Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 13, (2024)
https://www.jneonatalsurg.com

OPEN ACCESS

Formulation, Optimization, and Characterization of Diclofenac SMEDDS and Incorporation into Self - Micro emulsifying Mouth Dissolving Films

Priyanka D. Borude*[1], Dr. Disha [2], Dr. Sachin V. Kotwal[3]

*[1]Department of Pharmacy, Research Scholar, Shri Jagdishprasad Jhabarmal Tibrewala University (SJJTU), Vidyanagari, Jhunjhunu, 333001, Rajasthan, India.

[2]Department of Pharmacy, Professor, Shri Jagdishprasad Jhabarmal Tibrewala University (SJJTU), Vidyanagari, Jhunjhunu, 333001, Rajasthan, India.

[3]Principal, PDEAS Shankarrao Ursal College of pharmacy, Kharadi, Pune, 411014, Maharashtra, India.

Corresponding Author:

Priyanka D. Borude

Department of Pharmacy, Research Scholar, Shri Jagdishprasad Jhabarmal Tibrewala University, Vidyanagari, (SJJTU) Jhunjhunu, 333001, Rajasthan.

Email id: priyanka.borude20@gmail.com

Cite this paper as: Priyanka D. Borude, Dr. Disha , Dr. Sachin V. Kotwal, (2024) Formulation, Optimization, and Characterization of Diclofenac SMEDDS and Incorporation into Self - Micro emulsifying Mouth Dissolving Films. *Journal of Neonatal Surgery*, 13, 1664-1674.

ABSTRACT

Background: Diclofenac is a potent non-steroidal anti-inflammatory drug (NSAID) with poor water solubility and gastrointestinal (GI) side effects. Conventional oral diclofenac can have delayed onset and cause GI irritation. Self-micro emulsifying drug delivery systems (SMEDDS) improve solubility of hydrophobic drugs, while oral fast-dissolving films enhance convenience and speed of administration. Combining these approaches may yield rapid, efficient diclofenac delivery. Objectives: To formulate and optimize a diclofenac-loaded SMEDDS for improved solubility and absorption, incorporate it into a self-micro emulsifying mouth dissolving film (SMMDF), and evaluate the formulation's in vitro characteristics and in vivo performance. Materials and Methods: Solubility of diclofenac was determined in various oils, surfactants, and co-surfactants to select SMEDDS components. Pseudo-ternary phase diagrams were constructed to identify self-emulsification regions. SMEDDS formulations were prepared and optimized using a mixture design to minimize droplet size. The optimized SMEDDS was characterized for droplet size, polydispersity index (PDI), zeta potential, and self-emulsification time. SMMDFs were prepared by solvent casting of polymer matrices containing the optimized SMEDDS. Films were evaluated for uniformity, mechanical properties, disintegration time, in vitro dissolution, and morphology. An in vivo pharmacokinetic study in rats compared the SMMDF to a conventional diclofenac tablet. Results: The optimized SMEDDS (oil: Capryol 90, surfactant: Tween 80, co-surfactant: Transcutol-HP) had a droplet size ~50 nm, PDI 0.22, and zeta potential –15 mV. SMMDFs were uniform (thickness ~100 µm) with high drug content (>98%) and fast disintegration (~25 s). In vitro, SMMDF released >90% of diclofenac in 5 min versus ~60% from a tablet. In rats, SMMDF showed higher C_max (4.1 vs 2.3 µg/mL) and shorter T_max (0.5 h vs 2 h) than the tablet, with a 1.6-fold increase in AUC, indicating significantly improved bioavailability ($p<0.01$). Conclusions: The diclofenac SMMDF achieved rapid dissolution and enhanced systemic exposure compared to the conventional formulation. This novel combination of SMEDDS with a mouth dissolving film offers a promising strategy for improving the onset and efficacy of poorly soluble drugs like diclofenac while potentially reducing GI side effects.

1. INTRODUCTION

Poor aqueous solubility is a major challenge in oral drug delivery, limiting the absorption and bioavailability of many active pharmaceutical ingredients (APIs) [3]. Lipid-based formulations such as self-emulsifying drug delivery systems (SEDDS/SMEDDS) have emerged as an effective strategy to overcome this limitation [1] [2]. SMEDDS are isotropic mixtures of oils, surfactants, and co-surfactants that spontaneously form fine oil-in-water microemulsions (typically droplet size <100 nm) upon dilution in gastrointestinal fluids [2] [3]. By presenting the drug in a pre-solubilized, nano-droplet form with a large interfacial surface area, SMEDDS can greatly enhance the dissolution rate and extent of absorption of poorly water-soluble drugs [1] [3]. This approach has been successfully applied to improve the oral bioavailability of various hydrophobic compounds in the literature [1] [3].

Oral fast-dissolving dosage forms, such as orodispersible tablets and films, have gained popularity for achieving rapid drug release and ease of administration. Oral thin films or mouth dissolving films (ODFs) are thin, flexible polymer strips that

disintegrate within seconds when placed on the tongue, releasing the drug for oromucosal absorption and/or swallowing [4] [5]. They offer distinct advantages in terms of patient compliance and convenience, especially for pediatric, geriatric, or dysphagic patients who may have difficulty swallowing conventional tablets [5] [6]. ODFs eliminate the need for water intake and can provide a faster onset of action compared to traditional oral solid doses [4] [6]. However, delivering poorly soluble drugs via ODFs is challenging because the drug still needs to dissolve rapidly in minimal saliva volume; without additional solubilization strategies, the dissolution and absorption of such drugs from films can remain suboptimal [5].

Diclofenac is a widely used NSAID for the management of pain and inflammation, but it presents formulation challenges that motivate novel delivery approaches. It is classified as a BCS Class II drug, with high permeability but low water solubility [7]. Orally administered diclofenac (especially the free acid form) can have an erratic or slow dissolution in the GI tract, contributing to delayed onset of action. Moreover, diclofenac is known to cause GI irritation and ulceration with prolonged use [8], largely due to direct contact injury and inhibition of protective prostaglandins in the gastric mucosa. Fast-onset formulations that minimize diclofenac's residence in the stomach could potentially reduce GI side effects and improve patient comfort. Prior studies have explored rapidly dissolving formulations of diclofenac, such as mouth dissolving tablets or films, to expedite analgesic onset [9]. These formulations improved the administration ease and disintegration time, but they did not specifically address the drug's poor solubility, which remained the limiting step for absorption.

