Bioavailability Amelioration of Zaleplon by developing self emulsifying drug delivery systems.

Abstract:
The goal of the current study is to create zaleplon-loaded self-emulsifying drug delivery systems (SEDDS) utilising different ratios of the lipid, Phosal® 53 MCT, surfactant, Tween 80, and cosurfactant Gelucire 44/14. With a droplet size of 289 ± 5 nm and a charge of +13.9 ± 1.5 mV, the preparation consisting of Phosal, Tween 80, and Gelucire 44/14 at levels of 80%, 12%, and 8% correspondingly was shown to be thermodynamically stable. The optimised formulation's dispersion parameters, such as particle size, viscosity, and pH, were also tested. Diffusion experiments demonstrated that the majority of the medication is encapsulated in the emulsion, resulting in the greatest absorption capability. The better in vitro dissolving behaviour of zaleplon from SEDDS over control was found, indicating that SEDDS has a greater ability to hold zaleplon in soluble state. Ex vivo investigations revealed a 3.65-fold increase in the amount of permeation as SEDDS as compared to zaleplon alone in pure state. SEDDS also increased bioavailability by 2.84-fold as compared to pure zaleplon solution in in vivo experiments. The preceding SEDDS data demonstrate SEDDS's capabilities as acceptable carriers for enhancing zaleplon oral bioavailability.

Keywords: Zaleplon, Phosal 53 MCT, Gelucire 44/14, Self emulsifying drug delivery systems, Bioavailability.

1.Introduction:

Insomnia is the most frequent sleeping condition in today's technology society, and it largely impacts a person's daily routine. [1,2]. This can happen alone or in conjunction with any of the psychiatric illnesses. [3]. Benzodiazepines have been the standard therapy for insomnia due to their demonstrated safety and effectiveness research. [4]. Benzodiazepines, regardless of their safety and efficacy, have been related to a number of significant adverse effects, including hangovers and rebound sleeplessness. [5]. We are employing Zaleplon, a novel family of medications known as non-benzodiazepine hypnotics, often known as Z drugs, in the current investigation [6]. Zaleplon is a pyrazolopyrimidine medication that operates on the gamma aminobutyric acid type A (GABAA) receptors in the brain. [7].

Because of its limited water solubility and dissolving rate limitation, zaleplon has a reported 30% bioavailability. Lipid carrier systems will be one of the most promising strategies for overcoming the problem of low bioavailability [8]. Although SEDDS is the most common and commercially accessible approach, its main disadvantage is the usage of a large amounts of surfactants, which may induce not only recrystallization but also precipitation of medication over time, which may cause in vivo GI discomfort. [9]. To prevent this, lipid excipients can be used to develop self-emulsifying drug delivery systems [10]. As a result, increased zaleplon bioavailability requires the development of novel lipid carriers that can tolerate dispersion, dilution, and digestion in the gastro-intestinal tract.

2.Materials:

Zaleplon was procured from Symed Labs Pvt Ltd, Tween 80 was purchased from Merck Pvt Ltd. Gelucire44/14, labrasol, Labrafil M 1944 CS, Transcutol P, Labrafil M 2125 CS, Capryol 90, Capmul PG8NF, Capmul MCM C8 were kind gift samples from gattefosse India pvt. Ltd. Phosal® 53 MCT was procured from Lipoid and D-α-tocopherol was ordered from ABITEC pvt Ltd USA.

3.Methodology:

3.1. Solubility screening Studies:

The solubility of zaleplon in different surfactants and co-surfactants was tested by placing excess of medication in a glass previously filled with 2 grams of vehicle. The mixture was then put in a water bath and heated for 2 minutes at 40 degrees Celsius to help in solubilization under vortex. A rotary shaker was used to stir the mixture for two days. The samples were then centrifuged for 15 minutes at 10,000 rpm, and the supernatant was collected. Methanol was added to dilute the solution, and the concentration of zaleplon was measured by HPLC [11].

3.2. Preparation SEDDS:

Phosal® 53 MCT, Tween 80, and Gelucire 44/14 as lipid, surfactant, and cosurfactant respectively were utilized in various blends, and a suitable quantity of each was vortexed. After adding the appropriate amount of Phosal to a vial, the appropriate amount of Tween 80 was added and vortexed.

Gelucire44/14 was melted and added to the previous mixture. Disperse 5mg of zaleplon in each of the following formulations before adding 10 mg of d-α-tocopherol and vortexing the mixture. The resulting mixture is then homogenized with a homogenizer (Heidolph, Diax900) for 10 minutes at 10,000 rpm. [12].

