Purified Millipore water was used for all experiments. Marketed tablets Valzaar 40 mg (Torrent Pharmaceutical Ltd., Ahmadabad, India) was procured from a local pharmacy.

Methods
Equilibrium solubility studies
Solubility of valsartan in different surfactants and co-solvents was determined by shake flask method (Elnaggar et al., 2009). An excess amount of valsartan was added to each vial containing 1 g of the selected vehicle and subjected to vortexing for 5 min in order to facilitate proper mixing. These mixtures were shaken for 48 h in a thermostatically controlled incubated shaker (JEIOTECH, Seoul, Korea) at 25 ± 0.5 °C. The mixtures were then centrifuged at 5000 rpm for 10 min, the supernatant was separated and filtered through a 0.45 μm Millipore filter and the samples were analyzed for dissolved valsartan using UV spectrophotometer at 250 nm. All the experiments were performed in triplicates.

Construction of pseudo ternary phase diagram
The emulsification region was obtained using pseudo ternary phase diagram by water titration method (Patel & Vavia, 2007). Capryol 90 (water-insoluble surfactant), Smin containing Cremophor RH40 or Tween 20 (water soluble surfactants) and propylene glycol or Transcutol HP (co-solvent) were mixed in different weight ratios (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1) and diluted with water by drop-wise addition under gentle agitation. The addition of water was continued up to the point where turbidity appears. Phase diagrams were constructed using ProSim software (demo version; ProSim, Labège, France) with 1:1, 2:1, 1:2 w/w surfactant to co-solvent ratio. The values of surfactant and co-solvent were used to determine the boundaries of emulsion region.

Preparation of SNEDDS
SNEDDS were prepared by selecting different points in the emulsion region obtained from optimized phase diagrams. Valsartan was dissolved in the mixture of surfactant and co-solvents by vortexing to obtain a final concentration of 10% w/w (Table 1).

Characterization
Robustness to dilution and pH
Robustness of drug-loaded SNEDDS was studied by diluting the formulation 50, 100 and 1000 times with various dissolution media 0.1 N HCl (pH 1.2), acetate buffer...
under continuous stirring (350–400 rpm) using magnetic SNEDDS (100 mg) was diluted to 100 mL with distilled water the SNEDDS after dilution. Accurately weighed quantity of with the help of emulsification time and visual appearance of The efficiency of self-emulsification process was observed droplet size

Determination of dispersibility/emulsification time and monitored for particle size using zeta sizer (Zen 3600, Malvern Instruments, Malvern, UK).

After emulsification, the samples were observed visually for presence of oil globules, turbidity or precipitation of drug. The droplet size of resulting emulsion was determined by photon correlation spectroscopy using Zetasizer (Zen 3600, Malvern Instruments). The samples were diluted 100-fold with distilled water prior to analysis. Each study was performed in triplicate to ensure reproducibility.

Stability studies

Freeze–thaw cycle

The formulations were subjected to six heating and cooling cycles for 48 h at 2–8 °C and 45 °C, respectively. The samples were subjected to centrifugation at 18 000 rpm for 30 min at 4 °C and observed for phase separation.

Centrifugation

The formulations were subjected to centrifugation at 3750 rpm for 5 h equivalent to one-year gravitational force during shelf life and visually observed for phase separation or creaming (Lachman et al., 1986).

Shape and morphology

The morphology of optimized SNEDDS formulation was observed using transmission electron microscope (TEM; H 7500, Hitachi, Tokyo, Japan). One drop of the diluted sample was placed on a film-coated copper grid and stained with 1% phosphotungstic acid solution for 30 s. The image was magnified and focused on a layer of photographic film (Singh et al., 2011).

In vitro dissolution studies

In vitro dissolution studies of SNEDDS were conducted in USP apparatus II paddle method at 50 rpm, and the dissolution rate was compared with the plain drug and conventional marketed formulation. The dissolution studies were performed in three different release media (0.1 N HCl, acetate buffer pH 4.5, phosphate buffer pH 6.8) at 37 ± 0.5 °C. An aliquot of 5 mL were withdrawn at different time intervals, and an equal volume of fresh dissolution medium was immediately replaced. The filtered samples were assayed after suitable dilution by UV spectrophotometer at 250 nm. All the experiments were performed in triplicates.

