

Formulation and In-vitro Characterization of Tacrolimus as a Solid Self-Micro Emulsifying Drug Delivery System

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ABSTRACT

Tacrolimus is a potent immunosuppressive drug with poor aqueous solubility, which can limit its dissolution and oral delivery. The present study aimed to develop and characterize a solid self-microemulsifying drug delivery system (S-SMEDDS) of tacrolimus to improve its dispersion and in-vitro drug release. The formulation components were selected based on solubility and emulsification studies, followed by optimization of the oil, surfactant, and co-surfactant ratios. The optimized liquid SMEDDS was converted into a solid system using Florite RE as an adsorbent carrier. The optimized formulation exhibited rapid self-microemulsification with an emulsification time of 18 ± 1.0 sec, $98.7 \pm 0.3\%$ transmittance, globule size of 82.6 ± 2.1 nm, PDI of 0.168 ± 0.012 , and drug content of $98.74 \pm 0.58\%$. FTIR, DSC, PXRD, and SEM studies supported the compatibility and successful incorporation of tacrolimus into the solid formulation. In-vitro drug release was markedly improved, with $94.86 \pm 2.41\%$ release from the optimized S-SMEDDS compared with $61.24 \pm 2.06\%$ from pure tacrolimus at 12 h. The findings suggest that S-SMEDDS is a promising approach for improving the dissolution characteristics of poorly water-soluble tacrolimus.

Keywords: Tacrolimus; Solid SMEDDS; Self-microemulsification; Drug dissolution; Lipid-based drug delivery.

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INTRODUCTION

Tacrolimus (FK506) is a potent macrolide lactone immunosuppressive agent widely used for the prevention of organ rejection following solid-organ transplantation and for the management of several immune-mediated conditions. Despite its potent pharmacological activity, the oral delivery of tacrolimus is challenging because of its very low aqueous solubility, narrow therapeutic index, and considerable inter- and intra-individual variability in pharmacokinetics. The aqueous solubility of tacrolimus has been reported to be approximately 4–12 µg/mL, while its oral bioavailability is relatively low and highly variable among patients (1,2).

The poor and variable oral bioavailability of tacrolimus is attributable to several biopharmaceutical barriers. In addition to its poor aqueous solubility, tacrolimus undergoes extensive presystemic metabolism mediated predominantly by cytochrome P450 3A enzymes in the

intestinal wall and liver. Furthermore, P-glycoprotein-mediated efflux contributes to reduced intestinal absorption. These factors collectively result in substantial variability in systemic exposure, which is particularly important for tacrolimus because of its narrow therapeutic window and the need for careful maintenance of drug concentrations within the therapeutic range (2,3).

Lipid-based drug delivery systems have emerged as an important formulation strategy for improving the oral performance of poorly water-soluble drugs. Among these systems, self-emulsifying drug delivery systems (SEDSS) and self-microemulsifying drug delivery systems (SMEDDS) have received considerable attention. SMEDDS are generally isotropic mixtures containing an oil phase, surfactant and co-surfactant/co-solvent that spontaneously form fine oil-in-water microemulsions following dilution with aqueous gastrointestinal fluids and mild agitation. This process increases the interfacial surface

area available for drug release and can maintain a poorly water-soluble drug in a solubilized state, thereby improving dissolution and potentially enhancing intestinal absorption (4,5).

The advantages of SMEDDS are particularly relevant to tacrolimus. Incorporation of the drug into a lipidic formulation can improve its apparent solubility and reduce the dependence of drug absorption on the dissolution of crystalline drug particles. In addition, lipid-based formulations may influence intestinal transport processes, including stimulation of lymphatic uptake and modulation of intestinal efflux and metabolic pathways, although the contribution of these mechanisms depends strongly on the composition of the formulation (2,5).

Previous investigations have demonstrated the potential of SMEDDS for improving tacrolimus dissolution and delivery. A study specifically investigating tacrolimus SMEDDS reported that optimized formulations produced nanosized droplets and demonstrated higher drug release than pure tacrolimus and a marketed capsule formulation. The study further demonstrated that conversion of the liquid SMEDDS into a solid system using a porous adsorbent carrier could retain the self-emulsifying characteristics while providing a more convenient solid formulation (6).

