RESEARCH ARTICLE

Formulation, Optimization and Evaluation of Solid SMEDDS of Pioglitazone

Manisha R Patil*, Sanjay K Kshirsagar

Department of Pharmaceutics, MET's Institute of Pharmacy, Affiliated to Savitribai Phule Pune University, Nashik, Maharashtra, India.

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ABSTRACT

This investigation assessed 32 formulations of liquid self-microemulsifying drug delivery system (L-SMEDDS) for pioglitazone (PGZ). The optimal PLS12 formulation comprises 40% capmul MC8 (oil), 40% cremophore RH40 (surfactant), and 20% PEG (co-surfactant). PLS12 exhibited approximately 75 nm droplet size, below 200 nm, and a PDI of 0.47, indicating nanosized droplets with uniform distribution. The formulation demonstrated stability, and achieved supreme drug loading capacity. The enhanced L-SMEDDS was solidified into solidified SMEDDS utilizing Sylloid 244 FP, subsequently in a free-flowing powder without drug interactions. Tablets were successfully formulated by incorporating S-SMEDDS with diverse tableting excipients. The selected tablet batch passed quality control and stability tests. The tablet exhibited a rapid and pH-independent release profile. The combined impact of SMEDDS and tablets collectively enhanced the solubility and dissolution of PGZ hydrochloride.

Keywords: Tablets, Solidified SMEDDS, Hardness, PGZ hydrochloride, Solubility enhancement, SEM, Bioavailability enhancement.

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INTRODUCTION

Over several decades, tackling solubility challenges has been a significant issue, leading to notable variability within and between subjects, a lack of dissolution post-disintegration, and ultimately reduced bioavailability. This is especially relevant considering the mainstream of NCE (new chemical entity) demonstrates poor water solubility.[1] Regardless of frequent preparation methodologies stated in the literature, for example, solid dispersions,[2] cyclodextrins complexation,[3] nanoparticles, as well as permeation enhancers,[4,5] the issue of poor solubility remains a primary concern for formulator researchers. In recent centuries, lipid formulations are popular for the solubility enhancement of lipophilic drugs, as supported by multiple research findings. These studies underscore the favorable effects of lipid formulations, including enhanced absorption through the facilitation of solubilized phases, addressing intrinsic limitations associated with the slower and restricted dissolution of poorly water-solvable drugs.[6]

Belonging to the thiazolidinedione class, pioglitazone (PGZ) serves as a regulator of postprandial glucose in the management of type 2 diabetes (T2DM). It advances glycemic control in T2DM patients by enhancing insulin sensitivity by interacting with peroxisome proliferator activation of receptors γ-1&2. Additionally, PGZ influences lipid metabolism by targeting PPAR-α. Despite demonstrating favorable bioavailability, the challenges of poor water solubility as well as slower dissolution adversely impact the attainment of therapeutic plasma levels, leading to the ineffectiveness of PGZ therapy. Moreover, the presence of food compounds affects absorption, delaying peak plasma concentration for up to 5 to 6 hours.[8]

Self-microemulsifying drug delivery system (SMEDDS), characterized by well-balanced blends of surfactants, lipids, and co-solvents or co-surfactants, have become widely popular as they significantly enhance solubility. These methods, when gently agitated and diluted in aqueous medium like gastrointestinal tract (GIT) fluids, spontaneously generate globules with a size ranging from 5 to 100 nm. SMEDDS possess unique solubilization characteristics, offering numerous benefits. They facilitate the delivery of lipophilic drugs to the GIT in a dissolved state, passing through the critical dissolution stage, which is particularly beneficial for drugs classified as biopharmaceutical classification system (BCS) Class 2 and 4, potentially enhancing absorption rates.

*Author for Correspondence: maneeshapatil17@gmail.com

Furthermore, SMEDDS contribute to minimizing both inter-subject and intra-subject variability, mitigating the impact of food on drug effects, streamlining manufacturing scale-up, and demonstrating a promising ability to transport peptides susceptible to enzymatic hydrolysis in the GIT.[8,9]

Numerous investigations have delved into formulating PGZ utilizing techniques for example, solid dispersions,[10,11] inclusion complexes,[12,13] and fast-dissolving formulations.[14] However, the primary focus of the current study revolves around the development of an SMEDDS for PGZ, with the aim of addressing challenges related to solubility and bioavailability. The research includes assessing kinetic parameters through bioavailability studies conducted in rats.[15,16] The principal goal is to overcome the poor aqueous solubility of PGZ by incorporating it into SMEDDS. The PGZ-loaded SMEDDS developed and optimized will undergo thorough characterization, encompassing dilution studies, evaluations of drug release, analyses of droplet size and size distribution, assessments of thermodynamic stability, as well as studies on morphology and stability

MATERIALS AND METHOD

Materials

Pioglitazone (PGZ), along with a variety of oils (Corn oil, Castor oil, Cotton seed oil, Olive oil, Oleic acid, Soybean oil, Captex 200, 500, and 300 EP NF, Capmul MCM C8 NF, and Capmul PG 8 NF), surfactants (Span 80, Tween 80, PEG 400, and propylene glycol), and other substances, including Labrafil M 2125, Labrafil M 1944, Labrafac™ Lipophile WL1349, Labrasol, Lauroglycol 90, Capryol 90, and Transcutol HP, were procured from Sigma Aldrich, India. Chremophor ELP and Chremophor RH40 were also supplied through BASF, Mumbai, India.

Method

Solubility study

Experiments were conducted to assess PGZ solubility in diverse oils, surfactants, and co-surfactant formulations. Additional PGZ was dissolved in 2 mL of every medium, and the mixtures were shaken for 72 hours using a shaker and occasionally vortex mixed. After 24 hours at room temperature, centrifugation at 3000 rpm for 15 minutes was performed utilizing a Remi PR-23 centrifuge. Un-dissolved PGZ was sieved via a 0.45 mm PVD membrane filter (Sigma Aldrich, India). PGZ concentration in each sample was determined through UV analysis.[17-20]

Emulsification efficiency (EE) study

- *Selection of surfactant*

The effectiveness of diverse surfactants in emulsification was investigated to identify the most suitable surfactant(s) for the spontaneous emulsification of the chosen oily phase, Capmul MCM C8 EP (Cap C8 EP). Cap C8 EP was selected as the oily phase because it effectively solubilizes PGZ. The emulsification efficiency (EE) of numerous surfactants was assessed utilizing the same procedure outlined in the solubility studies.[21-23]