3.3. Characterization of SEDDS:

3.3.1. Visual observations and construction of ternary phase diagram:

The glass vial was filled with lipid (Phosal® 53 MCT), surfactant (Tween80), and co-surfactant (Gelucire44/14) and homogenized by continuous vertexing. After that, the mixture was maintained at room temperature until utilized, and any drug precipitation was tested after 24 hours [13]. With the Tri plot v1-4 programme, a ternary phase diagram was generated, and the optimal self-emulsifying zone was discovered.

3.3.2. Phase separation and appearance:

As previously reported, 300 ml of Simulated gastric fluid (SGF) was placed in a beaker and 100 L of SEDDS was added dropwise with stirring, and observations were made after 4, 6, 8, 12, and 24 hours. [14].

3.3.3. self-emulsification time

As previously reported, 300 ml of Simulated gastric fluid (SGF) was placed in a beaker, and 100 L of SEDDS was added dropwise with stirring, with observations obtained after 4, 6, 8, 12, and 24 hours. [15].

3.4. Thermodynamic stability:

The formulations' thermodynamic stability was examined using two separate processes: centrifugation (to check if there was any phase separation) and the freeze-thaw cycle (to see whether the formulations were stable at different temperatures). Centrifugation of optimized formulations at 10,000 RPM was carried out for about 15 minutes. If no precipitation was discovered after centrifugation, the samples were frozen and thawed for 48 hours at temperatures ranging from -21 to +25 degrees Celsius. [16].

3.5. Robustness to dilution

The formulations were diluted with distilled water and simulated stomach juice (pH 1.2) 10, 100, and 1000 times, and any physical changes, such as phase separation or precipitation, were detected. [17].

3.6. Cloud point measurement

The cloud point was found using a method adapted from prior published studies in which the temperature of the water bath in which the sample was placed was progressively elevated and the development of cloudiness was documented [18].

3.7. Properties of SEDDS:

3.7.1. Dispersion properties:

The viscosity of the optimized formulation was measured at 10rpm using a Brookfield programmed

DV-Pro II+ viscometer with spindle S61 (Brookfield Engineering Laboratories, Inc., USA). The particle size of the SEDDS formulation was determined using a stage microscope, and the pH of the SEDDS optimized formulation was measured using a Digital pH meter (Systronics 802) [19].

3.7.2. Emulsion properties:

3.7.2.1. Globule size and zeta potential:

The Smoluchowski equation was utilized to calculate the average size and size distribution of produced globules photon correlation spectroscopy utilising zetasizer, as in previous studies [20].

$$\zeta = U_E \, \eta / \varepsilon$$

where $'\zeta'$is zeta potential, $'U_E'$is electrophoretic mobility, $'\eta'$is viscosity of the medium and $'\varepsilon'$is dielectric constant.

3.7.2.2. Morphology of the particles (TEM analysis):

Transmission electron microscopy was used to examine the morphology of globules generated by optimised SEDDS. On a carbon-coated copper grid, a drop of dispersion was utilised to generate a thin layer. The film was negatively stained with 0.2% w/v sodium phosphotungstate solution before drying on the grid; any surplus solution was drained off using filter paper. Before examining the materials using a transmission electron microscope (Tecnai G2, Jeol-100CX-II, Netherlands), the grid was allowed to dry naturally. [21].

3.8. Permeation studies:

3.8.1. *In vitro* diffusion studies:

According to previous research, the diffusion experiments were carried out utilising an open tube dialysis technique using a UV spectrophotometer at a wavelength of 232 nm [22].

3.8.2. ***In vitro*** **dissolution studies:**

Using HPLC and single dosage filled capsules, the Type II USP (paddle) technique was utilised to determine the mean dissolving time and rate, as well as the cumulative drug quantities, at 15 and 60 minutes (Q15 and Q60, respectively). Dissolution efficiency (DE) was calculated using the trapezoidal method. [23].

3.8.3. *Ex-Vivo* **Permeation Studies:**

Wistar type male rats weighing 180-200 gm were murdered by breathing excess ether, and the ileum was separated and washed with Krebs-Ringer solution before one end of the ileum was tied and the diluted SEDDS emulsion corresponding to 2 mg of zaleplon was and then the other end was likewise closed. Following earlier research, the material was allowed to diffuse through the membrane before being examined using a UV spectrophotometer at 232 nm. The SEDDS are tested against a control having the same quantity of drug dispersion [24].

3.8.4. Permeation Data Analysis:

Time was plotted against the total quantity of medication penetrated (Q) per unit area [25]. The Enhancement ratio (ER) was calculated using the equation below.

$$ER = \frac{\text{Jss of formulation}x}{\text{Jss of control}}$$

3.9. Qualitative analysis:

3.9.1. Fourier transform infrared (FT-IR) spectroscopy

At a resolution of 4 cm^{-1} and a scanning range of 4000-650 cm^{-1}, the infrared spectra of zaleplon and the improved SEDDS formulation were obtained [26].