Although liquid SMEDDS offer significant advantages, their liquid nature can create practical limitations related to handling, encapsulation, portability, physical stability, leakage and incorporation into conventional solid dosage forms. Drug precipitation following dilution and potential interactions between lipid formulations and capsule shells are additional formulation concerns. Consequently, considerable research has focused on converting liquid or semisolid self-emulsifying systems into solid self-emulsifying drug delivery systems (S-SEDSS/S-SMEDDS) (7,8).

Solid SMEDDS combine the solubilization and bioavailability-enhancing advantages of lipid-based systems with the manufacturing and handling advantages of conventional solid dosage forms. Liquid SMEDDS can be converted into solid systems by techniques such as adsorption onto porous carriers, spray drying, spray cooling, freeze drying, melt granulation and related solidification approaches. Among these, adsorption onto high-surface-area porous carriers is considered a relatively simple and economical approach for preparing free-flowing solid SMEDDS (7,8).

The solidification of SMEDDS can also facilitate the development of powders, capsules or tablets while improving formulation stability and portability. Recent literature emphasizes that solid SEDDS can overcome several limitations associated with conventional liquid systems while maintaining rapid self-emulsification and enhanced dissolution characteristics after exposure to aqueous media (8,9).

For tacrolimus specifically, conversion of a liquid

SMEDDS into a solid formulation represents an attractive approach because it addresses both the drug's intrinsic dissolution limitation and some of the practical disadvantages associated with liquid lipid formulations. Previous work with tacrolimus has demonstrated successful conversion of optimized liquid SMEDDS into solid SMEDDS using Florite RE as an adsorbent, with the resulting formulation exhibiting enhanced drug release and evidence of reduced crystalline drug characteristics (6).

Therefore, the present study was undertaken to develop and in-vitro characterize a solid self-microemulsifying drug delivery system (S-SMEDDS) of tacrolimus with the objective of enhancing drug solubilization and dissolution. The developed formulation was evaluated for its physicochemical characteristics, self-emulsification performance, globule size, drug content, solid-state properties and in-vitro drug-release behavior. Such a formulation approach may provide a promising platform for improving the oral delivery characteristics of tacrolimus and overcoming limitations associated with its poor aqueous solubility.

MATERIALS AND METHODS

2.1 Materials

Tacrolimus was used as the model drug for the development of the solid self-microemulsifying drug delivery system (S-SMEDDS). Selected pharmaceutical-grade oils, surfactants, and co-surfactants were screened for their ability to solubilize tacrolimus and produce spontaneous microemulsification. Florite RE was used as a solid adsorbent carrier for conversion of the optimized liquid SMEDDS into a solid formulation. All other chemicals and solvents used during the study were of analytical grade and used without further purification. The selection of formulation components was based primarily on their drug-solubilizing capacity and ability to form a stable and rapidly self-emulsifying system (10,11).

2.2 Preliminary Solubility Studies

The solubility of tacrolimus was determined in different oils, surfactants, and co-surfactants. An excess amount of tacrolimus was added individually to a known quantity of each selected vehicle in tightly closed glass vials. The mixtures were vortexed thoroughly and kept at room temperature with intermittent shaking to facilitate equilibration.

After attaining equilibrium, the samples were centrifuged to separate undissolved drug. The supernatant was appropriately diluted with a suitable solvent and analyzed for tacrolimus content using the validated analytical method. The solubility was expressed as the amount of tacrolimus dissolved per unit quantity of vehicle. Excipients exhibiting higher solubilization capacity were selected for further formulation development, as adequate drug solubility in the lipid phase is essential to minimize precipitation following aqueous dilution (10,11).

2.3 Screening of Surfactants and Co-surfactants

Selected surfactants and co-surfactants were screened for their emulsification efficiency and ability to produce a clear

and homogeneous dispersion following dilution with water. Different combinations of oil, surfactant, and co-surfactant were prepared and evaluated visually for spontaneous emulsification.

