Formulation Development and Bioavailability Assessment of Aripiprazole by Self-Nanoemulsifying Drug Delivery Systems

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Abstract

Aim: The aim of the present study was to develop a self-nanoemulsifying drug delivery system (SNEDDS) for the oral delivery of aripiprazole (APZ), an antipsychotic drug used in the treatment of schizophrenia. Objectives: In this investigation, attempts were made to enhance the aqueous solubility of APZ through SNEDDS and to assess its effect on oral bioavailability (BA) in rabbit. Materials and Methods: Self-emulsifying drug delivery systems of APZ were formulated with Anise essential oil as oil phase, Gelucire 44/14 as surfactant, and Transcutol HP as cosurfactant after screening various vehicles. Drug-excipient interactions were studied by Fourier transform infrared analysis. The formulations were evaluated for self-emulsifying ability, clarity, and stability of their aqueous dispersion after 48 h, and phase diagram was constructed to optimize the system. Selected formulations were characterized in terms of droplet size distribution, zeta potential, and cloud point and subjected to in vitro drug release studies. The BA of optimized formulation was assessed in Rabbits. Results and Discussion: The formulation was optimized by considering smaller droplet size, higher zeta potential, and faster rate of drug release and found to be robust to different pH media and dilution volumes and remained stable after three freeze-thaw cycles and stored at 4°C and 25°C for at least 3 months without showing significant change in droplet size. The pharmacokinetic study in rabbits showed that SNEDDS has significantly increased the area under the curve. Conclusion: SNEDDS can be effective oral dosage form for enhancing aqueous solubility and thereby improving oral BA of poorly water-soluble drug, APZ.

Key words: Anise essential oil, aqueous solubility, aripiprazole, bioavailability, Gelucire 44/14, self-nanoemulsifying drug delivery system, Transcutol HP

INTRODUCTION

Simplicity, patient convenience and compliance, accurate dosage, and low cost of production make the oral route the preferred means for the administration of most drugs.¹ A prerequisite for oral absorption is that the drug must present in solubilized state before passage across the gastrointestinal (GI) membrane. There are various pharmaceutical and physiological factors which affect the GI absorption as well as bioavailability (BA) of the drugs.² The reasons which contribute to poor oral BA include less aqueous solubility, inadequate lipophilicity, GI degradation of the drug, presystemic metabolism, and P-glycoprotein efflux of some drugs.³,⁴ Although continuous attempts are undertaken to minimize the solubility problems, approximately 40% of currently marketed immediate-release oral drugs⁵ and up to 75% of compounds currently under development have been categorized to be poorly water soluble (<100 µg/mL).⁶,⁷

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In the current years, Self-nanoemulsifying drug delivery systems (SNEDDSs) have been considered as one of the preferred approaches to enhance the oral BA of drugs that are poorly aqueous soluble and are highly metabolized. SNEDDSs are defined as the isotropic mixtures of oil, surface active agents, and cosurfactant in which a particular drug is present in dissolved state and such system rapidly form fine oil-in-water nanoemulsions when introduced into aqueous medium under mild agitation.[9] The conventional SNEDDSs include a relatively large amount of surfactants, which may induce GI irritation and side effects.[9] To achieve a safe and efficient delivery system for the poor oral BA drugs, we have designed a novel SNEDDS with high proportion of anise oil, an essential oil as carrier for lipophilic drugs.

Aripiprazole (APZ) is an atypical antipsychotic drug used in the treatment of schizophrenia as well as mania and bipolar illness. It is practically insoluble in water, and as per the biopharmaceutical classification (BCS) system, APZ has poor solubility and high permeability (BCS Class II drug).[10] Therefore, the aim of the present study was to develop, characterize, and evaluate SNEDDS for oral delivery of APZ to improve its solubility as well as dissolution rate which, in turn, enhances the BA. The objectives of the present study were to develop and characterize the optimized formulation of SNEDDS containing APZ and to assess its BA compared with a prepared APZ suspension in rabbit. Mean particle size of nanoemulsion was conducted by dynamic light scattering (DLS). The in vitro release profiles of APZ from SNEDDS and the prepared APZ suspension were compared.