3.9.2. NMR

The NMR spectra of zaleplon and optimised SEDDS were obtained using the same method as in previous research [27].

3.10. Bioavailability study

3.10.1. Study protocol

Male wistar rats weighing 180-200 g were starved overnight before being divided into two groups of three rats each. The control group received zaleplon oral suspension, whereas the test group received SEDDS (Z5) at a dosage of 10 mg/kg body weight. Blood was drawn from the retro orbital plexus using heparinized capillary tubes, centrifuged, and preserved for future research [28].

3.10.2. Extraction procedure of zaleplon from serum:

As previously documented in studies, the zaleplon-containing serum samples were processed and then treated with specified volumes of methanol and internal standard before being injected into HPLC for quantitative detection [29].

3.10.3. Pharmacokinetic parameters:

The Phoenix programme was utilized to determine the pharmacokinetic properties of SEDDS as well as its relative bioavailability in contrast to a control oral preparation as suspension. [30].

3.11. Statistical analysis

The data was evaluated using Instat GraphPad prism software and the 't' test, as in prior investigations [31].

4.Results and Discussion:

4.1. Solubility studies

The solubility of zaleplon in various oils, surfactants, and co-surfactants was tested, as shown in Figure 1 with the high loading capacity, safety, and rapidity in dispersion formation in mind. [32].

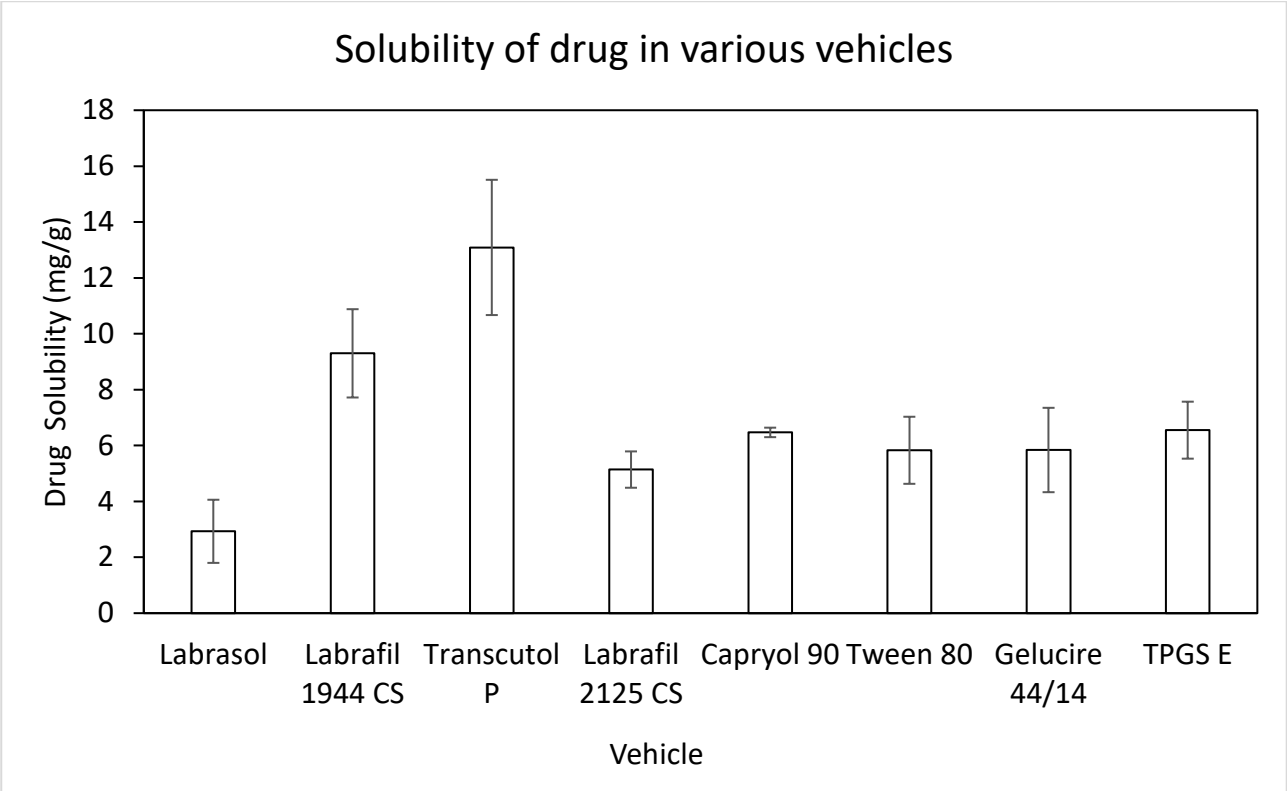

Figure 1. Solubility of zaleplon in different vehicles (surfactants and co surfactants) (mean ±SD, n=3)

4.2. Preparation of SEDDS

All formulations of SEDDS were prepared with different ratios of lipid and Smix (surfactant: co-surfactant) by simple mixing and homogenization method. Formulations were showed in the table 1.