- *Assortment of co-surfactant*

The available co-surfactants for per oral delivery were screened to improve the emulsification capability of selected surfactant Cremophor RH40 (Cr-RH 40) to emulsify oily phase Cap C8 EP. The same experiment was performed as described earlier in solubility studies. Based on the solubility, emulsification and co-surfactant efficiency analysis Oil: Capmul MCM C8 EP, Surfactant: Cremophor RH 40 and Co-surfactant: PEG 400 was selected to develop L-SMEDDS of PGZ.[24]

- *Building of ternary phase diagram*

Flask inversion technique was used to construct the phase diagram, subsequent the guidelines established through Pouton (2000) for spontaneously emulsifying systems, with concentrations ranging from 35 to 60% for the oily phase, 30 to 65% for surfactant, and 0 to 30% for co-surfactant. The chosen self-emulsifying system comprised Cap MC8, Cr-RH40, and PEG 400. Thirty-two diverse systems were prepared by altering the oil, surfactant, and co-surfactant concentrations. Each system's ability to form a micro-emulsion was assessed through diluting 50 mg of the mixture with 50 mL of distilled water and performing flask inversions. Systems requiring less than 10 flask inversions to achieve a clear, transparent, or slightly bluish solution with over 95% (%T) at 638.2 nm were deliberated by micro-emulsion manufacturing. Further classification distinguished grade-I micro-emulsions as clear and transparent systems requiring fewer than 5 flask inversions and grade-II as clear or bluish-tinged transparent systems requiring 5 to 10 flask inversions. Turbid emulsions with more than 95% transmittance were categorized as grade-III coarse emulsion-producing systems, while those remaining turbid (>70% transmittance) after more than 20 flask inversions were classified as grade-IV systems incapable of producing emulsion. Ternary phase diagrams were constructed for all systems, and regions capable of producing grade-I micro-emulsions were identified within the diagrams.[24,25]

Preparation of PGZ L-SMEDDS

This research selected three diverse systems based on the saturated solubility investigation of PGZ, maintaining a consistent PGZ concentration of 15 mg per unit formula. These systems were transformed into L-SMEDDS by adjusting the concentrations of Cap MC8 (oil), Cr-RH40 (surfactant), and PEG400 (co-surfactant). To maintain a specific formulation volume, 15 mg of PGZ was utilized. The formulation process included combining PGZ with Cap MC8 in a vial, and heating the oily mixture at 60°C in a water bath. Subsequently, pre-warmed amounts of Cr-RH40 and PEG400 were mixed together, followed by homogenization for 10 to 15 minutes using a cyclomixer, and subsequent in an isotropic scheme by comprehensive PGZ solubilization. The formulated product was then stored at room temperature for further *in-vitro* assessment. The optimized L-SMEDDS formulation, containing 15 mg PGZ (total 955 mg), was accurately filled into a clean, dry vial, sealed, and stored at room temperature for

future use. This detailed process ensures a systematic approach to progressing and optimizing a PGZ-loaded L-SMEDDS preparation for potential pharmaceutical applications.[24,25]

Optimization of PGZ L-SMEDDS

- *Freeze thaw cycles and centrifugation*

Each cycle involved freezing the formulations at -4°C for 24 hours, monitored through thawing at 40°C for 24 hours. After each freeze-thaw cycle, visual inspections for phase separations and drug precipitation were performed. Subsequent the completion of three cycles, the PGZ L-SMEDDS underwent centrifugation at 3000 rpm for five minutes. Subsequently, visual assessments were conducted to identify some phase or drug separation indications. Only formulations exhibiting no drug or phase separation indications were chosen for further investigations.[18]

- *Robustness to dilution*

L-SMEDDS formulations containing PGZ were subjected to numerous degrees of dilution in diverse medium with changing pH levels, aiming to replicate the gradual dilution encountered in *in-vivo* conditions. Each L-SMEDDS was diluted to 100- and 1000-fold concentrations in three distinct dissolution mediums: SGF, SIF, and SAB, individually. The diluted micro-emulsions were deposited at room temperature for 12 hours and examined for parameters such as %Transmittance, appearance, and drug precipitation. The formulation demonstrating resilience to dilution was deemed optimized.[24]

Estimation of optimized formulation of PGZ L-SMEDDS

- *Globule size, PDI and zeta potential analysis*

A volume of 50 mg from the optimized PGZ L-SMEDDS was mixed with 50 mL of SGF, SIF, and SAB. The globule size, PDI, zeta potential (ZP) were recorded utilizing the Horiba Zetasizer (SZ-100 nanopartica series instrument).[19]

- *Morphology of globules through TEM*

The structure of the globules within the micro-emulsion, derived from the dilution of the optimized PGZ L-SMEDDS in distilled water, was examined through transmission electron microscopy (TEM) analysis. Before analysis, the PGZ L-SMEDDS samples were diluted through a factor of 1000 in distilled water to create the micro-emulsion. Subsequently, they were stained with 2% (w/v) phosphor tungstic acid for 30 seconds and positioned on 400-mesh Cu grids with films for observation. Tecnai Imaging and Analysis software was employed to visualize the images.[19]

- *Drug content analysis*

Precisely measure the optimized PGZ L-SMEDDS, corresponding to 15 mg of PGZ, and transfer it to a 50 mL volumetric flask. The flask was filled with methanol and then subjected to sonication for 15 to 20 minutes in the direction of extracting PGZ. After sonication, filter the methanolic extract utilizing Whattman filter paper. Subsequently, the extract was diluted with methanol, and its absorbance was measured at 269 nm utilizing a UV-visible spectrophotometer. This is done in comparison to a similarly treated and diluted placebo L-SMEDDS.[19]

- *In-vitro dissolution study*

The dissolution of pure PGZ powder and an optimized batch of PGZ L-SMEDDS (15mg) in was examined utilizing USP-I apparatus at 37 ± 2°C with 100rpm rotation. Tests were conducted in SGF, SIF, and SAB to evaluate pH impact on drug release. About 5 mL aliquots were withdrawn at interims and replaced with fresh buffer. Aliquots were filtered, and PGZ quantity was determined at 269 nm utilizing a UV-visible spectrophotometer. Placebo L-SMEDDS dissolution served as blanks to account for the influence of self-emulsifying components on absorption values.[20]