Pharmacokinetic study

Bioavailability studies

All animal experiments were carried out according to the protocol approved by Institutional Animal Ethics Committee (IAEC no: NIP/02/2013/PE/42) of National Institute of Pharmaceutical Educational and Research, Hyderabad, India. The experimental procedures were in accordance with the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines for the safe use and care of experimental animals. Oral bioavailability of valsartan in SNEDDS was compared with the valsartan plain drug dispersed in water with the aid of sodium carboxymethyl cellulose (CMC). Male Wistar rats weighing 180–200 g were used in this study. The animals were kept in the animal house at a temperature of 25 ± 2 °C with 12 h of dark and light cycles. Animals were fasted overnight but allowed free access to water. Twelve rats were divided into two groups. The first group received valsartan plain drug dispersed in Sodium CMC, and the second group received SNEDDS formulation equivalent to a dose of 10 mg/kg body weight orally. Blood samples (0.5 mL) were collected by retro-orbital venous plexus puncture with an aid of glass capillary at 0.25, 0.5, 1.2, 4, 6 and 8 h post oral dose. All samples were collected in EDTA-coated Eppendorf tubes. Plasma was separated by centrifugation at 5000 rpm for 5 min and stored at −20 °C for further analysis. Valsartan concentration in plasma was determined using HPLC (Shimadzu, Kyoto, Japan).

Sample preparation and HPLC analysis of valsartan in plasma

Drug extraction was carried out by protein precipitation method using acetonitrile. The samples were prepared by

| Formulation | Capryol 90 (mg) | Cremophor RH 40 (mg) | Transcutol HP (mg) | Emulsification time (s) | Size (nm) | Poly disperity index (PDI) |
|-------------|----------------|---------------------|-------------------|------------------------|----------|-------------------------|
| F1          | 100            | 150                 | 150               | >3 min                 | 184.3 ± 5.4 | 0.668 ± 0.10 |
| F2          | 100            | 200                 | 200               | 15                     | 103.9 ± 5.6 | 0.307 ± 0.11 |
| F3          | 100            | 225                 | 225               | 14                     | 103.5 ± 3.0 | 0.112 ± 0.02 |
| F4          | 100            | 300                 | 300               | 10                     | 92.14 ± 1.8 | 0.221 ± 0.09 |
| F5          | 200            | 150                 | 150               | >3 min                 | 218.7 ± 3.9 | 0.895 ± 0.10 |
| F6          | 200            | 200                 | 200               | 20                     | 41.21 ± 1.1 | 0.132 ± 0.06 |
| F7          | 200            | 225                 | 225               | 14                     | 42.13 ± 1.7 | 0.121 ± 0.03 |
| F8          | 200            | 300                 | 300               | 10                     | 52.93 ± 2.6 | 0.196 ± 0.08 |
Results and discussion

To develop an optimum SNEDDS, it is very important to evaluate the drug solubility in various formulation components, the self-emulsifying region in the phase diagram and the droplet size distribution. The optimization was performed by investigating all these factors involved in formulation of SNEDDS to obtain a product with improved dissolution and enhanced bioavailability.

Solubility studies

SNEDDS should form a clear monophasic liquid at body temperature when introduced into the GIT in vivo. Hence, the drug solubility in the given surfactants and co-solvents is an important criterion in the formulation development process to achieve optimum drug loading and also to minimize the final dosing volume of SNEDDS (Pouton, 2006). Solubility studies showed that higher amount of valsartan was soluble in (Table 2) surfactants (Capryol 90, Tween 20 and Cremophor RH 40) and co-solvents (Transcutol HP and propylene glycol). Furthermore, the combination of surfactant having low and high hydrophilic–lipophilic balance (HLB) values with hydrophilic co-solvents usually results in high drug solubilizing capacity for drugs with log P ≤ 2 (Cannon, 2011; Kommuru et al., 2001). Hence, Capryol 90 (HLB 5), Tween 20 and Cremophor RH 40 (HLB >10) and co-solvents (Transcutol HP and propylene glycol) were selected for the construction of pseudo ternary diagrams.