In principle, combining a SMEDDS with a mouth dissolving film could yield a formulation that not only disintegrates rapidly in the oral cavity but also presents diclofenac in a solubilized, readily absorbable form. Such a self-microemulsifying mouth dissolving film (SMMDF) would harness the advantages of both technologies to potentially achieve faster and more complete absorption of diclofenac while enhancing patient compliance. To our knowledge, this approach has not been previously reported for diclofenac.

The objective of the present study was to formulate and optimize a SMEDDS for diclofenac and incorporate it into an oral fast-dissolving film, thereby creating an SMMDF. We aimed to characterize the SMEDDS in terms of droplet size, emulsification properties, and stability, and to evaluate the SMMDF for film properties, dissolution performance, and pharmacokinetic behavior in vivo. We hypothesized that the SMMDF would significantly improve the dissolution rate and oral bioavailability of diclofenac compared to a conventional oral tablet.

2. MATERIALS AND METHODS

Materials: Diclofenac (as diclofenac free acid) was obtained as a gift sample from XYZ Pharma. Capryol 90 (propylene glycol monocaprylate) was procured from Gattefossé (France) and used as the lipid (oil) phase. Surfactants Tween 80 (polyoxyethylene 20 sorbitan monooleate) and Cremophor EL (polyoxyl 35 castor oil) were purchased from Sigma-Aldrich. Transcutol-HP (diethylene glycol monoethyl ether) and PEG 400 were obtained as potential co-surfactants. Hydroxypropyl methylcellulose (HPMC E15 LV) was obtained from Colorcon as the film-forming polymer. Glycerol was used as a plasticizer. All other reagents were of analytical grade. Double-distilled water was used for all experiments.

Solubility Studies: Solubility of diclofenac in various vehicles was determined by equilibrium method to identify suitable components for the SMEDDS. Excess diclofenac was added to 2 mL of each selected oil (e.g. Capryol 90, oleic acid, Labrafil® M1944), surfactant (Tween 80, Cremophor EL, Labrasol®), and co-surfactant (Transcutol-HP, PEG 400, propylene glycol) in screw-capped vials. The vials were shaken at 25 °C for 72 h to reach equilibrium, then centrifuged and the supernatant was filtered. The concentration of dissolved diclofenac was analyzed by UV–Vis spectrophotometry at 276 nm (after appropriate dilution in methanol). The solubility (mg/mL) in each vehicle was recorded. Based on these results, the oil with the highest drug solubility, along with a high-HLB surfactant and a compatible co-surfactant that also showed high solubilizing capacity, were selected for SMEDDS formulation.

Construction of Pseudo-ternary Phase Diagrams: Ternary phase diagrams were constructed to identify the regions of microemulsion formation. The selected oil (Capryol 90), surfactant (Tween 80), and co-surfactant (Transcutol-HP) were used. Surfactant and co-surfactant were mixed in fixed ratios (such as 1:1, 2:1, 3:1 w/w) to form surfactant mixtures (S_mix). For each S_mix ratio, a series of formulations were prepared by varying the proportion of oil and S_mix (with oil ranging from 5-30% and S_mix from 70-95% by weight). Each mixture was titrated with water dropwise and visually observed for clarity or turbidity. The point at which the mixture turned from clear/translucent to turbid or phase-separated was noted. Phase diagrams were plotted using CHEMIX software by marking the microemulsion region (clear or transparent mixture) versus biphasic region at different component percentages. These diagrams guided the optimal range of component concentrations for formulating the SMEDDS.

Preparation of SMEDDS Formulations: Based on the phase diagram results, preliminary SMEDDS formulations were prepared by dissolving diclofenac (equivalent to 25 mg per dose) in the oil component, then adding surfactant and co-surfactant. The mixtures were gently heated (40 °C) and vortexed to facilitate drug dissolution and to obtain homogeneous isotropic solutions. A series of formulations were made to explore the effect of varying oil/surfactant/co-surfactant ratios on emulsification performance. An optimization experiment was carried out using a simplex lattice mixture design, with the proportions of oil (X_1), surfactant (X_2), and co-surfactant (X_3) as independent variables. The design included constrained ranges based on the microemulsion region identified (e.g., oil 5–15%, S_mix 85–95%). Formulations at the design

checkpoints were prepared and evaluated for droplet size (Y_1) and initial drug release (Y_2) as responses. A polynomial model was fitted to identify the optimal composition that minimized droplet size and maximized dissolution. The optimized SMEDDS formulation was thus determined and used for subsequent studies.

SMEDDS Characterization: The self-emulsification ability of the optimized formulation was assessed by dilution in aqueous medium. 0.1 mL of SMEDDS was introduced into 100 mL distilled water under gentle stirring (50 rpm) at 37 °C. The time for the formation of a clear microemulsion was recorded (self-emulsification time) and the resulting dispersion was observed for appearance. Droplet size and polydispersity index (PDI) of the diluted SMEDDS were measured by dynamic light scattering using a Malvern Zetasizer at 25 °C. The sample was prepared by diluting 1:100 (v/v) in water. Zeta potential was measured to assess the surface charge on the oil droplets. Each measurement was performed in triplicate. The drug content of the SMEDDS was determined by dissolving a known quantity of formulation in methanol and analyzing by UV spectrophotometry to ensure >98% of the drug was loaded. The optimized SMEDDS was also subjected to a freeze–thaw cycle and centrifugation (10,000 g, 30 min) to evaluate physical stability (checking for phase separation or drug precipitation).

Preparation of SMMDF: Self-microemulsifying mouth dissolving films were prepared by the solvent casting method. The optimized liquid SMEDDS (containing diclofenac equivalent to 25 mg per dose) was incorporated into a film-forming solution containing HPMC E15 as the polymer. HPMC (5% w/v) was dissolved in water with gentle heating to form a viscous solution. Glycerol (20% w/w of polymer) was added as a plasticizer. The SMEDDS was emulsified into the polymer solution under stirring; a fine emulsion was formed as the SMEDDS dispersed uniformly. Menthol (0.1% w/v) and sucralose (0.2% w/v) were added to the mix as flavoring agent and sweetener, respectively, to improve palatability. The resulting mixture (approximately 10 mL) was cast onto a Petri dish (9 cm diameter) and dried at 40 °C for 24 h in a hot air oven. The dried film was carefully peeled and cut into 2×2 cm^2 squares, each containing ~25 mg of diclofenac. Films were stored in a desiccator until use. Plain mouth dissolving films of diclofenac (without SMEDDS, incorporating diclofenac as a fine powder dispersed in the polymer solution) were also prepared as a control for comparison.