Preparation and Characterization of Solidified SMEDDS

The binding capacity of Sylloid 244 FP (S2F) as an adsorbing agent was determined based on its demonstrated significant binding capacity in the reported study. Selected as the solidifying agent (solid carrier), S2F was employed to develop powdered P-SMEDDS of PGZ.[24,25]

DSC thermogram

Thermal analysis of thermotropic characteristics was conducted utilizing a Shimadzu DSC-50. Samples (3–5 mg) were heated at 10ºC/min beneath dry N_2 flow (20 mL/min) from 0 to 230ºC in aluminum pans. Pure PGZ, a 1:1 w/w mixture of Sylloid 244 FP, and the Powdered (P-SMEDDS) formulation were analyzed, and differential scanning calorimetry (DSC) thermogram were recorded.[22]

P-XRD pattern

The physical state of PGZ in powder SMEDDS was assessed through powder X-ray diffraction (PXRD) utilizing a Bruker D2 Phase XRD (Germany). Measurements were conducted at room temperature with CuKα-radiation, covering a 2Θ range of 10 to 50° at a scanning speed of 5°/min. Samples included pure PGZ powder, Sylloid 244 FP, a 1:1 w/w physical mixture of PGZ and Sylloid 244 FP, and PGZ P-SMEDDS.[23]

Morphological examination of P-SMEDDS through SEM

The external macroscopic structure of plain PGZ powder, Sylloid 244 FP, and PGZ P-SMEDDS was analyzed utilizing scanning electron microscopy (SEM) with Quanta 200 and Nova-Nano SEM 600 at 10kV. Samples were affixed to SEM stubs, coated with a thin layer of gold ions, and examined for surface morphology at numerous magnification levels.[24]

Effect of solidification on globule size, PDI and zeta potential

A magnetic agitator set to 500 rpm was used to dissolve 100 mg of P-SMEDDS in 100 mL of distilled H2O over the course of 15 to 20 minutes. The subsequent dispersion was let to stand for two hours to give the adsorbing agent time to settle. The upper portion of the micro-emulsion was subjected to centrifugation at 8000 rpm for 10 minutes. The obtained supernatant after centrifugation was analyzed to determine the globule size, PDI, and ZP utilizing the Horiba Zetasizer (SZ 100).[24]

Development and Evaluation of Tablet SMEDDS (T-SMEDDS) of PGZ

Development of tablet blend of PGZ (PGZ T-SMEDDS blend)

Microcrystalline cellulose (MCC) served as a directly compressible diluent, and talc & magnesium stearate (Mg ST) were included as a glidant and lubricant. The P-SMEDDS of PGZ was combined with MCC, and monitored through the addition of Mg St (2% w/w) and talc (2% w/w). The subsequent combination was mixed meticulously.[25]

Evaluation of PGZ T-SMEDDS Blend

Micromeritic characteristics[26-28]

- *Angle of repose*

It was determined utilizing the fixed height funnel technique. The calculation of the given property was performed utilizing the subsequent formulary:

Angle of repose (θ) = $\tan^{-1}(2h/d)$ ------- (1)

Where,
θ = Angle of repose (^{o}),
h = Height of the pile (mM),
d = Average diameter (n=3) of the powder cone (mM)

- *Bulk density*

It was measured by gently pouring 10 g of P-SMEDDS through a glass funnel into a 50 mL graduated measuring cylinder. The volume employed through the P-SMEDDS was illustrious, and the bulk density (BD) was estimated utilizing the subsequent technique:

BD (g/mL) = Weight of blend (g)/Volume occupied through blend (mL) ------- (2)

- *Tapped density*

Tapped density (TD) of PGZ T-SMEDDS blend was calculated by pouring 10 g into a 50 mL graduated cylinder, tapping from 2 inches until a consistent volume was achieved. The recorded volume (mL) after tapping was used to calculate TD utilizing a formula:

Tapped Density (g/mL) = Weight of blend (g)/Volume occupied through blend after tapping (mL) ------- (3)

Carr's Index (%Compressibility)

Carr's index (CI) of blend was evaluated utilizing the formula provided below:

%Compressibility = (TD-BD/TD) x 100 ------- (4)

Hausner ratio (HR)

The hausner ratio (HR), regarded as an indirect indicator of powder flowability, was estimated utilizing the formula outlined below:

HR = TD/BD -------- (5)

- *Compression of PGZ T-SMEDDS blend to produce PGZ T-SMEDDS*

The PGZ T-SMEDDS blend was compacted into a tablet utilizing a single-punch tablet machine equipped with a capsule-shaped punch. Adequate pressure was utilized in the direction of achieve hardness within the range of 3 to 4 kg/cm^2.[26-28]

Evaluation of T-SMEDDS

Physical characteristics of tablets[29]

- *Tablet thickness*

The average thickness of 6 randomly collected tablets was assessed utilizing a Vernier caliper and communicated in millimeters.

- *Hardness*

The mean hardness of 6 arbitrarily selected tablets was assessed using a Monsanto hardness tester and articulated in kg/cm^2.

- *Weight variation*

A total of 20 tablets were arbitrarily designated, and the average weight was determined. <2 individual weights diverged from the average through over 5%, and no one diverged through >2 that %.

- *Friability test*

Tablet friability was tested utilizing a Roche friability. 6.5 g of arbitrarily designated tablets were initially weighed (W1) and subjected to the friability at 100 rpm. Afterwards, the tablets were reweighed (W2), and the %friability was estimated utilizing the formula, with a loss < 1% considered acceptable.
Percentage Friability = (W1–W2)/W1*100 ---- (6)

- *Disintegration time*

It was performed on 6 tablets utilizing the USP disintegration test apparatus with distilled H_2O at 37 ± 0.5°C.

- *Drug content*

About 10 tablets were powdered, and an amount 15 mg of PGZ was exactly weighed and transported to a 50 mL volumetric flask. The volume was made up with 50 mL, followed by 10 minutes of bath sonication for PGZ extraction, followed by extraction dilution. The samples were analyzed at 269 nm utilizing a UV-visible spectrophotometer.