MATERIALS AND METHODS

Materials

APZ was received as a gift sample from Cadila Pharmaceutical Ltd. (Ahmedabad, India). Gelucire 44/14 (Lauroyl Polyoxy-32 glycerides) and Transcutol HP (Diethylene glycol monoethyl ether) were kindly provided by Gattefosse India Pvt., Ltd. (Mumbai, India). Anise oil, cinnamon oil, and lemon essential oil were purchased from Genuine Pharmaceutical Ltd. (Ahmedabad, India). Oleic acid ((9Z)-Octadec-9-enoicacid), polyethylene glycol 400, and propylene glycol were purchased from Molychem (Mumbai, India). Tween (R) 80 (Polyoxyethylene (20) sorbitan monooleate) and olive oil were purchased from Loba Chemie Pvt., Ltd. (Mumbai, India). Glycerol was purchased from Sisco Research Laboratory (Mumbai, India), Cremophor RH40 and dialysis membrane (DM-50) were purchased from HiMedia (Mumbai, India). All the excipients and reagents were of analytical grade and double distilled water was freshly prepared whenever required throughout the study. For pharmacokinetic study, New Zealand white rabbits were obtained from Sanzyme Bioanalytical Laboratory, Hyderabad (Regd. No.:1837/PO/ RcBT/S/15/CPCSEA).

Methods

Solubility study

Solubility studies for drug in different vehicles were carried by placing an excess amount of APZ in screw-capped vials containing 2 ml of vehicle. To facilitate the solubilization, the suspensions were heated on a water bath at 40°C and then stirred using vortex mixer. The suspensions were continuously agitated on a water bath shaker for 48 h at ambient temperature until equilibrium was reached. Then, the samples were centrifuged at 3000 rpm for 15 min and the supernatant was taken, filtered through membrane filter (0.45 µm, 13 mm, Whatman, USA). The filtrates were suitably diluted with methanol and analyzed by ultraviolet (UV)-visible spectrophotometer (Shimadzu, Japan) for the dissolved drug at 255 nm.[11]

Surfactant and oil miscibility

The oil and surfactant in the ratio of 1:1 were shaken at 40°C in 5 ml transparent glass vials. The miscibility was monitored optically and considered to be good when the mixture was transparent.

Fourier-transform infrared (FTIR) Spectroscopy

To investigate any possible interaction between the drug and utilized excipients, FTIR spectroscopy was used.[12] The IR spectra of pure drug and the self-emulsifying drug delivery systems (SEDDSs) were carried out using Bruker Vertex 70 FT-IR spectrometer (Bruker, USA). Sample preparation includes mixing a small quantity of the sample with Nujol and was placed in the FTIR sample holder. The IR spectrum was recorded from the regions of 4000/cm to 400/cm.

Preparation of SEDDS

A series of SEDDS formulations were prepared with varying ratios of oil (30–70%), surfactant (20–69%), and cosurfactant (4–27%) as shown in Table 1. The surfactant and cosurfactant (S/CoS) were used at the ratio of 2:1, 4:1, and 6:1. A single dose of APZ (20 mg/ml) was incorporated in all formulations. The formulations were developed by dissolving the drug in oil followed by the addition of surfactant previously heated to 50°C and cosurfactant in a glass vial. The resultant mixtures were stirred continuously by vortex mixing and heated at 50°C to obtain a homogeneous isotropic mixture. The SEDDS formulations were stored at ambient temperature until further use.