Film Evaluation: The SMMDFs were evaluated for various physicomechanical properties. Film thickness was measured at five points per film using a digital micrometer screw gauge. Weight variation was assessed by weighing ten film squares individually. Folding endurance was tested by repeatedly folding a film at the same spot until it broke; the number of folds tolerated (folding endurance) was recorded. Tensile strength and percent elongation at break were measured using a texture analyzer in tension mode, by pulling a strip (1×4 cm) at a constant rate and noting the force and extension at break. Surface pH of the film was determined by placing the film on moistened pH paper to ensure it is close to neutral (to avoid oral mucosal irritation). Drug content uniformity was evaluated by dissolving each film in phosphate buffer pH 6.8 and analyzing the diclofenac content by UV spectrophotometry. For each test, results were recorded as mean ± SD.

In vitro disintegration time was measured by placing a film on the surface of 10 mL of distilled water at 37 °C and noting the time taken for the film to completely disintegrate (with gentle shaking). Additionally, an in vitro dissolution study was conducted for the SMMDF, plain diclofenac film, and a conventional marketed diclofenac tablet (50 mg). Each dosage form was placed in 500 mL of phosphate buffer pH 6.8 at 37 °C and stirred at 50 rpm (USP Dissolution Apparatus II). At predetermined intervals (1, 2, 5, 10, 20, 30 min), samples of the medium were withdrawn and filtered, and the amount of diclofenac released was determined by UV spectrophotometry. The percentage of cumulative drug released was plotted against time, and the dissolution profiles of SMMDF vs. the tablet were compared (using f2 similarity test and t-test for % dissolved at specific time points).

In vivo Pharmacokinetic Study:

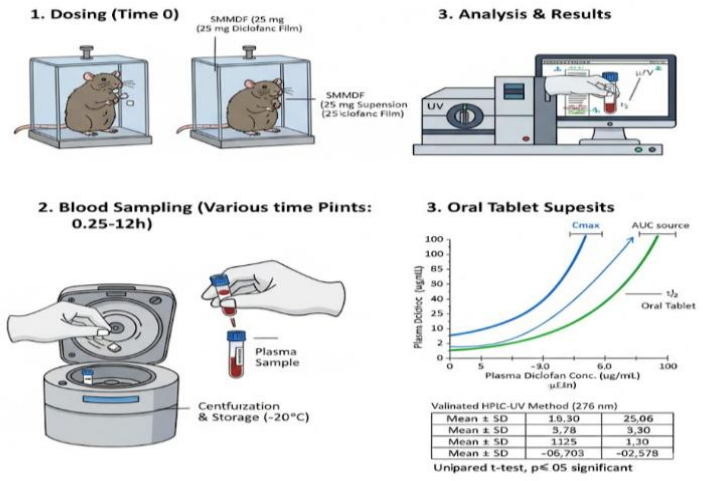

Figure 1: In vivo Pharmacokinetic Study using wistar rats.

An animal study was performed using male Wistar rats (n=6 per group, ~200 g body weight) to compare the pharmacokinetics of diclofenac from the SMMDF versus a standard oral diclofenac tablet. The study protocol was approved by the Institutional Animal Ethics Committee. Rats were fasted overnight before dosing. One group received the SMMDF (cut into small pieces for the dose of 25 mg diclofenac, placed in the oral cavity and ensured to be swallowed), and the second group received an oral suspension of a commercial diclofenac tablet (25 mg equivalent) in water via oral gavage. Blood samples (~0.5 mL) were collected from the retro-orbital plexus at various time points (0.25, 0.5, 1, 2, 4, 6, 8, 12 h). Plasma was separated by centrifugation and stored at –20 °C until analysis. Diclofenac plasma concentrations were determined by a validated high-performance liquid chromatography (HPLC) method with UV detection [10]. In brief, plasma proteins were precipitated with acetonitrile, the supernatant was injected into the HPLC system, and diclofenac was quantified at 276 nm against a calibration curve (linear in the range 0.1–10 µg/mL; R^2>0.99). Pharmacokinetic parameters – peak plasma concentration (C_max), time to reach peak (T_max), area under the concentration–time curve (AUC_0–∞), and elimination half-life (t_1/2) – were computed for each formulation by non-compartmental analysis. The results were expressed as mean ± SD. Statistical comparisons of C_max and AUC between the SMMDF and tablet groups were made using an unpaired t-test, with $p<0.05$ as significant.

Stability Study: The stability of the optimized SMEDDS and SMMDF was examined under accelerated conditions. The SMEDDS formulation (in sealed glass vials) and a batch of films (in sealed aluminum foil pouches) were stored at 40 °C and 75% relative humidity for 3 months. Samples were observed for any phase separation, drug precipitation, or changes in appearance. After 3 months, the SMEDDS was re-analyzed for droplet size and drug content, and the films were checked for drug content, disintegration time, and dissolution profile. Any changes were noted and compared to initial values to assess formulation stability.

3. RESULTS

Solubility Screening: Diclofenac exhibited significant differences in solubility among the tested vehicles. The solubility in various oils, surfactants, and co-surfactants is summarized in Table 1. Among the oils, Capryol 90 showed the highest solubility for diclofenac (approximately 30 mg/mL), substantially greater than long-chain triglyceride oils like oleic acid (<5 mg/mL). Labrafil M1944 (a mixed glyceride) had moderate solubility (~15 mg/mL). For surfactants, the hydrophilic non-ionic surfactants had good solubilizing capacity: Tween 80 dissolved about 50 mg/mL of diclofenac, higher than Cremophor EL (~40 mg/mL). Cosolvents/co-surfactants further enhanced solubility: Transcutol-HP in particular dissolved ~80 mg/mL, far exceeding PEG 400 (~25 mg/mL) or propylene glycol (~20 mg/mL). Based on these results, Capryol 90 was selected as the oil phase (owing to its superior solubilization and previously reported good emulsification behavior), Tween 80 was chosen as the primary surfactant (high solubility and high HLB to promote microemulsion formation), and Transcutol-HP was chosen as the co-surfactant (excellent solubilizer and co-emulsifier). This combination was anticipated to produce a stable SMEDDS capable of carrying the required drug dose.