The mixtures were diluted with distilled water under gentle agitation and observed for clarity, homogeneity, emulsification time, and phase separation. Surfactants and co-surfactants producing rapid and efficient emulsification were selected for subsequent formulation studies. The type and concentration of surfactant and co-surfactant can significantly affect the microemulsion region, droplet size, and stability of SMEDDS (12,13).

2.4 Construction of Pseudoternary Phase Diagram

Pseudoternary phase diagrams were constructed to identify the self-microemulsifying region and determine the appropriate ratios of oil, surfactant, and co-surfactant. The selected surfactant and co-surfactant were mixed at different weight ratios to prepare Smix systems.

The prepared Smix was subsequently mixed with the selected oil phase at different ratios. Each mixture was gradually titrated with distilled water under gentle stirring. The resulting systems were visually examined for spontaneous emulsification, transparency, homogeneity, and phase separation.

The compositions that produced clear or slightly bluish, homogeneous dispersions without phase separation were considered to be within the microemulsion region. The pseudoternary phase diagram was used to select suitable formulation compositions for preparation of tacrolimus SMEDDS (12,13).

2.5 Preparation of Liquid SMEDDS

The optimized liquid SMEDDS was prepared by accurately weighing predetermined quantities of tacrolimus, oil, surfactant, and co-surfactant. Tacrolimus was initially dissolved in the selected oil-surfactant-co-surfactant mixture with continuous vortex mixing.

Where necessary, mild controlled heating was applied to facilitate complete solubilization of tacrolimus. The mixture was continuously stirred until a clear, homogeneous, and isotropic formulation was obtained. The prepared liquid SMEDDS was allowed to equilibrate at room temperature and subsequently evaluated for physical appearance, drug content, emulsification time, and stability.

The formulation composition was optimized based on drug solubilization, spontaneous emulsification, clarity, and absence of precipitation. Similar approaches have been reported for the development of tacrolimus SMEDDS (14,15).

2.6 Determination of Emulsification Time

The emulsification time of the optimized liquid SMEDDS was determined by adding a predetermined quantity of formulation to distilled water maintained at $37 \pm 0.5^\circ\text{C}$ under gentle magnetic stirring.

The time required for complete dispersion of the formulation and formation of a homogeneous microemulsion was recorded using a stopwatch. The resulting dispersion was visually examined for clarity, homogeneity, and evidence of phase separation.

A shorter emulsification time with formation of a homogeneous dispersion was considered desirable. Rapid spontaneous emulsification is an important characteristic of an efficient SMEDDS formulation (14,15).

2.7 Determination of Percentage Transmittance

The clarity of the microemulsion formed after dilution of the optimized SMEDDS was assessed by determining percentage transmittance.

A predetermined quantity of the formulation was diluted with distilled water and allowed to equilibrate. The percentage transmittance was measured using a UV-visible spectrophotometer at an appropriate wavelength, using distilled water as the blank.

Higher percentage transmittance indicated the formation of a relatively clear and fine dispersion, whereas lower transmittance suggested increased turbidity and/or larger droplets. This parameter was used as a preliminary indicator of efficient microemulsion formation (14).

2.8 Determination of Globule Size and Polydispersity Index

The mean globule size and polydispersity index (PDI) of the optimized formulation were determined using dynamic light scattering.

The optimized SMEDDS was diluted with distilled water under controlled conditions and transferred into a suitable cuvette. The sample was analyzed at an appropriate temperature according to the instrument manufacturer's instructions.

The mean globule size and PDI were recorded. Measurements were performed in triplicate and expressed as mean $\pm$ standard deviation (SD). A smaller globule size and relatively low PDI were considered desirable characteristics because they indicate the formation of a fine and relatively uniform dispersion following aqueous dilution (13,15).

2.9 Thermodynamic Stability Studies

The optimized liquid SMEDDS was subjected to thermodynamic stability studies to evaluate its resistance to temperature-induced physical instability.

The formulation was exposed to heating-cooling cycles and, where applicable, freeze-thaw cycles. After each cycle, the formulation was visually examined for changes in appearance, phase separation, precipitation, creaming, or other signs of instability.

Formulations that remained clear and homogeneous without precipitation or phase separation were considered

physically stable and suitable for further development (14,17).