- *In-vitro dissolution assessment*

T-SMEDDS of PGZ (15 mg) was assessed utilizing USP-II apparatus at 37 ± 0.5°C through a revolving speed of 50 rpm in three diverse dissolution media: 0.05 M Sodium acetate buffer pH 4.5, SGF, and SIF towards examining the outcome of pH on drug release. Aliquots were withdrawn at specific time intervals. The quantity of PGZ released was estimated through computing absorbance at 269 nm. Dissolution of placebo T-SMEDDS was performed simultaneously, and the aliquots were utilized as blanks to nullify the effect of self-emulsifying components on absorption values.[24,25]

- *In-vivo study*

The pharmacokinetic investigation of PGZ was carried out in healthy wistar rats that had been fasted for 12 hours in a crossover study design. The body weight of the wistar rats ranged from 0.25 to 0.3 kg. Animals in groups 1, 2, and 3 were administered with PGZ API dispersion, a marketed product's dispersion, and a test product's dispersion at concentrations similar to the marketed product, respectively. Blood specimens (approximately 0.5 mL each) were withdrawn utilizing a 2-2-2-2-2 replicates sparse sampling design. The blood specimens were drawn from the tail vein, and PGZ concentration was assessed at 0, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours. Reserved blood samples from each time point were centrifuged at 5,000 rpm for 10 minutes. The plasma specimens were then removed and stored at -18°C awaiting further examination. Our animal study received approval from the ethical committee.

RESULTS

Solubility Study of PGZ in Numerous Vehicles (Buffer medium and Oily phases)

The solubility profile of PGZ in water and numerous buffer solutions is depicted in Figure 1. The results indicate that PGZ exhibits pH-dependent solubility. In water, PGZ demonstrates poor aqueous solubility, with a solubility of just 0.015 ± 0.005 mg/mL. Among the tested buffers, the solubility of PGZ is highest in 0.1N HCl (0.457 ± 0.012 mg/mL), monitored through Sodium acetate buffer at pH 4.5 (0.042 ± 0.008 mg/mL). Conversely, the lowest solubility of PGZ is observed in SIF pH 6.8, measuring 0.007 ± 0.003 mg/mL.

Findings of the approximate solubility research and primary screening of oils (Table 1) reflect that natural oils failed to solubilize PGZ to more than 30 mg/g. On the other hand, synthetic medium-chain triglycerides could solubilize PGZ more than 30 mg/g. Five oils, namely Captex 200, 500, and 300 EP NF, Capmul MCM C8 NF and Capmul PG 8 NF (PGZ solubility more than 30 mg/g of oil) were chosen from the above screening for the quantitative measurement of PGZ solubility.

The results presented in Figure 2 illustrate the solubility of PGZ in selected oils. PGZ solubility in Captex 200, 500, and 300 EP NF, Capmul MCM C8 EP NF, and Capmul PG 8 NF was found to be 28.26 ± 3.07, 33.39 ± 2.19, 35.21 ± 4.85, 46.55 ± 4.78, and 33.52 ± 3.08 mg/g, respectively. Among all the oils tested, Capmul MCM C8 EP NF (Cap C8 EP) exhibited the highest solubility of PGZ at 46.55 ± 4.78 mg/g. Cap C8 EP is composed of mono and di-glycerides of medium-chain fatty acids, with approximately 97% glyceryl mono and di-ester exclusively of caprylic acid and about 3% capric acid. Capric acid possesses a longer alkyl chain than caprylic acid. The higher caprylic acid content and lower capric acid content in Cap C8 EP facilitate its emulsification. Based on these findings, Cap C8 EP was used for the production of L-SMEDDS of PGZ because of its superior potential for solubilizing PGZ and its relatively straightforward micro-emulsification capability.

Emulsification Efficiency Study

Selection of surfactant

The flask inversion technique was employed to evaluate the emulsification capability of numerous surfactants on the chosen oily phase, Capmul MCM C8 EP NF (Cap C8 EP). The EE was determined by quantifying the number of flask inversions (FI) necessary to achieve a homogeneous emulsion and assessing the subsequent emulsion's transmittance values (%T).

The emulsification efficiencies of diverse surfactants were compared for the selected oily phase, Cap C8 EP. Table 2 presents the transmittance values of numerous mixtures. The results indicate that Cap C8 EP demonstrated variable emulsification tendencies with the tested surfactants. Among the employed surfactants, Cremophor RH40 (Cr-RH 40) ranked first with a transmittance value of 97.56%, requiring only 8 flask inversions (8FI) for the formation of a homogeneous fine microemulsion. Subsequent closely, Cremophor EL (Cr-EL) ranked 2nd with a transmittance of 94.23%, also requiring 8 flask inversions (8FI) for emulsion formation, similar to Cr-RH 40.

On the other hand, PoL-407 (94.53 %T) and PoL-188 (92.44 %T) produced fine transparent or slightly bluish emulsion but both of these emulsifiers required more flask inversion (30FI) to emulsify Cap C8 EP. The reason behind this finding is because of their solid nature which on heating, converted to liquid state but rapidly re-solidify after aqueous dilution. So, even though they produce fine microemulsions, such behavior of Poloxamers is unfavorable to select them as a surfactant for further study.

Both Cr-RH 40 and Cr-EL are non-ionic surfactants commonly used in oral delivery systems due to lesser toxicity than ionic surfactants. Cr-RH40, identified as Polyoxy 40 hydrogenated castor oil and exploited in Neoral®, is a rare advertised SEDDS merchandiser. Cr-RH40 is believed to enhance the bioavailability of lipophilic drugs through solubilization and is preferred because of its bioactive characteristics. Cr-RH40 is described as exhibiting bioactive effects, including inhibitory impacts on p-gp and CYP enzymes. Cr-RH40 enhances the bioavailability of specific drugs like atorvastatin and probucol when formulated as self-emulsifying preparations. Considering these reports and the aforementioned findings from the EE study, it is rational towards selecting Cr-RH40 as the surfactant for supplementary examination in producing PGZ Liquid SMEDDS, aiming to enhance the oral bioavailability of PGZ.

Selection of co-surfactant

In the context of the existing examination, 10 co-surfactants were compared to enhance the spontaneity of EE of the chosen surfactant (Cr-RH40) in emulsifying the oily phase Cap C8 EP.

The research clearly showed how several lipophilic and hydrophilic co-surfactants work well together to enhance the micro-emulsification of a particular surfactant. Table 3 outlines co-surfactants ability to spontaneously emulsify Cap C8 EP in conjunction with the surfactant (Cr-RH40).