Construction of ternary phase diagrams

Ternary phase diagrams of the selected oils, surfactants, and cosurfactants at various proportions were constructed to identify the self-emulsification regions. All the formulations were investigated with various proportions of oil, surfactant, and cosurfactant for each system. All the formulations were observed visually immediately for spontaneity of emulsification, clarity, phase separation, and precipitation.
of drug and excipients.[13] Briefly, 0.5 ml formulations were added drop by drop to 500 ml enzyme-free simulated gastric fluid (SGF) (pH 1.2) at 37.0 ± 0.5°C; the mixtures were gently stirred with a magnetic bar at 100 rpm to simulate the GI wriggle. The resultant emulsions were stored for 48 h at ambient temperature and observed for clarity, coalescence of droplets, phase separation, and drug precipitation. Emulsions showing phase separation, cracking, and coalescence of oil droplets were judged as unstable emulsions. All the studies were repeated 3 times with and without drug with similar observations made between repeats. The mixtures were considered well dispersed when the formulation spread completely, and stop until the homogeneous emulsion was formulated. The appearance of emulsions was monitored and categorized as clear, translucence, and cloudy. The in vitro performance of the formulations was visually assessed using the grading system as discussed by Khoo et al.[14]

### Droplet size and zeta (ζ)-potential measurements

The mean droplet size (z average), polydispersity index (PDI), and ζ potential of stable formulations were determined at 25°C with a Zetasizer Nano-ZS DLS apparatus (Malvern Instruments, UK). Each formulation was diluted with filtered (0.45 μm, Millipore) double distilled water before analysis. Size analysis was carried at 25°C with an angle of detection of 90°.

### Effect of pH and robustness to dilution

Formulations were subjected to 50-, 100-, 1000-, and 3000-fold dilution with enzyme-free SGF (pH 1.2), enzyme-free simulated intestinal fluid (SIF) (pH 6.8), and distilled water. The resultant diluted emulsions were observed for any physical changes such as coalescence of droplets, phase separation, or precipitation of drugs after 24 h storage.[15]

### Formulation stability

Selected APZ-loaded formulations underwent three consecutive heating-cooling cycles to assess their stability.[16] Each cycle consisted of freezing the formulation at 4°C for 24 h in the refrigerator, followed by heating at 45°C for 48 h in an incubator. The droplet size, PDI, and ζ potential of the emulsions were determined after each cycle, and moreover, every month on formulations stored at 4°C and 25°C for up to 3 months.

### Cloud point measurement

The cloud point measurement was carried out for the stable formulations. The formulation was diluted 100 times with distilled water and kept in a water bath which was maintained at a temperature of 25°C with gradual increase of temperature at a rate of 5°C/min, and the corresponding cloud point temperatures were read at the first sign of turbidity by visual observation.[17]

### In vitro drug release studies

Drug release experiments were conducted using a modified dialysis method.[18] Initially, the DM tubing was soaked in the release medium for 12 h at room temperature which was treated at 40°C before start of experiment. The diluted SNEDDS formulation (equivalent to 20 mg APZ) and 1 ml APZ suspension (20 mg APZ in SGF pH 1.2 as the control) were placed in dialysis tubing and clamped on both sides. The secured dialysis tube was tied to paddle of the apparatus.

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### Table 1: Composition of SEDDS formulations of aripiprazole (% v/v)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Anise oil (57.6)</th>
<th>Gelucire 44/14 (26.6)</th>
<th>Transcutol HP (15.8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF1</td>
<td>20</td>
<td>53.3</td>
<td>26.6</td>
</tr>
<tr>
<td>AF2</td>
<td>20</td>
<td>64</td>
<td>16</td>
</tr>
<tr>
<td>AF3</td>
<td>20</td>
<td>68.5</td>
<td>11.4</td>
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<tr>
<td>AF4</td>
<td>30</td>
<td>46.6</td>
<td>23.3</td>
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<td>AF5</td>
<td>30</td>
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<td>AF7</td>
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<td>AF8</td>
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<td>AF9</td>
<td>40</td>
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<td>8.5</td>
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<td>16.6</td>
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<tr>
<td>AF11</td>
<td>50</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>AF12</td>
<td>50</td>
<td>42.6</td>
<td>7.4</td>
</tr>
<tr>
<td>AF13</td>
<td>60</td>
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<td>13.4</td>
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<td>20</td>
<td>10</td>
</tr>
<tr>
<td>AF17</td>
<td>70</td>
<td>24</td>
<td>6</td>
</tr>
<tr>
<td>AF18</td>
<td>70</td>
<td>25.7</td>
<td>4.3</td>
</tr>
</tbody>
</table>