Pseudo ternary phase diagrams

Pseudo ternary diagrams were constructed to identify the combination of surfactant, co-surfactant and co-solvent that could give a system with maximum emulsification area. The optimum ratio of surfactant and co-solvent mixture required to prepare a formulation that gives clear monophasic system on dilution was also determined from the phase diagram. Pseudo ternary phase diagram constructed with Capryol 90 and different S mix. From the phase diagrams (Figure 1 and supplementary data), it was evident that SNEDDS containing Transcutol HP (Figure 1) produced wide emulsifying area compared to that of the system containing propylene glycol (supplementary Figure 1). This is due to higher water solubility of Transcutol HP when compared to propylene glycol (Wei et al., 2005). The formulations containing Cremophor RH 40 (HLB 16) spontaneously produced clear emulsion on dilution when compared to the translucent to turbid emulsion with oil globules floating on the surface with the pre-concentrates containing Tween 20. Cremophor RH 40 showed good emulsification with Capryol 90, which was in accordance to the literature (Rahman et al., 2013; Sermkaew et al., 2013). In addition, Transcutol has the ability to enhance absorption and permeability of drugs (Mahmoud et al., 2014), while Cremophor RH 40 exhibits better emulsification property (Elsheikh et al., 2012; Parmar et al., 2011) and

### Table 2. Solubility of valsartan in different surfactant, co-solvents and dissolution media.

| Surfactant/co-solvent | Solubility (mg/mL) | Co-solvents/dissolution media | Solubility (mg/mL) |
|-----------------------|--------------------|-------------------------------|--------------------|
| Capryol 90            | 237.90 ± 5.12      | Polyethylene glycol 600       | 83.91 ± 2.89       |
| Labrafil M2125CS      | 11.04 ± 2.67       | Polyethylene glycol 400       | 69.57 ± 1.98       |
| Tween 20              | 69.73 ± 2.38       | Transcutol HP                 | 47.10 ± 6.43       |
| Tween 80              | 76.57 ± 2.67       | 0.1 N HCl                     | 0.074 ± 0.031      |
| Cremophor RH40        | 42.21 ± 3.03       | Acetate buffer pH 4.5         | 1.31 ± 0.45        |
| Propylene glycol      | 109.20 ± 3.21      | Phosphate buffer pH 6.8       | 5.54 ± 1.02        |
| Polycetethene glycol  | 65.41 ± 1.23       | Distilled water                | 0.205 ± 0.03       |

All values (mean ± SD).
also inhibitory effects on P-gp and metabolic enzymes (Tayrouz et al., 2003). Hence, the combination of surfactant with low HLB (Capryol 90) and high HLB (Cremophor RH 40) along with hydrophilic co-solvent (Transcutol HP) were finally selected, and further optimization was performed by changing the concentration of Cremophor and Transcutol.

The emulsifying area was decreased in the phase diagram constructed (supplementary Figures 2 and 3) using $S_{\text{mix}}$ (Cremophor RH40 and Transcutol HP) in 1:2 and 2:1 ratio compared to the emulsifying area obtained with 1:1 ratio (Figure 1). Furthermore, drug precipitation was observed after dilution from the formulation containing higher co-solvent and hydrophilic surfactant due to diffusion of surfactant/co-solvent into the aqueous phase. Hence, eight formulations (Table 1) were prepared with Capryol 90 and $S_{\text{mix}}$ (Cremophor RH40 and Transcutol HP) in 1:1 ratio and were used for further characterization. The formulations were selected in such a way that the total concentration of surfactant was less than 60% w/w (Tang et al., 2008). Formulation F1 and F5 showed small visible particles after dilution. This was due to high concentration of surfactants compared to co-solvent in the formulation. These surfactants take a considerable time to dissolve due to the formation of viscous liquid crystalline phase leading to precipitation. The formulations (F2, F3, F4, F6, F7 and F8) gave clear solution as the amount of co-solvent was sufficient to solubilize the surfactant in water.