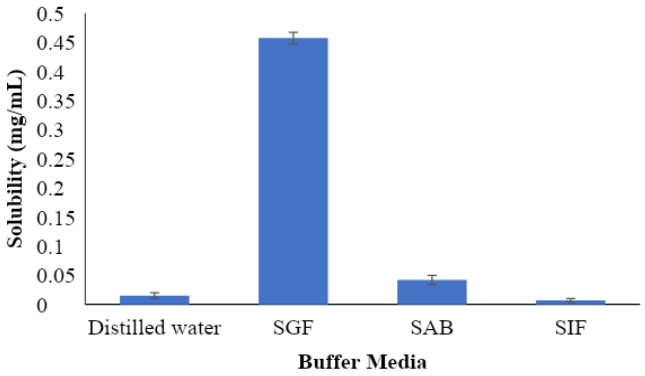

Figure 1: Solubility profiling of PGZ in numerous medium

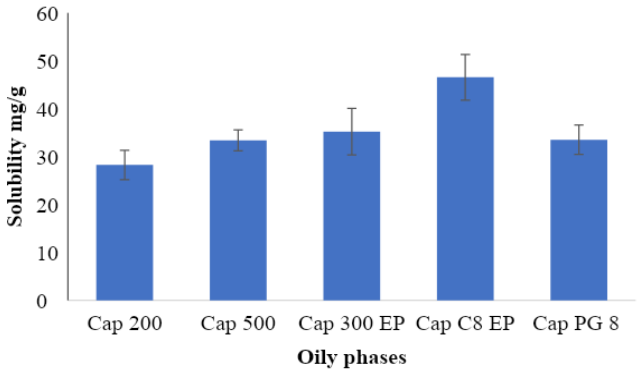

Figure 2: Quantitatively estimated of solubility of PGZ in numerous oils

Table 1: Solubility of PGZ in oily phases

S. No.	*Oil*	*No. of unit dose (15 mg) added*	*Visual observation*	*Approximate solubility (mg/g)*
1.	Arachis oil	1	Insoluble	<15
2.	Coconut oil	1	Insoluble	<15
3.	Sesame pure oil	1	Insoluble	<15
4.	Linseed oil	1	Insoluble	<15
5.	Tea tree oil	1	Insoluble	<15
6.	Clove oil	2	Slightly soluble	<30
7.	Olive oil	2	Slightly soluble	<30
8.	Anise oil	2	Slightly soluble	<30
9.	Sunflower oil	1	Insoluble	<15
10.	Soyabean oil	1	Insoluble	<15
11.	Shark liver oil	1	Insoluble	<15
12.	Iso-propyl myristate	2	Slightly soluble	<30
13.	Ethyl oleate	1	Insoluble	<15
14.	Oleic acid	1	Insoluble	<15
15.	Maissine CC	2	Sparingly soluble	<30
16.	Captex 200	3	Sparingly soluble	<45
17.	Captex 500	3	Sparingly soluble	<45
18.	Captex 300 EP NF	3	Sparingly soluble	<45
19.	Capmul MCM C8 NF	3	Sparingly soluble	<45
20.	Capmul PG 8 NF	3	Sparingly soluble	<45

The results indicated that almost all co-surfactants increased the spontaneity of microemulsion formation of Cr-RH40, irrespective of their hydrophilicity, except for Plurol oleique CC 497 (PO-497), which exhibited poor ability as a co-surfactant for Cr-RH40, likely because of its oleate backbone leading to an increased molecular volume.

Labrafil M 1944 CS and Labrafil M 2125 Cs demonstrated superior performance in enhancing the spontaneity of EE of Cr-RH40 in emulsifying Cap C8 EP, producing a transparent microemulsion (with more than 94% transmittance and 4 flask inversions). This is likely attributed to their greater hydrophilicity and surfactant-like characteristics. Among all co-surfactants tested, PEG 400 exhibited the highest ability to increase the spontaneity of emulsification of Cap C8 EP in conjunction with Cr-RH40. The subsequent microemulsion was clear and transparent with 99.32% transmittance and required only 2 flask inversions. These findings support the usage of PEG 400 as a co-surfactant to aid surfactants like Cr-RH40 in emulsifying Capmul MCM C8 EP NF (Cap C8 EP) for the development of liquid SMEDDS of PGZ (PGZ L-SMEDDS).

Ternary phase diagram

Illustration on the emulsification capabilities of surfactants and their improvement through co-surfactants, two distinct systems were elected for the creation of a ternary phase diagram to identify potential mixtures for micro-emulsion formation. The system Cap MC8: Cr-RH40: PEG400 is explained in Figure 3, wherever the outer parallelogram characterizes the explored area for locating the region of micro-emulsion formation.

Table 2: EE of surfactants for capmul MCM C8 EP (Cap C8 EP)

Sr. No.	*Surfactant*	*No. of FI**	*%Transmittance**	*Appearance*
1	Cremophor EL	08	93.23	Slightly bluish
2	Cremophor RH 40	08	97.56	Transparent
3	Caprol PGE 860	45	63.23	Colloidal
4	Gelucire 48/16	40	87.10	Bluish white
5	Tween 20	20	77.22	Colloidal
6	Tween 80	25	74.62	Colloidal
7	Span 20	20	77.65	Colloidal
8	Span 80	27	58.62	Colloidal
9	Lauroglycol 90	16	91.20	Slightly bluish
10	Kolliphor CS 12	15	90.14	Slightly bluish
11	Kolliphor CS 20	12	87.56	Bluish white
12	Poloxamer L-407	30	93.53	Slightly bluish
13	Poloxamer L-188	30	92.44	Slightly bluish
14	Labrasol	14	80.24	Colloidal
15	Labrafac CC	12	78.58	Colloidal

*Values are expressed as mean (n = 2)

Table 3: Spontaneity of emulsification through co-surfactants for surfactant for Cremophor RH40

S. No.	*Co-surfactant*	*No. of flask inversion**	*%Transmittance**	*Appearance*
1	Lauroglycol FCC	9	92.74	Bluish white
2	Ethanol	6	94.32	Slightly bluish
3	N-Butanol	4	96.65	Slightly bluish
4	Iso-propyl alcohol	6	92.55	Bluish white
5	Propylene glycol	6	96.22	Slightly bluish
6	Transcutol HP	5	95.88	Slightly bluish
7	PEG 400	2	99.32	Clear and Transparent
8	Plurol Oleique 497	23	65.79	Colloidal
9	Labrafil M 2125 Cs	4	94.70	Transparent
10	Labrafil M 1944 Cs	4	95.55	Bluish white

*Values are expressed as mean of two individual observations

It is commonly understood that schemes with 100% transmittance indicate globule sizes in the nano range. The results demonstrate that the scheme exhibits the capability to produce fine micro-emulsion (>95% T) until the concentration of the oily phase (Cap MC8) reaches 45% (w/w). Beyond this point, with an increase in the concentration of Cap MC8, the surfactant mixture Cr-RH40:PEG400 ceases to produce fine micro-emulsion, instead yielding a coarse emulsion (<85% T) and eventually a turbid emulsion (<50% T). This turbid emulsion cannot be considered an emulsion and is denoted as a no emulsion.