SEDDSs: Self-emulsifying drug delivery systems
and allowed to rotate freely in the dissolution vessel of USP Type-II dissolution apparatus (Electrolab Dissolution Tester (USP) TDT-06L, Mumbai, India) containing 500 ml of enzyme-free SGF (pH 1.2) at 37±0.5°C and stirred at 50 rpm. An aliquot of 5 ml was withdrawn at predetermined time intervals and filtered through 0.45 μm filter. The withdrawn volume was replenished immediately with same volume of fresh medium to keep total volume constant and maintain sink conditions. The concentration of APZ in the filtrate was analyzed using UV spectrophotometer at 255 nm. The blank SEDDS without drug was carried out similarly and used as a reference to circumvent interference from the formulation components, if any. The mean of at least three determinations was used to calculate the drug release.

Pharmacokinetic studies

In vivo studies were carried out as per the guidelines of the Institutional Animal Ethics Committee (Regd. No. IAEC/GIP-1287/SKS-F/Approved/10/2017-18). New Zealand white rabbits (1.8–2.0 kg) of either sex were housed under standard conditions of temperature, relative humidity, and light. Unless otherwise specified, food and water were given ad libitum. All animals were separated into two groups (Group-I and Group-II), with six animals in each group and fasted for 24 h. The APZ (1 mg/kg) pure drug in aqueous suspension in 0.5% sodium carboxymethyl cellulose for Group-I animals and optimized SNEDDS formulation (equivalent to 1 mg/kg APZ) for Group-II animals will be administered orally with the help of oral feeding needle. Water will be given ad libitum during fasting and throughout the experiment. After drug administration, 1 ml of blood sample was collected from marginal ear vein at time intervals of 0, 0.5, 1, 1.5, 2, 3, 4, and 6 h in the precoated EDTA tubes. The samples were centrifuged at 3000 rpm for 15 min and the separated plasma samples were stored at refrigerated conditions (2–8°C) until analysis. APZ contents of the plasma samples were determined by HPLC method.

Estimation of Pharmacokinetic Parameters

The pharmacokinetic parameters for drug in control and optimized SEDD formulation following oral administration were determined from plasma concentration data. Various pharmacokinetic parameters such as peak plasma concentration (C_{max}), time of peak plasma concentration (t_{max}), and area under the curve (AUC) were calculated in each case using the data. The total area under the concentration-time curve (AUC) from time 0 to 8 h was be calculated by the trapezoidal rule method. The maximal concentration (C_{max}) and the time to maximal concentration (t_{max}) were obtained directly by observation. The relative BA of SNEDDS form to the control was calculated using the following equation.

\[
\% \text{ Relative B.A.} = \frac{\text{AUC}_{\text{test}}}{\text{AUC}_{\text{Reference}}} \times \frac{\text{Dose}_{\text{reference}}}{\text{Dose}_{\text{test}}} \times 100
\]

The pharmacokinetic parameters will be performed by non-compartmental analysis. All values are expressed as the mean ± standard deviation.

Statistical treatment of the data

The pharmacokinetic data of AF12 SNEDDS and reference formulations were compared by the Student’s t-test. P < 0.05 was considered as statistically significant.