**Evaluation of selected SNEDDS**

**Emulsification time**

Emulsification time indicates the dispersion ability of SNEDDS in aqueous phase. The efficiency of self-emulsification ability of surfactant is related to their HLB value. Furthermore, the stability of emulsion is improved by rapid formation of mechanical barrier due to coalescence of dispersed droplets and reduction in interfacial energy by absorption of surfactant and co-surfactant at the o/w interface. Emulsification time along with particle size and PDI of different formulation is listed in Table 1. All the formulation except F1 and F5 showed ease of dispersion with an emulsification time of less than 30 s indicating good emulsifying capability of surfactant mixture. F1 and F5 took more than 3 min due to formation of viscous liquid crystalline phase by Cremophor RH 40. The emulsification time decreased with increase in surfactant concentration. Generally, 30–60% w/w of surfactant is required to produce a stable SNEDDS formulation. However, considering the fact that high dose of surfactant produces gastric irritation, the ratio of surfactant and co-surfactant was kept below 50% w/w in the final formulation.

**Globule size analysis**

The droplet size of emulsion is a crucial factor in self-emulsification performance as it determines the rate and extent of drug release and drug absorption. The formulations containing Capryol 90, Cremophor RH 40 and Transcutol HP produced fine emulsion with mean particle size less than or equal to 100 nm (Table 1) except formulation F1 and F5. PDI for all formulation was in the acceptable range of ≤0.3, indicating uniform size distribution (Markham & Goa, 1997; Park et al., 2010; Rao et al., 2003). Increase in the concentration of Capryol 90 from 10% to 20% w/w reduced the particle size from 100 nm to 40 nm. Further increase in surfactant increases the total surfactant concentration above 50% w/w. Hence, based on the study results, formulations F6, F7 and F8 were selected as optimized formulations and further evaluated for *in vitro* drug release.
In vitro dissolution studies
Cumulative percentage of drug released from SNEDDS (F6, F7 and F8), plain drug and marketed tablets in 0.1 N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8 are reported in Figure 2. All the three SNEDDS formulations showed 90% of drug release within 15 min. No significant difference ($p \leq 0.05$) was found between dissolution profiles of three formulations at different pH. However, all the formulations showed significant dissolution enhancement ($p < 0.05$) when compared to plain drug and marketed formulation at three pH conditions. The higher release of valsartan from marketed product compared to plain drug in acetate buffer and phosphate buffer may be due to the use of disintegrants and hydrophilic ingredients used in the formulation. However, these excipients did not show significant improvement at lower pH conditions. Valsartan is a weak acid with an absorption window in the upper part of GIT. The drug also has pH-dependent solubility (insoluble at lower pH). Hence, the drug may precipitate due to low solubility of the drug in the stomach resulting in reduced absorption and

Figure 2. In vitro dissolution profile of valsartan plain drug, marketed tablet and SNEDDS in different pH media.
erratic bioavailability of conventional formulations. It was presumed that the significant \((p<0.05)\) improvement in dissolution rate of valsartan at lower pH with the optimized SNEDDS may lead to enhanced absorption and improved bioavailability. Similarly, factor \(f_2\) was calculated for all formulations to show that release was same at all pH. It was found that formulation (F7) showed more degree of similarity compared to F6 and F8 formulation at all pH. Hence, formulation F7 containing 20% w/w Capryol 90, 25% w/w of Cremophor RH 40 and 25% w/w of Transcutol HP was selected based on the results and subjected to robustness to dilution, stability studies and \textit{in vivo} studies.