It was also observed that co-surfactant is required for the spontaneity of micro-emulsion formation. The scheme containing less than 10% of co-surfactant (PEG400) requires more than 5 FI to produce a micro-emulsion; hence, it is considered a micro-emulsion of grade: II. To produce grade: I micro-emulsion surfactant (Cremophor RH40) requires in the range of 40 to 50%.

Preparation of liquid SMEDDS (PGZ L-SMEDDS)

Utilizing the findings from the saturated solubility study of PGZ, four distinct schemes with the maximum solubility of PGZ were chosen for the development of L-SMEDDS. The formulation involved adjusting the concentrations of Oil: Cap MC8, Surfactant: Cr-RH40, and co-surfactant: PEG400 while maintaining a constant level of PGZ in all formulations (15 mg per unit formula). The specific composition of this scheme s is detailed in Table 4.

Optimization of PGZ L-SMEDDS

Freeze-thaw cycles and centrifugation

SMEDDS demonstrate thermodynamic stability and form without phase separation, creaming, or cracking at particular oil, surfactant, and co-surfactant concentrations. This thermal stability sets them apart from emulsions that possess kinetic stability and are prone to eventual phase separation. The chosen formulations underwent numerous thermodynamic stress tests,

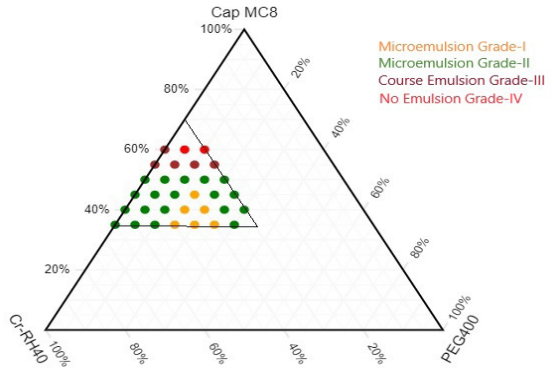

Figure 3: Ternary phase diagram of PGZ L-SMEDDS showing micro-emulsion forming region

Table 4: Composition of PGZ L-SMEDDS preparations

Constituents (mg) per unit formula	*PGZ L-SMEDDS preparation*		
	PLS_{11}	PLS_{12}	PLS_{18}
PGZ	15.00	15.00	15.00
Capmul MCM C8 EP	375.00	375.00	425.00
Cremophor RH 40	425.00	375.00	375.00
PEG 400	140.00	190.00	140.00
Mass per unit dose (mg)	955.00	955.00	955.00

including freeze-thaw cycles monitored through centrifugation. Preparations that withstood these thermodynamic stress tests were then subjected to supplementary assessment to determine their resilience in a dilution study.

The comparison of three tested formulations is tabulated in Table 5. The findings from the current investigations indicate that all three formulations show no phase separation but the formulation PLS_{11} shows instability on centrifugation monitored after 3rd freeze-thaw cycle and suffers from separation of a drug. This may be because of the low concentration of co-surfactant (15%), so centrifugation drugs get separated. The concentration of co-surfactant was even the same (15%) in the PLS_{18} formulation but it is made of up of a high concentration of oily phase (45%), which contributes majorly for solubilization of the drug and keeps the drug un-separated even after three cycles of centrifugation. PLS_{12} and PLS_{18} demonstrated stability throughout all three cycles, and drug separation or phase separation was nope even after centrifugation.

Table 5: Optimization of PLS L-SMEDDS preparation through freeze-thaw cycle and centrifugation examination

Test and parameter	*PGZ L-SMEDDS formulation code*		
	PLS_{11}	PLS_{12}	PLS_{18}
Freeze-thaw cycle			
1st cycle			
Phase separation		Stable	
Drug precipitation			
2nd cycle			
Phase separation		Stable	
Drug precipitation			
3rd cycle			
Phase separation		Stable	
Drug precipitation			
Centrifugation study			
Phase separation		Stable	
Drug separation	Un-Stable	Stable	

Robustness to dilution study

In this context, two stable PGZ L-SMEDDS formulations (PLS12 and PLS18) underwent dilution with aqueous phases at changing pH levels. The impact of dilution and pH on SMEDDS encompassing PGZ is detailed in Table 6. Both L-SMEDDS formulations spontaneously dispersed and formed micro-emulsions, exhibiting no indications of drug precipitation even after 12 hours of dispersion.

Micro-emulsion clarity was evaluated based on transparency, which was recorded as %T. As SMEDDS forms an o/w micro-emulsion, water serves as the exterior phase. Preparation PLS12, required fewer than 3 flask inversions (FI) to achieve a uniform micro-emulsion, proved robust to all dilutions, displaying %transmittance values exceeding 95% and maintaining a clear and transparent appearance. Furthermore, after 12 hours of dispersion, no drug precipitation was seen, independent of the dilution medium's pH. For PLS18, %T values ranged from approximately 93 to 96%, and the micro-emulsion appeared slightly bluish. This bluish tint may be attributed to the larger globule size in the preparation. The increased globule size in PLS18 could reduce micro-emulsion transparency, affecting %T values. This phenomenon might be associated with a higher oil-to-surfactant ratio in PLS18 compared to PLS12. Additionally, PLS18 did not exhibit drug precipitation. In summary, all the evaluation points like saturation solubility of PGZ, stability thermodynamic stress study and robustness to dilution study supports the rationale for selecting PLS12 as an optimized formulation scheme for developing L-SMEDDS of PGZ.

Estimation of Optimized Formulation of PGZ L-SMEDDS

Globule size, PDI and ZP analysis

The results of globule size and surface charge analysis for PGZ L-SMEDDS formulations are summarized in Table 7 & Figures 4 and 5. The mean globule size attained from the optimized batch was approximately 75 nm. The PDI of the optimized formulation in numerous medium fell within the series of 0.41 to 0.52. These findings specify that the subsequent micro-emulsion from the optimized PGZ L-SMEDDS formulation has a smaller mean size and a narrower distribution of globule sizes.