Formulation	Lipid: S_{mix}	Surfactant: co-surfactant (S_{mix})	Drug (mg)	Lipid (mg)	Surfactant (mg)	Co-surfactant (mg)
Z1	2:1	3:2	5	300	90	60
Z2	2:1	4:1	5	300	120	30
Z3	3:1	3:2	5	450	90	60
Z4	3:1	4:1	5	450	120	30
Z5	4:1	3:2	5	600	90	60
Z6	4:1	4:1	5	600	120	30

Table 1: Formulations of SEDDS with different ratios of lipid, surfactant, co surfactant and fixed amount of drug

4.3. SEDDS characterization

4.3.1 Visual observations and construction of phase diagram

For any drug precipitation in formulation, all formulations (Z1-Z6) were visually examined. Except for Z5 and Z6, all other formulations showed drug precipitation. This indicates that as lipid proportion increased, drug precipitation disappeared due to lipid's improved ability to disperse the drug effectively within the formulation vehicle. This demonstrates that increasing the lipid proportion improved drug uniform distribution. Drug aggregation was observed in the formulations Z1, Z2, Z3, and Z4, indicating that Z5 and Z6 are stable and can be processed for further evaluation studies. [33].

Ternary phase diagram:

The appropriate oil-Smix combination was determined by creating a ternary phase diagram, and a better emulsion region with no phase separation appeared. The constituents and percentages of each contributor in the blend influenced not only emulsion stability but also globule size and emulsification time [34].

4.3.2. Phase separation and Appearance:

After standing at room temperature for 24 hours, the Z5 and Z6 formulations showed no phase separation and appeared milky white, indicating their stability. As a result, these formulations were further characterised [35].

4.3.3 Assessment of self-emulsification time:

The increase in lipid proportion was found to increase emulsification time, indicating that the increase in lipid proportion decreases the rate of emulsification, which may be responsible for the prolonged emulsification time. Z1, Z2, Z3, Z4, Z5 and Z6 formulations showed emulsification times of 2min 43sec±1sec, 2min 52sec±3sec, 3min 7sec±1sec, 3min 16sec±4sec, 3min 23sec±3sec and 3min 52sec±2sec respectively. Because the Z5 and Z6 formulations did not exhibit any drug aggregation, they were extended for further characterization [36].

4.3.4. Thermodynamic stability:

Two different processes were used to conduct the thermodynamic analysis. First, Z5, Z6 formulations were centrifuged at 10,000rpm for 15 minutes. The Z6 formulation demonstrated phase separation, whereas the Z5 formulation did not. As a result, the Z5 formulation was subjected to 48-hour freeze-thaw cycles at temperatures ranging from -21 to +25 ° C. There was no evidence of phase separation, indicating its stability [37].

4.3.5. Robustness to dilution

The prepared SEDDS were stable without phase separation after 10-, 100-, or 1000-time dilution with SGF (pH1.2) or distilled water [38].

4.3.6. Cloud point measurement

The cloud points of stable formulations Z5 and Z6 were found to be 72.6±3.42 and 68.1±4.056

respectively indicating the stability of these SEDDS formulations in the GIT temperature [39].

4.4. Properties of SEDDS

4.4.1 Dispersion properties (Viscosity, Particle size and pH)

The dispersion properties of the Z5 formulation were within acceptable ranges exhibiting a particle size of 2.5±0.3 µm, viscosity of 594±5 cPs and a pH of 6.15 ± 0.09 [40].

4.4.2 Emulsion properties

4.4.2.1 Globule size and Zeta potential:

When dispersed in SGF, the Z5 formulation exhibited a positive zeta potential with a poly-dispersibility index of 0.257±0.032, indicating a homogeneous dispersion. The globule size was 289±5 nm and Zeta potential value was found to be +13.9±1.5 mV [41].

4.4.2.2.TEM Analysis:

According to the TEM analysis of the formulation, all formed globules were found spherical in shape and uniform in size, as shown in figure 2. [42].