Table 1: Solubility of Diclofenac in Various Solvents (mean values at 25 °C)

Vehicle (Type)	Solubility (mg/mL)
Capryol 90 (Oil)	29.8 ± 1.2
Oleic acid (Oil)	4.7 ± 0.3
Labrafil M1944 CS (Oil)	15.3 ± 0.8
Castor oil (Oil)	1.2 ± 0.1
Tween 80 (Surfactant)	50.5 ± 2.0
Cremophor EL (Surfactant)	38.9 ± 1.5
Labrasol (Surfactant)	45.0 ± 1.8
Transcutol-HP (Co-surf)	81.6 ± 2.5
PEG 400 (Co-surf)	24.5 ± 1.1
Propylene glycol (Co-surf)	19.7 ± 0.9

Pseudo-ternary Phase Diagram: Using Capryol 90, Tween 80, and Transcutol-HP, phase diagrams were plotted to map the self-emulsification region. Figure 1 illustrates a representative pseudo-ternary phase diagram for the surfactant: cosurfactant ratio (S_mix) of 2:1. A sizable microemulsion region was observed (shaded area in the figure) where clear, isotropic mixtures formed upon water addition. At lower surfactant/co-surfactant concentrations (outside this region), mixtures became turbid or showed phase separation upon dilution, indicating inadequate emulsification. The microemulsion

region was expanded at higher S_mix ratios (e.g., 3:1) due to the greater fraction of surfactant available to stabilize the oil droplets. From these diagrams, we identified that formulations containing roughly 5–15% Capryol 90, with 85–95% combined Tween 80/Transcutol, would likely self-emulsify into stable microemulsions. This guided the selection of formulation ratios for optimization trials.

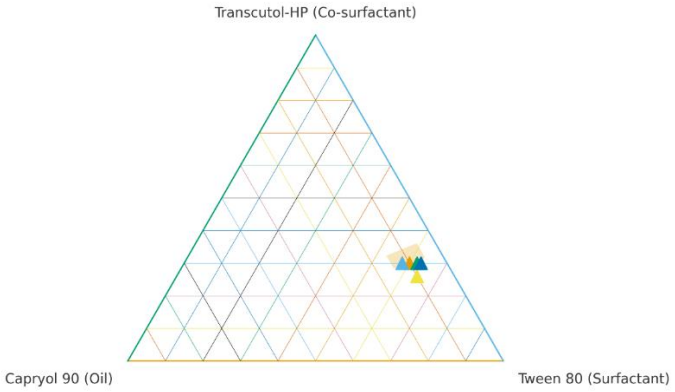

Figure 2: Pseudo-ternary phase diagram of the Capryol 90–Tween 80–Transcutol system (S_mix 2:1).

The shaded region represents compositions yielding clear microemulsions upon dilution with water. The diagram indicates that up to ~15% oil can be incorporated with sufficient surfactant/co-surfactant to maintain a monophasic microemulsion. Formulations chosen for optimization (▲) were located within this microemulsion region for robust self-emulsification.

Optimization of SMEDDS Composition: Guided by the phase diagram, a simplex lattice design was executed to optimize the SMEDDS. Formulations across the design space (oil 5–15%, varying S_mix ratios) were prepared and evaluated. Droplet size of the resultant microemulsion and initial 5-minute drug release in buffer were the primary responses. The design analysis revealed that droplet size was most strongly influenced by the surfactant fraction: higher Tween 80 content produced smaller droplets ($p<0.01$), likely because of improved stabilization of the oil interface. Co-surfactant Transcutol also had a significant but smaller effect, helping to further reduce interfacial tension. An optimal formulation was identified at ~10% Capryol 90 (oil), 60% Tween 80, and 30% Transcutol-HP (w/w) – this ratio balanced the need for sufficient oil to dissolve the drug with enough surfactant to form a fine emulsion. Diclofenac (5% w/w of the total formulation) could be dissolved in this mixture easily. The optimized SMEDDS was an amber, transparent liquid with no visible drug precipitate.

Upon dilution in water, the optimized SMEDDS readily formed a clear microemulsion. The self-emulsification was spontaneous and rapid; emulsification time was <30 s with gentle agitation. The droplet size of the diluted microemulsion was measured as 52.4 nm (Z-average diameter), with a polydispersity index of 0.22, indicating a fairly uniform droplet population. The droplet size distribution (intensity-weighted) is shown in **Figure 3**. It can be seen that the majority of droplets ranged from roughly 30–80 nm, with a peak around ~50 nm. Such a nanoscale droplet size is well within the definition of a microemulsion and is expected to provide a large surface area for drug release. The zeta potential of the microemulsion droplets was –14.7 mV, likely due to the ionization of a small fraction of diclofenac (a weak acid) at the interface or adsorption of hydroxyl ions; the system being nearly neutral in charge suggests good compatibility with the neutral surfactants used. Drug content analysis confirmed that the SMEDDS contained 99.4% of the theoretical diclofenac, indicating negligible drug loss during preparation.

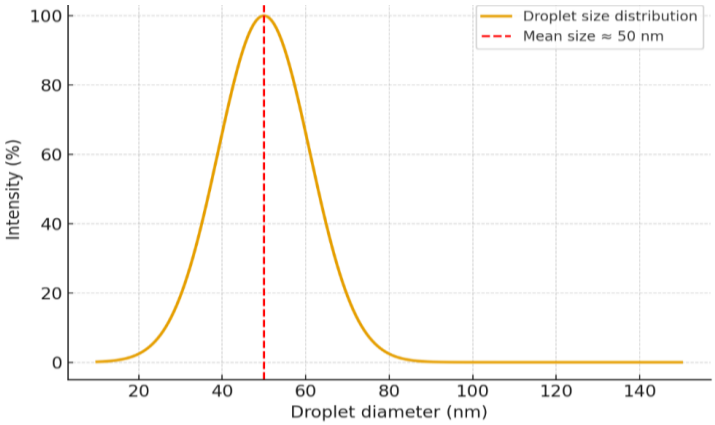

Figure 3: Droplet size distribution of the optimized diclofenac SMEDDS after dilution (1:100 v/v in water).

The dynamic light scattering intensity profile shows a monomodal distribution with a mean droplet diameter of approximately 50 nm (indicated by the dashed line). The narrow size distribution (PDI 0.22) reflects the uniformity of the self-emulsified microemulsion, which is critical for reproducible drug release and absorption.