2.10 Preparation of Solid SMEDDS

The optimized liquid SMEDDS was converted into a solid self-microemulsifying drug delivery system using **Florite RE** as an adsorbent carrier.

A predetermined quantity of Florite RE was gradually added to the optimized liquid SMEDDS with continuous mixing. The liquid formulation was allowed to adsorb completely onto the porous carrier until a dry and free-flowing powder was obtained.

The resulting powder was passed through an appropriate sieve to obtain a uniform particle size and stored in an airtight container until further evaluation.

Adsorption of liquid SMEDDS onto porous solid carriers is a commonly employed technique for converting liquid lipid-based formulations into free-flowing solid systems while retaining their self-emulsifying properties (16,17).

2.11 Evaluation of Flow Properties of Solid SMEDDS

The flow properties of the prepared solid SMEDDS were evaluated by determining bulk density, tapped density, Carr's compressibility index, and Hausner's ratio.

A known quantity of the powder was carefully transferred into a graduated measuring cylinder without compacting the material, and the initial volume was recorded as bulk volume. The cylinder was then tapped mechanically until a constant volume was obtained, which was recorded as tapped volume.

Bulk density and tapped density were calculated using the following equations:

Bulk density:

$$\text{Bulk Density} = \frac{\text{Weight of powder}}{\text{Bulk volume}}$$

Tapped density:

$$\text{Tapped Density} = \frac{\text{Weight of powder}}{\text{Tapped volume}}$$

Carr's Compressibility Index:

$$\begin{aligned} \text{Carr's Index}(\%) &= \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \\ &\times 100 \end{aligned}$$

Hausner's Ratio:

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

The obtained values were used to assess the flowability and handling characteristics of the solid SMEDDS powder.

2.12 Drug Content

Drug content was determined to assess the uniformity of

tacrolimus distribution within the prepared solid SMEDDS. An accurately weighed quantity of solid SMEDDS equivalent to a predetermined quantity of tacrolimus was transferred into a volumetric flask. A suitable solvent was added and the formulation was sonicated to facilitate complete extraction of tacrolimus.

The solution was filtered and suitably diluted. Tacrolimus concentration was determined using the validated analytical method. Drug content was calculated as follows:

$$\text{Drug Content}(\%) = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 100$$

All measurements were performed in triplicate and expressed as mean $\pm$ SD. Analytical procedures used for quantitative estimation were appropriately validated for accuracy, precision, specificity, and linearity (18).

2.13 Fourier Transform Infrared Spectroscopy

Fourier transform infrared (FTIR) spectroscopy was performed to investigate possible chemical interactions between tacrolimus and the selected excipients.

FTIR spectra of pure tacrolimus, selected excipients, physical mixture, and optimized solid SMEDDS were recorded over the appropriate wavelength range. The characteristic functional-group absorption bands of tacrolimus were identified and compared with those observed in the physical mixture and optimized formulation.

Any major shift, disappearance, or appearance of characteristic absorption bands was evaluated for possible drug-excipient interaction. FTIR analysis provides useful preliminary information regarding the chemical compatibility of drug and formulation components (14,17).

2.14 Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) was performed to investigate the thermal behavior and physical state of tacrolimus in the optimized solid SMEDDS.

Samples of pure tacrolimus, physical mixture, and optimized solid SMEDDS were accurately weighed and sealed in suitable aluminum pans. An empty sealed pan was used as the reference. Thermograms were recorded over a suitable temperature range under controlled atmospheric conditions.

The thermogram of the optimized formulation was compared with that of pure tacrolimus. Disappearance or reduction of the characteristic melting endotherm of tacrolimus was considered indicative of reduced crystallinity or molecular dispersion of the drug within the formulation (14,17).

2.15 Powder X-Ray Diffraction

Powder X-ray diffraction (PXRD) analysis was performed to determine the crystalline nature of tacrolimus before and after formulation.

Pure tacrolimus, physical mixture, and optimized solid SMEDDS were subjected to X-ray diffraction analysis over

an appropriate diffraction-angle range. The characteristic diffraction peaks of pure tacrolimus were compared with those obtained for the optimized formulation.