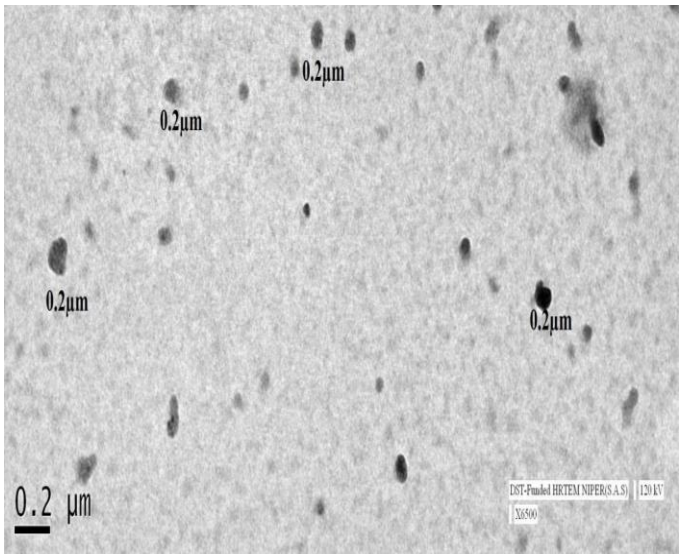

Figure 2: TEM images of globules from SEDDS (Z5)

4.5. Permeation studies:

4.5.1. *In vitro* diffusion studies:

Table 9 shows the permeation of drug and cumulative% drug release of pure drug and SEDDS formulation in in vitro drug release studies. In vitro drug release of pure zaleplon was found to be 54.72% after 24 hours, while Formulation Z5 showed 28.89% after 24 hours. Drug release from SEDDS was lower, indicating maximum drug encapsulation within the formed globules, which leads to complete absorption of the formulation. [43].

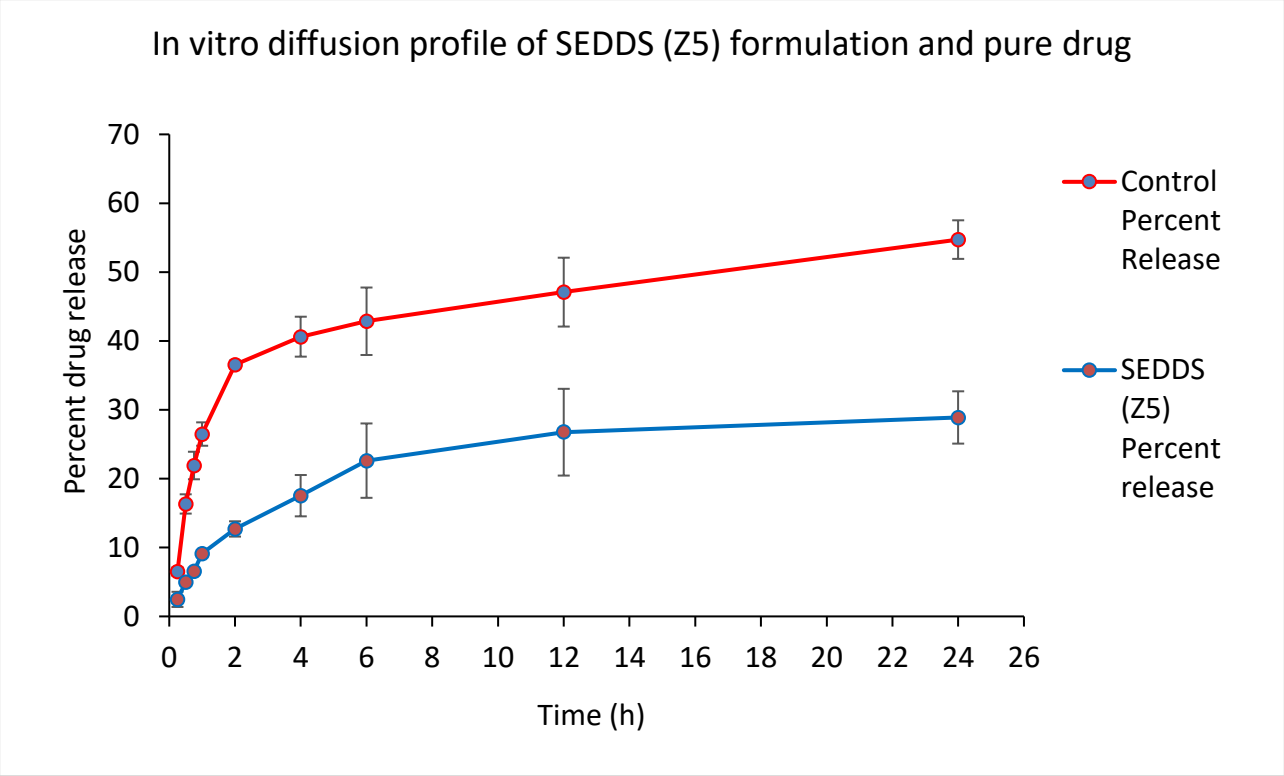

Figure 3: *In vitro* diffusion profile of SEDDS (Z5) formulation and pure drug (mean ± S.D, n=3).