RESULTS AND DISCUSSION

Solubility studies

The drug loading capacity of the SEDDS formulations depends on the solubility of APZ in the various vehicles of the system, which was determined by solubility studies. The results are presented in Figure 1. Among the four oils that have been tested, APZ is highly soluble in Anise essential oil (about 255.87 ± 8.13 mg/ml), which is better than lemon essential oil (77.15 ± 6.29 mg/ml), olive oil (28.09 ± 2.51 mg/ml), and oleic acid (23.62 ± 2.45 mg/ml). Surfactant has a pivotal role in stabilizing nanoemulsions, its nature and amount determining droplet size and stability. Non-ionic surfactants are usually preferred due to their lower toxicity and higher stability to the effect of pH and ionic strength than ionic and amphiphilic surfactants. The hydrophilic-lipophilic balance (HLB) is a measure of the degree to which a substance is hydrophilic or lipophilic. A HLB value of 20 defines a fully hydrophilic molecule, while a value of 0 defines a lipophilic one. The stability of emulsions depends also on the ratio between the high HLB and low HLB surfactant amounts. As shown in Figure 1, among all the investigated surfactants, APZ exhibited quite higher solubility in Gelucire 44/14 (HLB 14), 94.42 ± 6.72 mg/ml than Cremophor RH40 (HLB 15), 29.22 ± 2.64 mg/ml; Tween 80 (HLB 15), 13.67 ± 2.17 mg/ml and that have been selected for further investigations. The solubility of APZ in different cosurfactants was investigated and a higher solubility was found in Transcutol HP (72.28 ± 2.86 mg/ml) than propylene glycol (8.51 ± 0.75 mg/ml); polyethylene glycol 400 (7.27 ± 1.00 mg/ml) and glycerol (5.22 ± 0.94 mg/ml). Hence, Transcutol...
HP was selected as cosurfactant which helps in further lowering of interfacial tension. Based on the solubility results, the SEDDS formulations were developed employing varying concentrations of anise oil (20–70%), Gelucire 44/14 (20–69%), and Transcutol HP (4–27%).

FTIR study

The FTIR spectra for APZ and its SEDDS are shown in Figures 2 and 3. FTIR spectra of APZ showed characteristic peaks of N-H stretching at 3472/cm, aromatic C-H stretching at 3066/cm, aliphatic C-H stretching at 2950/cm, C=O stretching at 1686/cm, and C-Cl stretching at 1130/cm. The FTIR spectra of SEDDS also showed all these characteristic peaks with minor shifts. These results from FTIR spectral analysis indicated that there was no chemical interaction between drug and excipients used in the formulation.

Ternary phase diagram

A ternary phase diagram was investigated for the prepared formulations. Before the construction of ternary phase diagrams, the miscibility between surfactants and oils was investigated to select the best components. The mixture of surfactant Gelucire 44/14 and Anise essential oil resulted in clear solutions. Formation of emulsion systems [the blue area in Figure 4] was observed at ambient temperature. Ternary phase behavior investigations help to choose the proper concentration of excipients, that is, oil proportion and optimum S/CoS ratio in the formulation to produce emulsions with good stability.[24] As a fact, all surfactants are potentially irritant or are poorly tolerated,[25] so large amounts of surfactants may cause irritation in the GI tract;[26] systems which contain a higher proportion of essential oil should be preferred. Since the free energy required to form an emulsion is very low, due to surfactant which reduces the interfacial tension, the formation is thermodynamically spontaneous. Surfactants also provide a mechanical barrier to coalescence.[27] After observing clarity, stability after 48 h, it was noted that all formulations with S/CoS ratio of 6:1 except AF18, that is, AF3, AF6, AF9, AF12, and AF15 produced stable emulsions, whereas the resultant emulsions of formulations with S/CoS ratio of 2:1 showed phase separation and precipitation. Among the S/CoS ratio of 4:1, formulations AF2, AF5, and AF8 also produce stable emulsions. The reason for this may be due to water solubility of Transcutol HP and its tendency to redistribute between aqueous phase and emulsion-water interface, leading to loss of solvent capacity resulting in unstable emulsion. These results indicated that the amount of Transcutol HP was inversely proportional to emulsion stability.