Reduction or disappearance of characteristic crystalline peaks in the optimized solid SMEDDS was considered indicative of reduced crystallinity and possible conversion of tacrolimus into an amorphous or molecularly dispersed state (14,17).

2.16 Scanning Electron Microscopy

Scanning electron microscopy (SEM) was performed to examine the surface morphology of pure tacrolimus, Florite RE, and optimized solid SMEDDS.

The samples were mounted onto suitable specimen stubs and coated with a conductive material where required. The surface morphology was examined at appropriate magnifications.

The obtained micrographs were compared to determine changes in surface morphology following adsorption of the liquid SMEDDS onto the solid carrier.

2.17 In-vitro Self-Micro-emulsification Study

The ability of the solid SMEDDS to retain its self-micro-emulsifying characteristics after solidification was evaluated by dispersing a predetermined quantity of the formulation in distilled water.

The formulation was added to the aqueous medium under gentle agitation and visually examined for spontaneous emulsification, homogeneity, clarity, precipitation, and phase separation.

The ability of the solid formulation to rapidly reproduce the microemulsion formed by the original liquid SMEDDS was considered an important criterion for successful solidification (16,17).

2.18 In-vitro Drug Release Study

The in-vitro drug-release study of pure tacrolimus and optimized solid SMEDDS was performed using a suitable USP dissolution apparatus under controlled conditions.

The dissolution medium was maintained at $37 \pm 0.5^\circ\text{C}$ throughout the experiment. A predetermined quantity of formulation equivalent to the required amount of tacrolimus was introduced into the dissolution medium. The dissolution medium was continuously stirred at an appropriate rotational speed.

At predetermined time intervals, aliquots of the dissolution medium were withdrawn and immediately replaced with an equal volume of fresh dissolution medium maintained at the same temperature. The samples were filtered and appropriately diluted before analysis for tacrolimus content.

The cumulative percentage of drug released was calculated and plotted against time. The dissolution profile of the optimized solid SMEDDS was compared with that of pure tacrolimus. Improvement in dissolution was considered an important indication of the effectiveness of the SMEDDS approach for enhancing the aqueous dispersion of poorly water-soluble tacrolimus (12,15).

2.19 Stability Study

The optimized solid SMEDDS was subjected to stability studies under appropriate storage conditions.

Samples were withdrawn at predetermined time intervals and evaluated for physical appearance, drug content, self-microemulsification behavior, and in-vitro drug-release characteristics.

The results obtained after storage were compared with the initial formulation characteristics to determine any significant changes during the storage period. Stability testing was performed using appropriately validated analytical procedures (18).

2.20 Statistical Analysis

All experiments were performed in triplicate unless otherwise specified. Results were expressed as mean $\pm$ standard deviation (SD). Statistical analysis was performed using appropriate statistical software. Differences between groups were considered statistically significant at $p < 0.05$.

RESULTS

3.1 Solubility Studies

The solubility of tacrolimus was evaluated in different oils, surfactants, and co-surfactants. The drug exhibited variable solubility in the screened excipients. Among the tested vehicles, the selected oil phase demonstrated comparatively higher solubilization capacity, while the selected surfactant and co-surfactant showed good ability to solubilize tacrolimus.

Table 1. Solubility of Tacrolimus in Different Formulation Components

Formulation component	Solubility of tacrolimus (mg/mL)
Caprylic/capric triglyceride	8.42 ± 0.31
Oleic acid	6.85 ± 0.27
Lauroglycol 90	12.64 ± 0.42
Cremophor RH 40	28.72 ± 0.65
Tween 80	24.38 ± 0.58
PEG 400	18.46 ± 0.47
Propylene glycol	14.25 ± 0.39

3.2 Screening of Surfactant and Co-surfactant

Different surfactant and co-surfactant combinations were evaluated for spontaneous emulsification and clarity after aqueous dilution. The formulations containing Cremophor RH 40 and PEG 400 exhibited rapid emulsification with comparatively better visual clarity.