The ZP of the globules present in the produced micro-emulsion ranged from -32 to -38 mV. The negative surface charge of the droplets is attributed in the direction of the fatty acids present in the employed excipients. This observation suggests that the particle size, PDI, and ZP values for PGZ are

Table 6: Optimization of PGZ L-SMEDDS formulation through robustness to dilution study

Formulation code	*Dilution medium*	*Dilution*	*Evaluation parameters*			
			*FI**	*%T**	*Appearance*	*Drug precipitation*
PLS_{12}	Distilled water	50	5	96.11	Slightly bluish	Stable
		100	5	98.17	Clear & Transparent	Stable
		1000	3	99.49	Clear & Transparent	Stable
	0.1N HCl (SGF)	50	5	95.13	Slightly bluish	Stable
		100	5	96.85	Slightly bluish	Stable
		1000	3	97.59	Clear & Transparent	Stable
	PB pH 6.8 (SIF)	50	5	95.65	Slightly bluish	Stable
		100	5	96.54	Clear & Transparent	Stable
		1000	3	97.29	Clear & Transparent	Stable
PLS_{18}	Distilled water	50	7	95.23	Slightly bluish	Stable
		100	7	95.23	Slightly bluish	Stable
		1000	5	96.51	Clear & Transparent	Stable
	0.1N HCl (SGF)	50	7	93.14	Bluish white	Stable
		100	7	94.52	Bluish white	Stable
		1000	5	96.41	Slightly bluish	Stable
	PB pH 6.8 (SIF	50	7	94.21	Bluish white	Stable
		100	7	95.21	Slightly bluish	Stable
		1000	5	96.46	Clear & Transparent	Stable

*Values are expressed as mean (n = 2)

within acceptable ranges. These formulations are anticipated to generate a micro-emulsion in biological fluids, ensuring stability upon oral administration until absorption occurs, as coalescence is not expected.

Morphology of globules through TEM

TEM examination was conducted on the optimized L-SMEDDS preparation subsequent a 1000-fold dilution with distilled water. The obtained image (Figure 6) validates the capability of PGZ L-SMEDDS to generate spherical oil globules in the nano size series (35–90 nm). The distribution of oil globules was uniform across the film. This TEM observation aligns with the outcomes gained from droplet size examination.

Drug content analysis

The measurement of drug content in the optimized batches revealed values within the acceptable range, ranging from 100.23 to 102.56%. These results indicate that PGZ is effectively dissolved and uniformly distributed within the scheme.

In-vitro dissolution study

Dissolution of pure PGZ in an aqueous solution and the optimized PGZ L-SMEDDS were evaluated in numerous dissolution mediums, including 0.1N HCL, pH 6.8, and sodium acetate buffer pH 4.5, as depicted in Figures 7 (a) and (b). Pure PGZ exhibited limited dissolution, with a maximum release of 45% within the 60-minute run time across all three dissolution mediums. Conversely, the optimized L-SMEDDS of PGZ demonstrated a remarkable improvement, achieving >95% drug release within 30 minutes, regardless of the pH of the dissolution medium. This observation highlights a substantial enhancement (more than 2-fold) in the profile comparison in the direction of plain PGZ in all three mediums. The optimized L-SMEDDS formulation (PLS12) effectively disperses PGZ in a dissolved form, generating fine globules that spontaneously disperse, irrespective of the pH of the medium. The rapid and extensive release of PGZ from PLS12 suggests that L-SMEDDS can enhance the oral bioavailability of PGZ.

Preparation and Characterization of Solidified SMEDDS

Based on the findings of earlier experiments, Sylloid 244 FP (S2F) was evaluated for its adsorbing capacity to adsorb L-SMEDDS of PGZ. It was observed that S2F was able to adsorb greater L-SMEDDS of PGZ. S2F could adsorb around 2800 mg of PGZ L-SMEDDS per 1-gm and still maintain good flow characteristics. The composition of developed P-SMEDDS of PGZ is illustrated in Table 8.

DSC thermogram

The DSC Thermogram presented in Figure 8 illustrates the thermal characteristics of plain PGZ, a physical blend of PGZ and Syloid 244 FP (1:1 w/w), and the P-SMEDDS formulation. Plain PGZ displayed distinct sharp endothermic peaks at 199.31°C, indicating its highly crystalline nature. Syloid 244 FP didn't exhibit whichever peaks within the considered temperature range, aligning with reported data. The physical blend of Syloid 244 FP and PGZ in equal proportions exhibited a less strong endothermic peak at 196.87°C, indicating the existence of crystalline PGZ. The absence of distinct PGZ peaks in the powder SMEDDS preparation implies modifying

Table 7: Globule size, P.I. and ZP of PTZ L-SMEDDS

Distilled water			*0.1N HCl (SGF)*			*Phosphate buffer pH 6.8 (SIF)*		
Globule size (nm)[#]	*P.I.*[*]	*ZP*[*] *(mV)*	*Globule size (nm)*[#]	*P.I.*[*]	*ZP*[*] *(mV)*	*Globule size (nm)*[#]	*P.I.*[*]	*ZP*[*] *(mV)*
78.25 ± 6.27	0.435	- 38.3	81.75 ± 5.54	0.523	-32.78	89.33 ± 5.15	0.417	-36.09

[#]Globule size is expressed as mean ± SD (n = 2) [*]P.I. and ZP are expressed as mean (n = 2)