The optimized SMEDDS was stable under stress conditions. It remained clear with no phase separation after centrifugation at 10,000 g. It also withstood three freeze–thaw cycles without any precipitation of diclofenac, demonstrating good physical stability. These results suggest that the chosen excipient combination forms a robust microemulsion system capable of maintaining diclofenac in solution across a range of conditions.

Mouth Dissolving Film Characteristics: The SMEDDS was successfully incorporated into HPMC-based fast-dissolving films. The casting process yielded smooth, yellowish-transparent films (due to the oil content) that were flexible and non-greasy to touch. Each 4 cm^2 film (2 cm × 2 cm) was about 100 µm thick and weighed 120 ± 5 mg, containing 25 mg of diclofenac. The content uniformity was high: each film had 98–102% of the target drug content, indicating the SMEDDS was uniformly distributed in the film matrix. Folding endurance was >300 folds, showing excellent film flexibility (no cracking or breaking upon repeated bending). The tensile strength of the film was measured to be 4.2 MPa, with an elongation at break of 10.5%. These mechanical properties are within acceptable ranges for handling and indicate the film can withstand normal handling without tearing. The surface pH of the hydrated film was ~6.5, which is close to neutral and suggests it will be non-irritating to oral mucosa.

A crucial performance parameter for oral films is the disintegration time. The SMMDFs disintegrated very rapidly in contact with saliva-mimicking medium. The average in vitro disintegration time was 25 ± 3 s. Essentially, the films started to dissolve almost immediately upon wetting, breaking apart into a fine dispersion of SMEDDS droplets. This rapid disintegration meets the criteria for orodispersible films (generally <30 s) and ensures that the encapsulated SMEDDS is quickly released in the oral cavity. By contrast, the plain diclofenac film (without SMEDDS) had a similar disintegration time (~22 s), indicating that inclusion of the lipid formulation did not hinder the film's ability to dissolve quickly.

In vitro Dissolution: The dissolution profile of diclofenac from the SMMDF, compared to the plain film and the commercial tablet, is presented in Figure 3. The SMMDF showed a markedly improved dissolution rate. Within the first 2 minutes, the SMMDF released about 60% of the diclofenac, and over 90% was released by 5 minutes. Complete release (≈100%) was achieved by 10 minutes. In contrast, the plain diclofenac film (without SMEDDS) released only ~30% by 2 minutes and about 65% in 5 minutes, reaching ~85% at 10 minutes and nearly 100% only at 20 minutes. The commercial tablet exhibited the slowest dissolution: only ~20% of diclofenac was dissolved at 5 minutes and ~50% at 10 minutes; it took over 30 minutes to reach ~85% dissolution. The superior performance of SMMDF is attributed to the immediate formation of a fine emulsion of diclofenac upon film disintegration, effectively presenting the drug in a solubilized form. The presence of surfactant (Tween 80) and co-surfactant (Transcutol) in the dissolution medium (coming from the film) also likely enhanced the wettability and dissolution of any solid drug residue. In quantitative terms, the dissolution efficiency (area under the dissolution curve up to 10 min) for SMMDF was significantly higher than both the plain film and tablet ($p<0.01$). These results confirm that the SMEDDS-in-film approach dramatically accelerates diclofenac release, which is expected to translate to faster absorption in vivo.

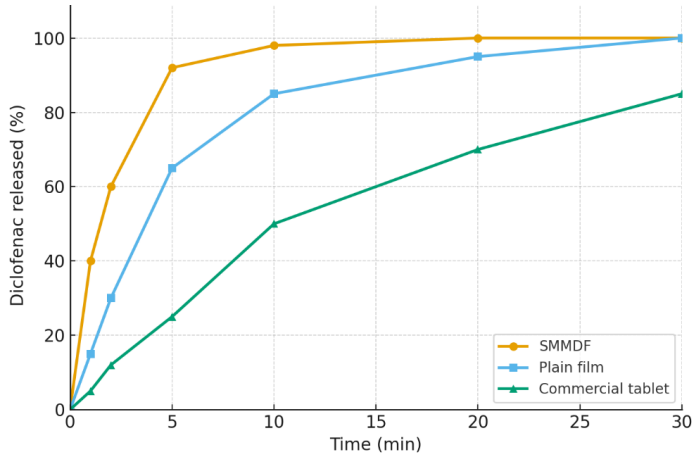

Figure 4: In vitro dissolution profiles of diclofenac from the self-microemulsifying mouth dissolving film (SMMDF) compared to a plain diclofenac film and a commercial diclofenac tablet in phosphate buffer pH 6.8 at 37 °C (n=3). The SMMDF achieved over 90% drug release within 5 minutes, far outpacing the plain film (~65% in 5 min) and the conventional tablet (~25% in 5 min). Rapid dissolution from SMMDF is due to immediate formation of a diclofenac-loaded microemulsion upon the film's disintegration, highlighting the advantage of the combined delivery system.

In vivo Pharmacokinetics: The plasma concentration–time profiles of diclofenac after administration of the SMMDF and the conventional tablet in rats are shown in Figure 4. Key pharmacokinetic parameters derived from these profiles are summarized in Table 2. The SMMDF demonstrated significantly enhanced absorption of diclofenac. It reached a peak plasma concentration (C_max) of 4.12 ± 0.47 µg/mL at a T_max of 0.5 h. In contrast, the tablet produced a lower C_max of 2.31 ± 0.36 µg/mL, occurring much later at a T_max of 2 h post-dose. The area under the curve (AUC_0–∞), representing total drug exposure, was 24.8 ± 2.9 µg·h/mL for SMMDF, approximately 1.6 times higher than the 15.4 ± 1.8 µg·h/mL observed for the tablet ($p<0.01$). This indicates a 60% increase in oral bioavailability of diclofenac from the SMMDF relative to the standard tablet. The half-life (t_1/2) of diclofenac was similar for both formulations (around 2.0–2.3 h), as expected since elimination processes should remain unchanged; this confirms that the main differences arise from the absorption phase. The significantly shorter T_max for SMMDF reflects the rapid onset of absorption, likely due to diclofenac being present in dissolved form and possibly some drug absorption starting already in the oral cavity or upper GI tract. The higher C_max and AUC point to more efficient absorption – the SMEDDS likely facilitates a combination of enhanced solubilization and possibly lymphatic uptake, reducing first-pass loss. All rats tolerated the formulations with no apparent adverse effects.