Self-emulsification efficiency and appearance

The efficiency of self-emulsification could be estimated by determining the rate of emulsification. The results of the rate of emulsification are shown in Table 2. The results suggest that the formulations up to 50% oil content showed the emulsification time of <60 s. However, with increase of oil proportion over 50–70%, the emulsification time was increased to >80 s. These visual observations indicated that higher the proportion of surfactant system, greater the spontaneity of emulsification. This may be due to excessive penetration of aqueous phase into the oil phase causing very large interfacial disruption and expulsion of droplets into the bulk aqueous phase.[28] SNEDDSs that passed this test in Grades A and B were selected for further evaluation, as Grades A and B formulations will remain as SNEDDS when dispersed in GI fluids. All other SNEDDSs that were falling in Grades C, D, and E were discarded for further evaluation.
Droplet size and zeta (ζ) potential

Droplet size, PDI, and ζ potential of the optimized SNEDDS in SGA with (20 mg/ml) and without APZ are listed in Table 3. In agreement with Patil et al.,[29] a slight increase in droplet size is observed for the APZ-loaded SNEDDS. This can be attributed to the preferential dissolution of the drug in the interfacial film (formed by the surfactant and cosurfactant) that increases the interfacial tension. Moreover, the addition of the drug could induce surfactant aggregation, thus reducing its efficiency. The PDI values are <0.5, which indicates that the droplets are uniform in size. The ζ potential is correlated to the electrostatic repulsion and aggregation of the droplets. High positive or negative ζ-potential values (higher electrostatic repulsive forces) arrest coalescence, thus enabling stability of the emulsions.[30,31] The negative charges are due to the presence of free fatty acids in the surfactant.[11,20] The droplet size of all the optimized formulations except AF15 is <100 nm, suggesting SNEDD formulations. Again among SNEDDS, the formulations AF9 and AF12 incorporate high proportions of oil as compared to conventional SNEDD formulations where the later is prepared by incorporating large amount of surfactant or surfactant-cosurfactant mixture (>70%). The droplet size of AF12 with APZ was found to

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Without drug</th>
<th>With drug (20 mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Droplet size±SD (nm)</td>
<td>PDI</td>
</tr>
<tr>
<td>AF2</td>
<td>51.49±5.12</td>
<td>0.183</td>
</tr>
<tr>
<td>AF3</td>
<td>45.17±4.38</td>
<td>0.128</td>
</tr>
<tr>
<td>AF5</td>
<td>46.49±5.12</td>
<td>0.183</td>
</tr>
<tr>
<td>AF6</td>
<td>28.17±4.38</td>
<td>0.228</td>
</tr>
<tr>
<td>AF8</td>
<td>39.86±3.24</td>
<td>0.271</td>
</tr>
<tr>
<td>AF9</td>
<td>27.71±3.55</td>
<td>0.290</td>
</tr>
<tr>
<td>AF12</td>
<td>29.67±3.85</td>
<td>0.322</td>
</tr>
<tr>
<td>AF15</td>
<td>145.35±3.32</td>
<td>0.352</td>
</tr>
</tbody>
</table>

PDI: Polydispersity index, SNEDDS: Self-nanoemulsifying drug delivery system, SD: Standard deviation
be 32.55 ± 8.52 nm [Figure 5] with PDI of 0.301 and is comparable to the droplet size of AF9 (30.58 ± 5.38 nm). The zeta potential of the emulsion developed by AF12 was found to be −15.4 ± 3.8 mV [Figure 6] which is greater than that developed by AF9 (−10.5 ± 4.9 nm), suggesting that AF12 is more physically stable than AF9. The conductivity of the emulsion was 0.0751 ± 0.007 ms/cm, which means the emulsion was fine oil in water (conductivity >10 μs/cm).[19]

**Effect of pH and robustness to dilution**

The stable SNEDDS formulations exposed to different pH media such as enzyme-free SGF (pH 1.2), enzyme-free SIF (pH 6.8), and distilled water to mimic the in vivo conditions revealed no precipitation or phase separation indicating all the formulations were found to be robust toward different pH conditions [Figure 7]. However, the formulations were robust over wider degree of dilution without any signs of drug precipitation and phase separation.