4.5.2. *In vitro* dissolution study:

The drug release rate from SEDDS was 83.57±3.4 % in 1 hour, which was significantly higher than the control (36.84±2.3%) ($p<0.001$). When zaleplon was formulated into SEDDS, its dissolution efficiency improved, as shown in Tables 2. ($P<0.001$). The reason for this significant increase in drug solubility could be due to a massive increase in effective surface area due to the incorporation of surfactants. In comparison to the control, drug dissolution as SEDDS increased by 2.3 fold. [44].

Formulation	Q_{15} (%)	Q_{60} (%)	DE (%)	MDT (min)	MDR
Control	22.20±2.7	36.84±2.3	25.13±1.7	34.76±1.1	0.59±0.08
Z5	44.73±2.2	83.57±3.4***	55.3±2.1***	28.60±1.3	1.23±0.09

Table 2: Dissolution parameters of zaleplon from SEDDS in SGF (pH1.2) (mean ± SD; n=3).
*** indicates significant difference at $p<0.001$ against control

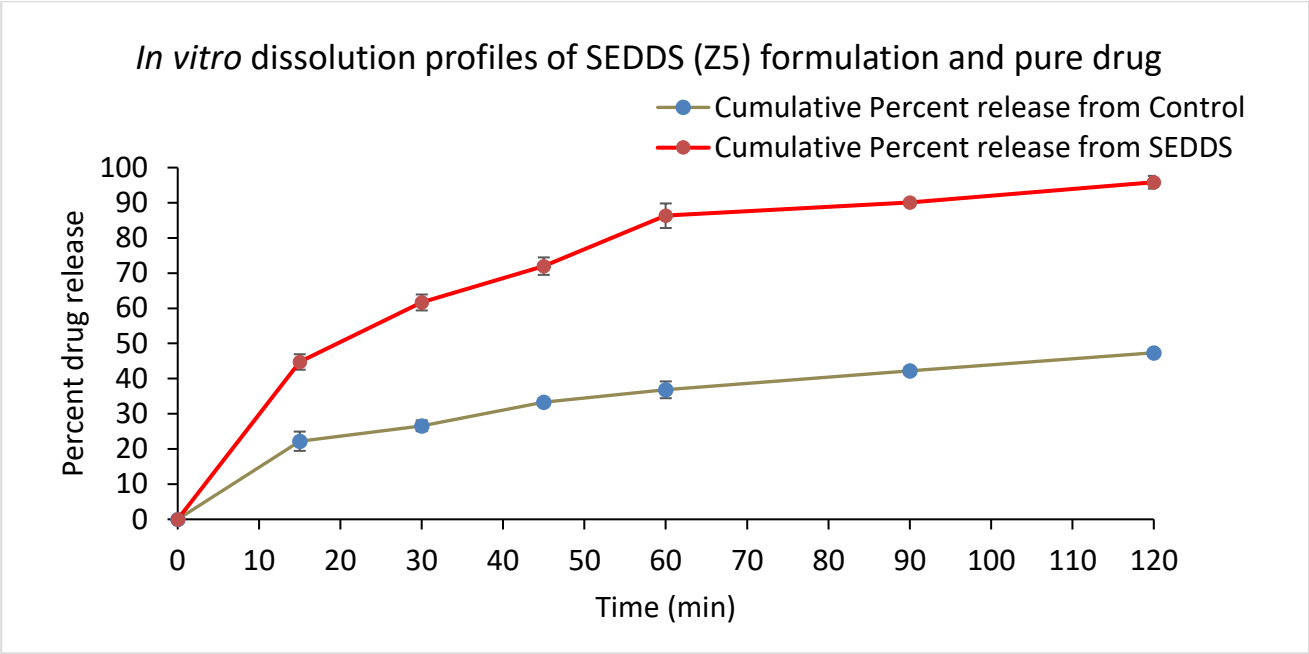

Figure 4: *In vitro* dissolution profiles of SEDDS (Z5) formulation and pure drug (mean ± SD; n=3)

4.5.3. *Ex vivo* permeation study

The effective permeability coefficient in rats (Peffrat) of the control and SEDDS were 7.11 $x10^{-4}$ and 25.98 $x10^{-4}$ cm/sec, respectively, and the enhancement ratio (ER) was 3.65. This could be due to the possibility of SEDDS reusing the gastrointestinal tract's barrier properties, favouring transport across the GIT via a variety of mechanisms. Tween 80 has the ability to modulate membrane fluidity and enhance permeation enhancers, which were even reflected in the obtained results. [45].