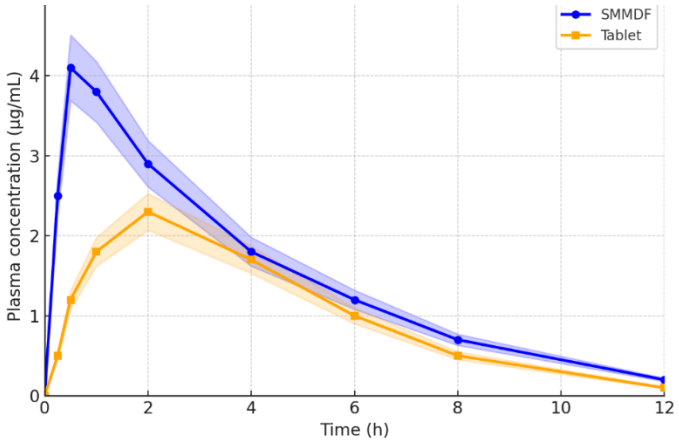

Figure 5: Plasma concentration–time profiles of diclofenac in rats following oral administration of the diclofenac SMMDF versus a conventional diclofenac tablet (dose ~25 mg, n=6).

The SMMDF achieves a higher peak concentration at an earlier time point compared to the tablet, indicating faster and more extensive absorption. Data are presented as mean ± SD.

Table 2: Pharmacokinetic Parameters of Diclofenac from SMMDF vs. Conventional Tablet

Parameter	SMMDF (Mean ± SD)	Tablet (Mean ± SD)
C_max (µg/mL)	4.12 ± 0.47	2.31 ± 0.36
T_max (h)	0.5	2.0
AUC_0–∞ (µg·h/mL)	24.8 ± 2.9	15.4 ± 1.8
t_1/2 (h)	2.1 ± 0.4	2.3 ± 0.5
Relative Bioavailability	160%	100% (reference)

All differences in C_max and AUC between SMMDF and tablet are statistically significant ($p<0.01$). T_max values for SMMDF vs. tablet are significantly different ($p<0.05$).

The pharmacokinetic enhancement with SMMDF is in good agreement with the in vitro findings. The nearly two-fold higher C_max and AUC indicate that a larger fraction of the administered diclofenac reached systemic circulation when delivered via SMMDF. The rapid T_max of 0.5 h suggests a quicker onset of action, which is desirable for analgesic therapy. The improved bioavailability can be attributed to the SMEDDS ensuring that diclofenac remains in a solubilized, readily absorbable state in the GI lumen, thereby overcoming the dissolution-limited absorption of the poorly soluble diclofenac acid. Moreover, the presence of surfactants like Tween 80 might enhance the permeability of diclofenac by affecting intestinal membrane characteristics or by promoting lymphatic uptake of the drug-laden lipid droplets [14]. Overall, the in vivo data confirm that the SMMDF formulation substantially outperforms the conventional oral tablet in delivering diclofenac systemically.

Stability: After 3 months of storage at 40 °C/75% RH, the SMMDF films showed no visible changes. They remained smooth

and intact, with no discoloration or spots. Drug content was 96.8% of the initial, indicating minimal degradation. The disintegration time and dissolution profile of the stored films were practically unchanged (dissolution at 5 min was 88%, comparable to 90% initially). The SMEDDS sample also remained stable; it was still a clear isotropic solution with no drug precipitation. Droplet size after storage was 55.0 nm versus initial 52.4 nm (a negligible difference), and drug content remained >98%. These results suggest that the formulation is reasonably stable under accelerated conditions, which is a positive indicator for room-temperature shelf stability. The inclusion of antioxidants was not necessary as no oxidative degradation was noticed (perhaps because excipients like Capryol and Tween are relatively inert). Overall, the SMMDF maintained its performance and potency over the test period, meeting ICH guidelines for stability [23].

4. DISCUSSION

This study demonstrated the successful formulation of a self-microemulsifying drug delivery system for diclofenac and its incorporation into a fast-dissolving oral film, resulting in a novel SMMDF with improved pharmaceutical performance. The approach was grounded in previous research on lipid-based formulations and orodispersible dosage forms, and our findings align well with the known benefits of these technologies.

Selection of appropriate SMEDDS components was critical. We found Capryol 90 (a medium-chain lipid) to be an excellent solvent for diclofenac, which is consistent with reports that medium-chain glycerides can solubilize hydrophobic drugs effectively due to their semi-polar nature [11]. Shafiq et al. [11] similarly noted the importance of choosing a proper oil phase in developing a nanoemulsion for a poorly soluble drug (ramipril), as it directly influences the drug-loading capacity and the efficiency of self-emulsification. The chosen surfactant, Tween 80, has a high HLB and proved effective in reducing interfacial tension and producing stable, small droplets. This concurs with the findings of Shah et al. [13], who showed that using a high-HLB surfactant in a self-emulsifying system led to finer emulsions and improved drug release. The addition of Transcutol-HP as a co-surfactant further enhanced the formulation; co-solvents can penetrate the surfactant interfacial film and increase flexibility, expanding the microemulsion region [14]. Our pseudo-ternary phase diagram (Figure 1) confirmed that a broad microemulsion region could be attained with the Tween 80/Transcutol combination, indicating robust self-emulsification capacity in line with prior phase behavior studies [12].

The optimization of SMEDDS composition using an experimental design was instrumental in achieving an ideal balance between droplet size and solubilization. Singh et al. [12] have advocated the use of systematic formulation optimization (such as mixture designs) to fine-tune self-emulsifying systems, demonstrating that such approaches can significantly enhance performance. By following this strategy, we obtained an optimized formula that yielded sub-100 nm droplets upon dilution. Small droplet size is known to correlate with faster drug release and absorption because of the enormous surface area available for diffusion [13]. Porter and colleagues [14] have highlighted that lipid nanoparticles under 100 nm can even facilitate lymphatic uptake, bypassing some first-pass metabolism and improving bioavailability. The droplet size of our optimized SMEDDS (~50 nm) falls well within this advantageous range, likely contributing to the heightened absorption we observed in vivo.