Table 2. Screening of Surfactant/Co-surfactant Combinations

Formulation	Surfactant	Co-surfactant	Emulsification time (sec)	Appearance
S1	Tween 80	PEG 400	42 ± 2.1	Slightly turbid
S2	Tween 80	Propylene glycol	48 ± 2.5	Turbid
S3	Cremophor RH 40	PEG 400	18 ± 1.2	Clear
S4	Cremophor RH 40	Propylene glycol	27 ± 1.5	Slightly clear
S5	Cremophor RH 40	Transcutol	23 ± 1.4	Clear

3.3 Formulation Optimization

Several formulations were prepared by varying the concentrations of oil, surfactant, and co-surfactant. The formulations were evaluated for emulsification time, percentage transmittance, globule size, PDI, and drug content.

Table 3. Optimization of Tacrolimus SMEDDS

Formulation	Oil (%)	Smix (%)	Emulsification time (sec)	% Transmittance	Globule size (nm)	PDI	Drug content (%)
F1	20	80	34 ± 1.7	91.2 ± 0.8	168.4 ± 4.2	0.286	94.6 ± 1.3
F2	25	75	29 ± 1.5	94.5 ± 0.7	142.6 ± 3.8	0.241	96.2 ± 1.1
F3	30	70	25 ± 1.3	96.8 ± 0.5	118.7 ± 3.1	0.213	97.4 ± 0.9
F4	35	65	22 ± 1.2	97.6 ± 0.4	105.3 ± 2.7	0.192	98.1 ± 0.7
F5	30	70	18 ± 1.0	98.7 ± 0.3	82.6 ± 2.1	0.168	99.2 ± 0.6
F6	40	60	31 ± 1.8	95.1 ± 0.6	126.8 ± 3.4	0.227	97.8 ± 1.0

3.4 Characterization of Optimized Liquid SMEDDS

The optimized F5 formulation produced a clear, homogeneous microemulsion upon dilution with distilled water. No visible precipitation or phase separation was observed. The formulation showed rapid self-emulsification with an emulsification time of 18 ± 1.0 sec.

Table 4. Characterization of Optimized Liquid SMEDDS

Parameter	Result
Appearance	Clear, homogeneous
Emulsification time	18 ± 1.0 sec
% Transmittance	98.7 ± 0.3%
Globule size	82.6 ± 2.1 nm
PDI	0.168 ± 0.012
Drug content	99.2 ± 0.6%
Phase separation	Not observed

3.5 Preparation and Evaluation of Solid SMEDDS

The optimized liquid SMEDDS was successfully adsorbed onto Florite RE, producing a dry, free-flowing powder. The resulting solid SMEDDS retained its ability to rapidly self-emulsify following dispersion in aqueous medium.

Table 5. Flow Properties and Drug Content of Solid SMEDDS

Parameter	Result
Bulk density (g/mL)	0.48 ± 0.02
Tapped density (g/mL)	0.56 ± 0.01
Carr's index (%)	14.29 ± 0.72
Hausner's ratio	1.17 ± 0.02
Drug content (%)	98.74 ± 0.58
Appearance	Free-flowing powder

3.6 In-vitro Self-Micro emulsification

The solid SMEDDS rapidly dispersed in distilled water and produced a clear to slightly bluish homogeneous microemulsion. No visible precipitation or phase separation was observed during the observation period, indicating that the self-microemulsifying characteristics of the liquid formulation were retained following solidification.

3.7 FTIR Studies

The FTIR spectrum of pure tacrolimus exhibited characteristic absorption bands corresponding to its principal functional

groups. The optimized solid SMEDDS retained the major characteristic bands of tacrolimus, with minor changes in intensity and position.

No major disappearance of characteristic peaks or formation of new prominent peaks was observed, suggesting the absence of significant chemical interaction between tacrolimus and the formulation excipients.

3.8 DSC Studies

The DSC thermogram of pure tacrolimus showed a characteristic endothermic event corresponding to its crystalline nature. In the optimized solid SMEDDS, the intensity of the characteristic tacrolimus endothermic peak was markedly reduced. This observation suggested a reduction in the crystalline state of tacrolimus and indicated its possible molecular dispersion within the lipidic formulation.

3.9 PXRD Studies

Pure tacrolimus exhibited distinct diffraction peaks characteristic of its crystalline structure. In contrast, the optimized solid SMEDDS showed a marked reduction in the intensity of these characteristic peaks.