4.6. NMR studies

NMR spectra of zaleplon and SEDDS formulation showed in figure 5. The pure drug zaleplon exhibit characteristic peaks at 7.53ppm (C-H aromatic), 1.31ppm (C-H aliphatic), 8.94ppm (C=N), 4.70ppm (C-N), 7.74ppm (C=C aromatic) and intense peak at 2.04ppm was amide carbonyl group respectively. All the peaks of zaleplon were also observed in SEDDS but some of the aromatic peaks intensity was decreased. However, the absence of extra peaks suggests that there was no possible chemical interaction between the drug and other excipients.

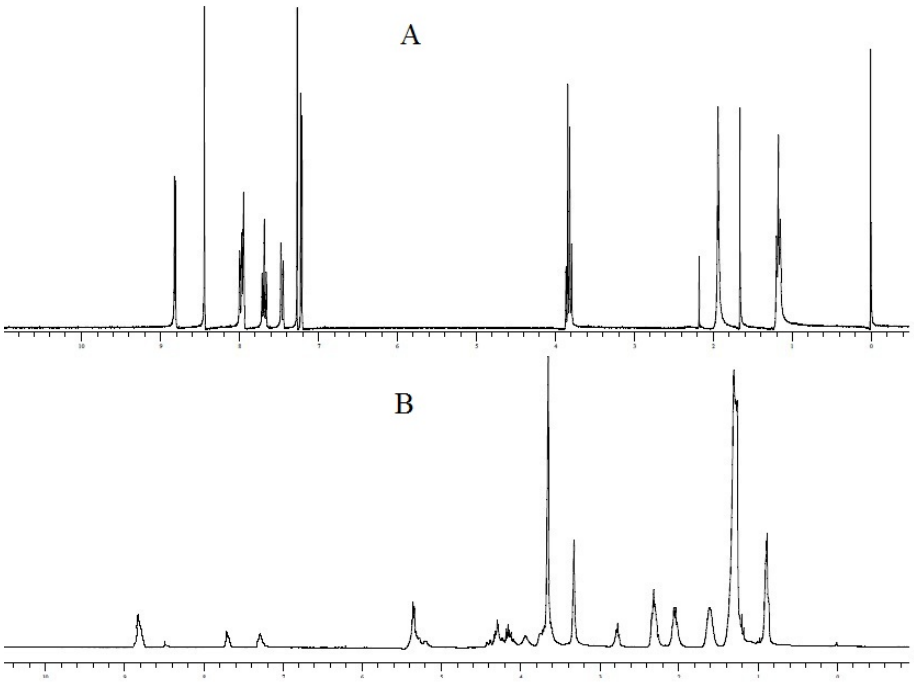

Figure 5: NMR spectra of A) zaleplon and B) SEDDS.

4.7. Bioavailability study

Figure 6 depicts the results of pharmacokinetic studies in rats, and the relevant pharmacokinetic parameters were derived and are represented in Table 3. Longer the Mean residence time (MRT) and prolonged t1/2 of Zaleplon in SEDDS, the more time it takes for elimination. The AUC for orally administered SEEDS was 897.9942.13 ng h mL-1 compared to the control (315.2730.56 ng h mL-1) (p0.001). Based on the outcomes of the study, it was ascertained that SEDDS are a better choice for increasing Zaleplon oral bioavailability [47].

Formulation	**Pharmacokinetic Parameters**					
	C_{max} (ng/ml)	**T_{max} (h)**	**$T_{1/2}$ (h)**	**$AUC_{0-\infty}$ (ng h ml^{-1})**	**$MRT_{0-\infty}$ (h)**	**F**
Control	132.02±17.46	1.5±0.0	1.78±0.21	315.27±30.56	2.74±0.17	-
SEDDS	267.74±23.54**	1.5±0.0	1.88±0.12	897.99±42.13***	3.01±0.25	2.84±0.36

Table 3: Pharmacokinetic parameters of zaleplon in rat serum following oral administration of SEDDS and control oral suspension (mean ± SD, n=3).

- MRT- Mean residence time; AUC - Area under the curve and F- Relative bioavailability

- and* indicates significant difference at p<0.01and p<0.001 respectively against control