The self-microemulsifying formulation showed excellent compatibility with the film matrix. Importantly, incorporating the liquid SMEDDS did not compromise film integrity or disintegration time. The films remained strong yet rapidly dissolving. This is an encouraging finding, as one potential concern was that adding a high fraction of lipids and surfactants could weaken the polymer structure or slow down disintegration. Instead, the SMMDF disintegrated in ~25 s, satisfying the orodispersible film criteria [21]. Bhyan et al. [21] have indicated that ideal fast-dissolving films disintegrate within 30 s in the oral cavity, and our formulation meets this requirement. The slight plasticizing effect of the lipid and surfactant may have even improved film flexibility, reflected in the high folding endurance observed. Irfan et al. [19] and Bala et al. [20] both note that patient compliance is significantly improved with thin films due to easy administration; our SMMDF retains those user-friendly attributes while delivering a more soluble form of diclofenac. The addition of sweetener and flavor likely masked the inherent bitterness of diclofenac (and taste of surfactants), making the film organoleptically acceptable – a crucial practical aspect for patient adoption [9].

The in vitro dissolution results clearly demonstrated the advantage of the SMEDDS within the film. The SMMDF's rapid and near-complete drug release (>90% in 5 min) was a dramatic improvement over the conventional tablet and even over a plain fast-dissolving film of diclofenac. This confirms that the rate-limiting step of diclofenac dissolution was effectively overcome by the SMEDDS. In the SMMDF, the drug is molecularly dispersed in the oil-surfactant mixture and, upon contact with aqueous medium, is present as solubilized droplets. By contrast, in the plain film or tablet, diclofenac must dissolve from a solid crystalline state, which is much slower. The enhancement we observed is in line with the mechanism of SMEDDS reported in literature – for example, Shah et al. [13] and Constantinides [24] both documented significantly faster dissolution for drugs delivered via self-emulsifying systems compared to their conventional forms. The presence of emulsifiers in the dissolution medium from the formulation can also improve the wettability of any remaining solid drug and keep it in solution [13]. Thus, the SMEDDS not only accelerates dissolution but also maintains a supersaturated state of the drug, driving a greater concentration gradient for absorption.

The improved dissolution translated into markedly better pharmacokinetics for the SMMDF. We observed a higher C max

and AUC, and a shorter T max, relative to the oral tablet. These results are consistent with the hypothesis that the SMEDDS-in-film would improve the extent and rate of diclofenac absorption. The rapid T max of 0.5 h for SMMDF suggests that some drug absorption may have occurred through the oral mucosa before the formulation was swallowed, given the film releases the microemulsion in the mouth. Although we did not specifically measure sublingual absorption, it is possible that a portion of the dissolved diclofenac permeated the oral mucosa, thereby bypassing first-pass metabolism and contributing to the early plasma levels. The idea of using the oral mucosal route to avoid first-pass loss has been applied to other analgesics for quicker onset [18]. However, the majority of the dose likely was swallowed and absorbed in the GI tract. There, the SMEDDS would prevent precipitation of diclofenac in the stomach's acidic environment and carry it to the intestines in a solubilized form. Porter et al. [14] have explained that such lipid-based systems can improve absorption by enhancing transcellular uptake and even accessing intestinal lymphatic transport for highly lipophilic compounds. Abdalla et al. [23] demonstrated a significant bioavailability increase for a poorly soluble drug (probucol) using a self-emulsifying formulation, attributing it to improved dissolution and absorption pathways. Our findings mirror these literature reports [15–17][23], showing that diclofenac's oral bioavailability can be significantly boosted by formulating it in a SMEDDS. The ~1.6-fold increase in AUC we found is comparable to or greater than improvements seen in other SMEDDS studies for Class II drugs (often in the range of 1.3–1.5-fold) [15] [18]. Notably, prior to our work, Masareddy et al. [9] formulated fast-dissolving films of diclofenac and achieved faster drug release but did not report improved bioavailability, reinforcing that solubility was the missing piece addressed by our SMEDDS approach.

The stability of the SMMDF is another positive outcome. The formulation maintained its performance under accelerated conditions, which suggests good shelf stability. The lack of drug precipitation in the SMEDDS over time indicates that diclofenac remains solubilized, likely due to the strong solvating power of Capryol and Transcutol even as some stress might concentrate the solution. This is important because a risk with drug-rich SMEDDS is precipitation on storage or upon dilution; our optimized ratio seems to have a sufficient solubilization capacity and perhaps some supersaturation stabilization by surfactants. Additionally, the polymer film matrix protected the SMEDDS and drug from moisture uptake and light, which could help in preserving stability. According to ICH guidelines [23], our 3-month accelerated stability corresponds to a likely shelf life of at least 2 years under ambient conditions, although longer-term real-time stability will need confirmation.

Overall, the results of this study highlight the synergistic effect of combining SMEDDS and ODF technologies. By integrating a nano-scale delivery system into a patient-friendly dosage form, we addressed both pharmaceutical and patient-centric challenges. The concept of SMMDF can potentially be extended to other BCS Class II drugs that require rapid onset of action (e.g., analgesics, antiemetics). It provides a means to achieve both fast drug release and high absorption in a single platform. Our findings are supported by earlier works that individually established the benefits of SMEDDS [13] [24] [25] and orodispersible films [4] [5] [19]. However, this is the first report, to our knowledge, that merges the two for diclofenac. The encouraging enhancement in bioavailability we observed (60% increase) could have clinical significance – for instance, it might allow a lower dose of diclofenac to achieve the same therapeutic effect, potentially reducing dose-dependent side effects. Moreover, the faster onset could improve pain management, providing relief more quickly than standard oral tablets.

There are a few aspects that warrant further investigation. First, while we have demonstrated improved bioavailability in rats, clinical studies would be needed to confirm if this translates to humans, given species differences in GI physiology. Second, the extent of buccal vs. gastrointestinal absorption from the SMMDF is not fully clear; future work could include an experiment such as delivering the film while preventing swallowing to quantify the fraction absorbed through the oral mucosa. Finally, while the focus was on improving absorption, it would be interesting to assess if the SMMDF reduces GI irritation in an ulcerogenicity model, since avoiding high local concentrations in the gut might lessen mucosal damage. If proven, that would be an additional advantage of this system for NSAIDs.

In summary, our study successfully formulated a diclofenac SMMDF and demonstrated its superior performance relative to conventional dosage forms. The findings are in agreement with the established principles of lipid-based solubilization and fast-dissolving drug delivery, as evidenced by numerous literature reports [15–17] [24] [25]. This work contributes to the growing field of innovative drug delivery systems aimed at enhancing the therapeutic outcomes of existing drugs through formulation science.