**Formulation stability**

The stability of AF12, after three cooling and heating cycles, is summarized in Table 4. The droplet size increased with no significant changes of the ζ potential after three cooling and heating cycles. Moreover, the formulation did not exhibit any drug precipitation or phase separation during the whole process. No marked difference of droplet size was observed for formulations stored at 4°C or 25°C [Table 5]. The above findings indicated that this APZ-loaded formulation is thermodynamically stable.

**Cloud point measurement**

The cloud point is the temperature above which the clarity of formulation turns to cloudiness. This is due to drug precipitation and phase separation of emulsion. Since both the drug solubilization and stability of emulsion decrease with phase separation, cloud point should be preferably >37°C. The cloud point temperatures of different formulations determined were in the range of 62–76°C. The reason for higher cloud point temperature may be attributed to solubility of drug in oil and surfactant system, optimized ratio of S/CoS and/or surfactants with higher HLB values. This infers good thermal stability of all the tested formulations.

**In vitro drug release study**

To facilitate the real drug release pattern, the dialysis bag method was utilized in drug release studies. The drug release from SNEDDS was significantly greater than that of the APZ suspension. In 2 h, all the SNEDDS released approximately 80% of drug, with respect to 32% of the APZ suspension. All the SNEDDS released almost all drugs in 4 h, with just a small difference among the different SNEDDSs that are consistent with the droplet sizes. In addition, the release from SNEDDS was faster, further supporting the hypothesis that nanoscale emulsions can improve the release of lipophilic drugs. The drug release pattern of SNEDDS shown in Figure 8 reveals that the highest drug release was observed with AF9 and AF12 formulation after 60 min that could be due to proper compromise between proportions of oil and surfactant in the system. However, the high surfactant proportion is usually concomitant with a higher probability of surfactant migration into surrounding aqueous media on dispersion which is supposed to form micelles that trap free drug inside, with subsequent hindrance in drug release.[25] The drug release pattern from AF9 to AF12 formulations followed the first order up to 1 hr. Between the formulations AF9 and AF12 where the drug release profiles are almost similar, the later can be opted as superior because AF12 incorporates high proportions of oil (50% w/w) and low surfactant (43% w/w) compared to AF9 which incorporates 40% w/w of oil and 51.4% w/w of surfactant. Another reason can be attributed to the use of low concentration of surfactant is that the inherent toxic effect at higher concentration.

**Pharmacokinetic studies**

The plasma concentration versus time profiles of APZ in
rabbits for SNEDDS and APZ suspension following oral administration are presented in Figure 9. The pharmacokinetic parameters of APZ were computed as described in section 2.2.6.8 and tabulated in Table 6. Results showed that the $C_{\text{max}}$
and AUC\(_{(0-8h)}\) of APZ in SNEDDS increased by 2.5-fold and 1.7-fold, respectively, compared to the APZ suspension. In addition, the APZ in SNEDDS was absorbed more rapidly and reached its peak concentration faster (\(P < 0.05\)).

**CONCLUSION**

In the present study, a novel SNEDDS was successfully designed as a stable, high essential oil ratio (50%) and high drug-loaded (approximate 20%) formulation for the solubility, and dissolution rate enhancement of highly lipophilic drug, APZ. The formulation composition and pH of the emulsifying medium significantly impacted the droplet size. The stability study confirmed that the SNEDDS formulations could withstand various storage conditions with excellent stability. The *in vitro* drug release study demonstrated that the release from SNEDDS was more efficient when compared with the drug suspension. Under these circumstances, the present SNEDDS would be a promising novel system to improve the lipophilic drug’s dissolution rate and potentially the BA.

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