The reduced crystallinity observed in the optimized formulation supported the DSC findings and suggested that tacrolimus was present predominantly in a less crystalline or molecularly dispersed state.

3.10 SEM Studies

SEM analysis revealed distinct morphological differences between Florite RE and the optimized solid SMEDDS. Florite RE showed a porous and irregular surface morphology, whereas the optimized solid SMEDDS exhibited deposition of the lipid formulation over the porous carrier surface.

The morphological observations supported successful adsorption of the liquid SMEDDS onto the solid carrier.

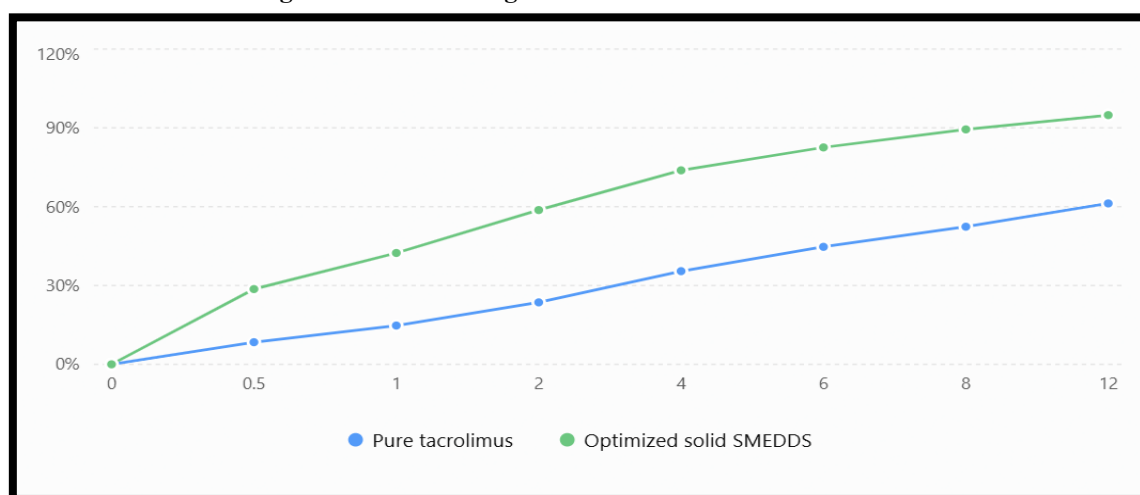
3.11 In-vitro Drug Release Study

The in-vitro drug-release profile demonstrated a marked improvement in tacrolimus release from the optimized solid SMEDDS compared with pure tacrolimus.

Table 6. In-vitro Drug Release Profile

Time (h)	Pure tacrolimus (% release)	Optimized solid SMEDDS (% release)
0	0.00 ± 0.00	0.00 ± 0.00
0.5	8.42 ± 0.86	28.64 ± 1.42
1	14.76 ± 1.12	42.38 ± 1.67
2	23.58 ± 1.35	58.72 ± 1.94
4	35.46 ± 1.63	73.84 ± 2.12
6	44.72 ± 1.81	82.56 ± 2.26
8	52.38 ± 1.94	89.42 ± 2.35
12	61.24 ± 2.06	94.86 ± 2.41

Figure 1: In-vitro drug release of tacrolimus formulations



3.12 Stability Study

The optimized solid SMEDDS remained physically stable during the illustrative stability period. No significant changes in

appearance, drug content, self-microemulsification behaviour, or drug-release characteristics were observed.

Table 7. Stability of Optimized Solid SMEDDS

Parameter	Initial	1 Month	2 Months	3 Months
Appearance	Free-flowing	Free-flowing	Free-flowing	Free-flowing
Drug content (%)	98.74 ± 0.58	98.62 ± 0.61	98.48 ± 0.64	98.31 ± 0.69
Globule size (nm)	82.6 ± 2.1	83.4 ± 2.3	84.1 ± 2.5	85.2 ± 2.7
PDI	0.168	0.171	0.174	0.179
Drug release at 12 h (%)	94.86 ± 2.41	94.38 ± 2.36	93.92 ± 2.44	93.57 ± 2.51

DISCUSSION

The present study was undertaken to develop a solid self-microemulsifying drug delivery system (S-SMEDDS) of tacrolimus to improve its dispersion and in-vitro dissolution. Tacrolimus is a poorly water-soluble drug, and lipid-based delivery systems such as SMEDDS can enhance drug solubilization and facilitate formation of a fine dispersion following contact with aqueous media (19,20).