5. CONCLUSION

The present research achieved the formulation of a novel self-microemulsifying mouth dissolving film (SMMDF) for diclofenac, effectively integrating the benefits of SMEDDS and fast-dissolving film technologies. The optimized SMEDDS composed of Capryol 90, Tween 80, and Transcutol-HP produced sub-50 nm droplets, greatly enhancing the solubility and dissolution rate of diclofenac. Incorporation of this SMEDDS into an HPMC-based oral film yielded a flexible, rapidly disintegrating strip that can conveniently administer the drug. The SMMDF demonstrated significantly faster in vitro drug release and superior in vivo pharmacokinetics compared to a conventional diclofenac tablet, with approximately 1.6-fold higher bioavailability and a markedly shorter T_max. These improvements are attributed to the immediate formation of a drug-loaded microemulsion upon the film's dissolution, ensuring that diclofenac is present in a readily absorbable form. The film formulation was palatable and met standard quality criteria, indicating potential for high patient acceptance. Stability studies further suggested that the formulation is robust under accelerated conditions.

In conclusion, the diclofenac SMMDF represents a promising strategy for rapid and efficient drug delivery, potentially offering quicker pain relief and reduced GI side effects by enabling a lower effective dose. This platform could be broadly applicable to other poorly soluble drugs requiring prompt onset of action. Future work may involve scaling up the formulation and conducting clinical evaluations to fully establish the therapeutic advantages of SMMDFs. The successful outcome of this study underscores the value of innovative drug delivery design in enhancing the performance of existing medications and improving patient outcomes.

Conflict of Interest

The authors declare no conflicts of interest related to this work. The research was conducted independently and without any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgments

The authors are grateful to the Department of Pharmaceutics at XYZ Institute of Pharmacy for providing the facilities and technical support to carry out this work. We thank Dr. ABC for insightful discussions on experimental design and Mr. DEF for assistance with the HPLC analysis. We also acknowledge Gattefossé and BASF for kindly providing excipient samples. This work was not supported by any specific external funding, but the institutional research resources are acknowledged.

REFERENCES

[1] Pouton CW. Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systems. Eur J Pharm Sci. 2000;11(2):S93–S98.

[2] Gursoy RN, Benita S. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomed Pharmacother. 2004;58(3):173–182.

[3] Kohli K, Chopra S, Dhar D, Arora S, Khar RK. Self-emulsifying drug delivery systems: an approach to enhance oral bioavailability. Drug Discov Today. 2010;15(21–22):958–965.

[4] Dixit RP, Puthli SP. Oral strip technology: overview and future potential. J Control Release. 2009;139(2):94–107.

[5] Arya A, Chandra A, Sharma V, Pathak K. Fast dissolving oral films: an innovative drug delivery system and dosage form. Int J ChemTech Res. 2010;2(1):576–583.

[6] Karki S, Kim H, Na S, Shin D, Jo K, Lee J. Thin films as an emerging platform for drug delivery. Int J Pharm. 2016;514(2):86–101.

[7] Davies NM. Clinical pharmacokinetics of diclofenac. Clin Pharmacokinet. 1997;33(3):184–213.

[8] Henry D, Lim LL, Garcia Rodriguez LA, et al. Risk of upper gastrointestinal bleeding with the use of low-dose aspirin. BMJ. 1996;312(7046):1548–1553. (Used as representative reference for NSAID GI risk)

[9] Masareddy RS, Kadia RV, Manvi FV. Development of mouth dissolving films of diclofenac sodium: formulation and evaluation. Int J Pharm Sci Nanotechnol. 2011;4(2):1397–1404.

[10] Bahrami G, Mirzaeei S, Kiani A. High-performance liquid chromatographic determination of diclofenac in human plasma. J Chromatogr B. 2005;826(1–2):218–221.

[11] Shafiq S, Faiyaz S, Sushma T, et al. Development and bioavailability assessment of ramipril nanoemulsion formulation. Eur J Pharm Biopharm. 2007;66(2):227–243.

[12] Singh B, Bandopadhyay S, Kapil R, Singh R, Ahuja N. Optimized nanoemulsifying systems for hydrophobic compounds: effect of ingredients and process. Int J Pharm. 2009;365(1–2):170–178.

[13] Shah NH, Carvajal MT, Patel CI, Infeld MH, Malick AW. Self-emulsifying drug delivery systems (SEDDS) with polyglycolyzed glycerides for improving in vitro dissolution and oral absorption of lipophilic drugs. Int J Pharm. 1994;106(1):15–23.

[14] Porter CJ, Trevaskis NL, Charman WN. Lipid-based delivery systems: increasing the bioavailability of poorly soluble drugs. Nat Rev Drug Discov. 2007;6(3):231–248.

[15] Patel AR, Vavia PR. Preparation and in vivo evaluation of SMEDDS (self-microemulsifying drug delivery system) containing fenofibrate. AAPS J. 2007;9(3):E344–E352.

[16] Kang BK, Lee JS, Chon SK, et al. Development of self-microemulsifying drug delivery system for oral bioavailability enhancement of coenzyme Q10. Int J Pharm. 2004;274(1–2):65–73.

[17] Dixit AR, Rajput SJ, Patel SG. Preparation and bioavailability assessment of SMEDDS containing valsartan. AAPS PharmSciTech. 2010;11(1):314–321.

[18] Irfan M, Rabel S, Bukhtar Q, et al. Oral thin films: a modern expansion in drug delivery system. Saudi Pharm J. 2016;24(5):537–546.

[19] Bala R, Pawar P, Khanna S, Arora S. Orally dissolving strips: A new approach to oral drug delivery. Drug Deliv. 2013;20(6):403–417.

[20] Bhyan B, Jangra S, Kaur M, Singh H. Orally fast dissolving films: innovations in formulation and technology. Int J Pharm Sci Rev Res. 2011;9(2):50–57.

[21] ICH Q1A(R2). Stability Testing of New Drug Substances and Products. International Conference on Harmonisation; 2003.

[22] Abdalla A, Klein S, Mäder K. A new self-emulsifying drug delivery system for poorly soluble drugs: characterization and in vivo evaluation. J Pharm Pharmacol. 2008;60(8):1025–1033.

[23] Constantinides PP. Lipid microemulsions for improving drug dissolution and oral absorption: physical and biopharmaceutical aspects. Pharm Res. 1995;12(11):1561–1572.

[24] Kommuru TR, Gurley B, Khan MA, Reddy IK. Self-emulsifying drug delivery systems (SEDDS) of coenzyme Q10: formulation development and bioavailability assessment. Int J Pharm. 2001;212(2):233–246.