Robustness to dilution

The valsartan-loaded optimized SNEDDS (F7) was subjected to different folds of dilution to mimic the \textit{in vivo} conditions of gradual dilution. The formulation was robust to all dilution with studied pH (1.2, 4.5 and 6.8) conditions. The particle size of all formulation was less than 50 nm. Similarly, no signs of phase separation were observed after 24 h of storage, indicating the existence of stable interfacial film around oil globules after dilution.

Stability studies

The formulation F7 was physically stable after subjecting them to freeze–thaw cycles for one month. Centrifugation was performed to determine the effect of gravity under normal storage conditions. No signs of creaming, coalescence or phase separation were observed after centrifugation for formulation (F7).

Shape and morphology

TEM images of the optimized formulation F7 shows discrete spherical globules in dark on a bright surrounding (Figure 3). The particle size was within the size range of 50 nm.

![Figure 3. TEM image of valsartan-loaded SNEDDS.](image)

Bioavailability studies

The mean plasma concentrations versus time profiles of valsartan are shown in Figure 4. In case of valsartan plain drug, the drug was not detectable in plasma after 6 h of administration. The plasma concentration of valsartan from the optimized SNEDDS formulation was significantly higher \((p<0.05)\) at each time point compared to plasma concentration of drug from valsartan plain drug. The pharmacokinetic parameters are summarized in Table 3. The area under the curve \((\text{AUC}_{[0-8\text{h}]}\) \(\) of valsartan from SNEDDS \((119.54 \pm 7.60 \mu g/mL\cdot h)\) significantly \((p<0.05)\) increased (2.3-folds) compared to valsartan plain drug \((52.04 \pm 8.68 \mu g/mL\cdot h)\). The \(C_{\text{max}}\) also showed significant \((p<0.05)\) improvement (1.68-folds). However, no significant difference \((p>0.05)\) was observed in other parameters like \(t_{\text{max}},\) half life and MRT (Table 3). Rapid and improved dissolution of valsartan in stomach (pH 1.2) increased the drug concentration at absorption site resulting in increased absorption and bioavailability. Large surface area due to small size and presentation of valsartan in solubilized form at its absorption window further contributed to improved dissolution and enhanced bioavailability of valsartan. The presence of the Capryol 90, a bioavailability enhancer, and Cremophor may further contribute to enhanced bioavailability of valsartan from the prepared SNEDDS.

![Figure 4. \textit{In vivo} profile of valsartan plain drug and valsartan SNEDDS in rats.](image)

| Pharmacokinetic parameter | SNEDDS        | Plain drug   |
|---------------------------|---------------|--------------|
| \(t_{\text{max}}\) (h)    | 0.25 \pm 0.00 | 0.29 \pm 0.10|
| \(C_{\text{max}}\) (\mu g/mL) | 41.95 \pm 9.34 | 25.00 \pm 8.94 |
| \text{AUC}_{[0-8\text{h}]} \mu g/mL \cdot h | 119.54 \pm 7.60 | 52.04 \pm 8.68 |
| \(t_{1/2}\) (h)           | 1.95 \pm 0.59  | 1.70 \pm 0.47 |
| MRT (h)                   | 3.44 \pm 0.96  | 2.73 \pm 0.56 |

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Conclusions

In this investigation, valsartan was incorporated into type IV lipid-based formulation composed of Capryol 90, Cremophor RH 40 and Transcutol HP. The formulation with mean particle size of 50 nm was obtained using a surfactant concentration of 45% w/w. The drug loading was 10% w/w. All formulation ingredients used were generally regarded as safe. The drug release was pH independent, rapid and significantly high compared to the plain drug and conventional marketed formulation. Significant improvement in the pharmacokinetic parameters (AUC, $C_{\text{max}}$) of valsartan was observed from in vivo studies in Wistar rats. The bioavailability of the SNEDDS formulation was found to increase by 2.3-fold when compared to plain drug. The results further conclude that type IV lipid-based SNEDDS can be explored as potential carrier to obtain higher drug loading, enhanced dissolution and enhanced bioavailability of poorly soluble drug with low partition coefficient like valsartan.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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Supplementary material available online
Supplementary Figures 1–3.