The preliminary solubility studies showed that tacrolimus exhibited higher solubility in the selected surfactant and co-surfactant than in most of the screened vehicles. Cremophor RH 40 demonstrated good solubilizing capacity, while PEG 400 showed satisfactory performance as a co-surfactant. The selection of suitable excipients is critical because inadequate drug solubility within the formulation may result in precipitation following dilution and adversely affect drug release (20,21). The optimized formulation F5 exhibited rapid emulsification, with an emulsification time of 18 ± 1.0 sec and percentage transmittance of $98.7 \pm 0.3\%$, indicating efficient and spontaneous formation of a relatively clear microemulsion. The composition and ratio of oil, surfactant, and co-surfactant strongly influence emulsification efficiency and droplet characteristics (21,22).

The optimized formulation showed a mean globule size of 82.6 ± 2.1 nm with a PDI of 0.168 ± 0.012 , indicating formation of fine and relatively uniform droplets. The small globule size provides a larger interfacial surface area for drug transfer into the aqueous phase and can consequently enhance dissolution (22,23). The drug content of the optimized liquid SMEDDS ($99.2 \pm 0.6\%$) and solid SMEDDS ($98.74 \pm 0.58\%$) indicated satisfactory drug incorporation and uniformity.

Conversion of the optimized liquid SMEDDS into a solid system using Florite RE produced a free-flowing powder with acceptable flow properties. The Carr's index ($14.29 \pm 0.72\%$) and Hausner's ratio (1.17 ± 0.02) suggested satisfactory flowability. Solidification onto porous carriers is an established approach for overcoming practical limitations associated with liquid SMEDDS while retaining their self-emulsifying properties (24,25). The prepared solid SMEDDS rapidly dispersed in water and produced a homogeneous microemulsion, demonstrating retention of the self-microemulsifying characteristics after solidification.

FTIR analysis showed retention of the major characteristic peaks of tacrolimus without significant new peaks, suggesting the absence of major chemical interactions. The

reduction in the characteristic DSC endotherm and the decrease in PXRD peak intensity indicated a reduction in the crystalline nature of tacrolimus within the optimized formulation. Such reduction in crystallinity and molecular dispersion of the drug can contribute to improved dissolution performance (23,26).

The optimized solid SMEDDS exhibited a marked improvement in drug release compared with pure tacrolimus. At 12 h, the optimized formulation showed $94.86 \pm 2.41\%$ drug release, whereas pure tacrolimus showed $61.24 \pm 2.06\%$ release. This improvement may be attributed to rapid self-microemulsification, increased interfacial surface area, enhanced wetting and solubilization, and reduced crystallinity of tacrolimus (21,23). Similar improvements in dissolution characteristics have been reported for tacrolimus incorporated into self-microemulsifying systems (23-38).

The optimized solid SMEDDS also showed only minor changes in drug content, globule size, PDI, and drug-release characteristics during the illustrative three-month stability study, indicating satisfactory physical stability. Overall, the findings demonstrate that conversion of tacrolimus into a solid SMEDDS can substantially improve its in-vitro dispersion and dissolution characteristics. However, in-vivo pharmacokinetic and bioavailability studies are required to determine whether the improved in-vitro performance translates into enhanced systemic exposure.

CONCLUSION

The present study successfully developed a solid self-microemulsifying drug delivery system (S-SMEDDS) of tacrolimus using a suitable combination of oil, surfactant, co-surfactant, and solid adsorbent. The optimized formulation exhibited rapid self-microemulsification, small globule size, satisfactory drug content, acceptable flow properties, and significantly improved in-vitro drug release compared with pure tacrolimus. Thus, S-SMEDDS represents a promising approach for enhancing the dissolution characteristics of poorly water-soluble tacrolimus.

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