- SEDDS represents lipid based self emulsifying drug delivery system

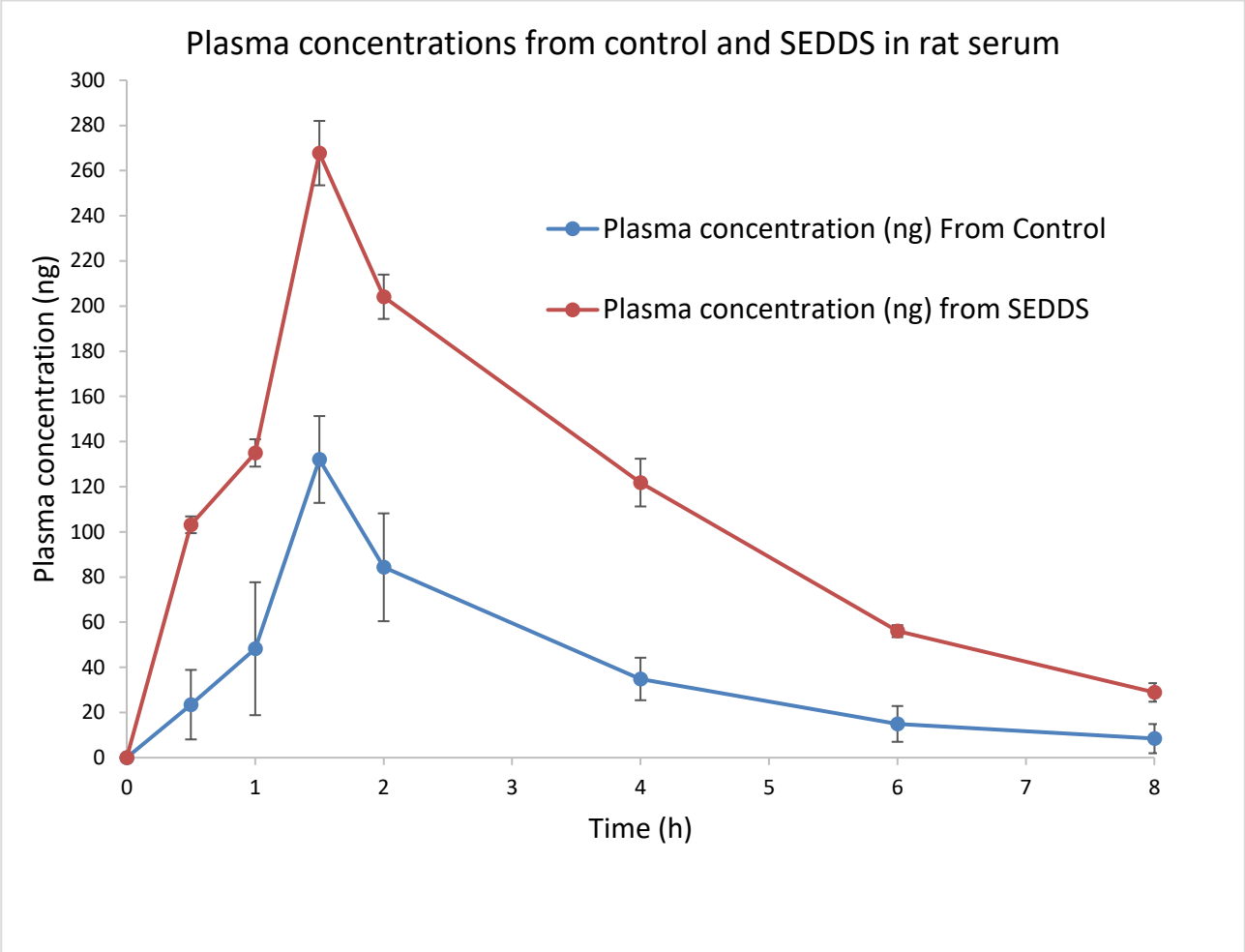

Figure 6: Plasma concentration time profile of zaleplon from control and SEDDS in rat serum (mean ± SD, n=3).

4.8. Stability studies:

The SEDDS formulation was stable even after 3 months with same emulsification time, clarity of emulsion without any phase separation and content uniformity of the drug as showed in table 4.

Time (months)	Emulsification time	Appearance	Content uniformity (% drug remain)
0.5	3min 22sec±2sec	Milky	98.9
1	3min33sec±4sec	Milky	98.17
2	3min36sec±4sec	Milky	97.83
3	3min26sec±1sec	Milky	97.7

Table 4: Stability studies of SEDDS formulation with respective of Emulsification time.

5. Conclusion:

Zaleplon-loaded SEDDS were created by optimizing the concentrations of tween 80, Gelucire 44/14, and Phosal® 53 MCT, yielding stable emulsions at a 1:4 Smix: lipid ratio. Z5 was found to contain a homogenous distribution of 289 nm spherical particles. There was no indication of phase separation after 24 hours, indicating that these formulations were more stable. The optimised formulation had the lowest invitro drug release compared to the pure drug, indicating that the majority of the medicine was encapsulated in the emulsion. Ex vivo permeation tests revealed that SEDDS had a 3.65-fold higher Peff value than pure medicine. The FT-IR spectra indicated that no chemical reactions occurred. NMR spectra confirmed this much further. When compared to the control, the bioavailability of SEDDS (Z5) formulation was increased 2.84 times, indicating that SEDDS have the potential to be regarded as a viable formulation providing improved efficiency and stability.

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