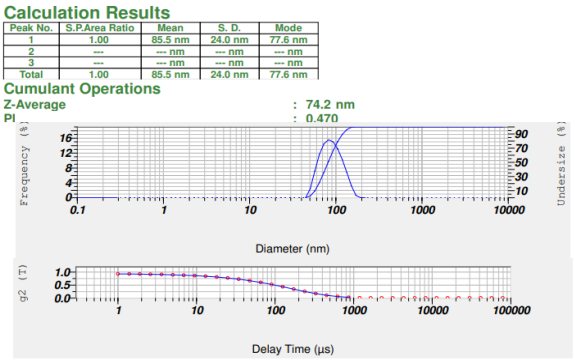

Figure 4: Size distribution and PDI batch in water

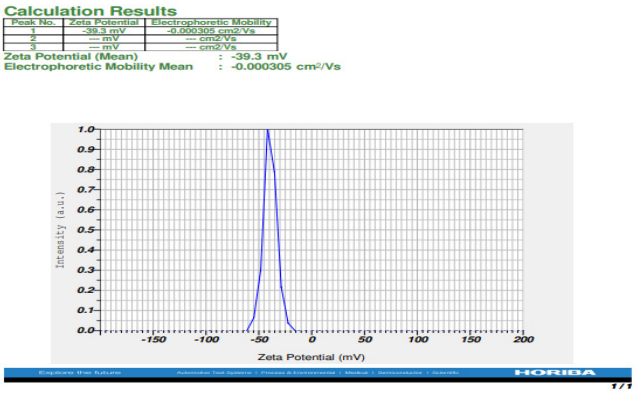

Figure 5: ZP distribution achieved from batch in SGF

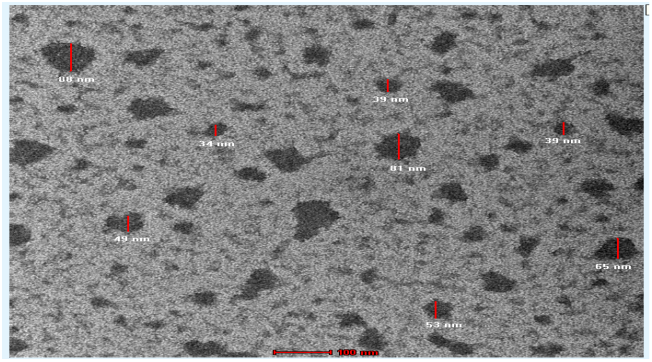

Figure 6: TEM image gained of PGZ L-SMEDDS in water

PGZ's melting behavior and preventing crystallization through lipid surfactants and solid carrier physical mixing.

Powder X-ray diffraction pattern

The XRD displayed in Figure 9 depicts of the plain PGZ (a), pure Syloid 244 FP (b), a physical blend of PGZ and Syloid 244 FP (c), and PGZ P-SMEDDS (d). The results reveal that plain PGZ (a) exhibited distinct sharp peaks at diffraction angles θ 26.004°, 22.577°, 19.884°, 18.669°, and 12.655°, indicating

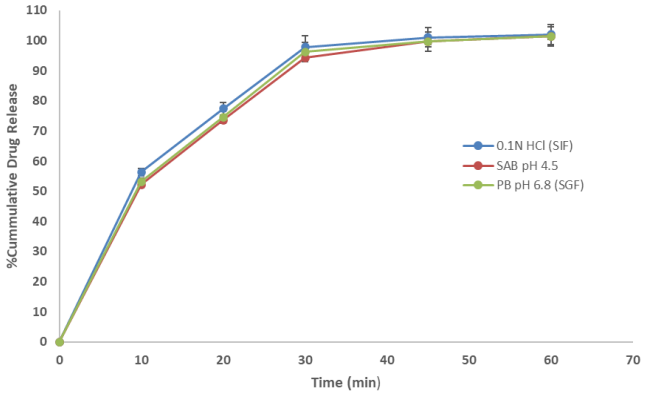

Figure 7(a): Release of PGZ L-SMEDDS in numerous dissolution medium

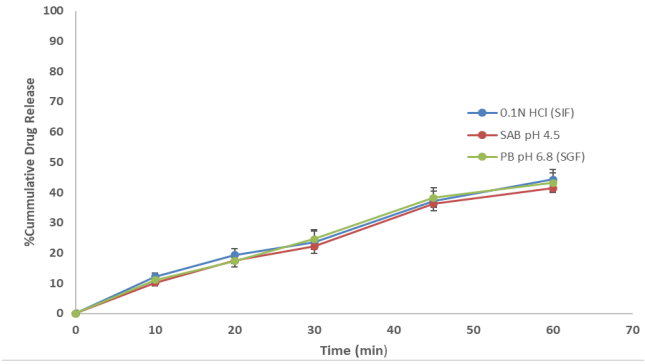

Figure 7(b): Release data of plain PGZ drug in numerous dissolution medium

a typical crystalline pattern. Syloid 244 FP (b) showed no inherent peaks. The foremost distinctive crystalline peaks of PGZ detected in the physical mixture with the solid carrier (Syloid 244 FP) (c) had reduced intensity, suggesting a partial conversion to the amorphous state for PGZ. The lack of intense peaks of PGZ in the preparation (d) specifies a complete alteration of the crystalline nature of PGZ to an amorphous state. Similar to the DSC findings, in P-SMEDDS formulations prepared with Syloid 244 FP, PGZ existed in a fully transformed amorphous state or a disordered crystalline phase within the lipid matrix. Importantly, no new peaks appeared in the P-SMEDDS formulation, indicating the compatibility of PGZ with Syloid 244 FP and the lack of interface amongst the drug and the carrier during physical mixing.

Morphological analysis of P-SMEDDS through SEM

The SEM analysis photo images presented in Figure 10(a) reveal that PGZ exhibits rectangular crystalline structures with sizes ranging from approximately 40 to 200 µm. Syloid

Table 8: Composition of PGZ Powder SMEDDS

Components	*Quantity (mg) per unit formula*
PGZ	15
CAPMUL MCM C8 EP	375
Cremophor RH 40	375
PEG 400	190
L-SMEDDS	955
Sylloid 244 FP	425
Powder SMEDDS	1380

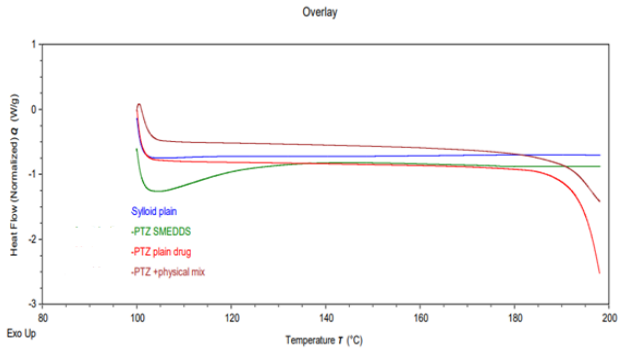

Figure 8: DSC Thermogram overlay of Plain PGZ, Plain Syloid 244 FP, PGZ + Syloid 244 FP physical mixture (1:1 w/w) and P-SMEDDS

244 FP [10 (b)] is observed as spherical porous, rough particles with sizes around 1 to 3 µm, displaying a small particle at the top of its surface. Micrographs of P-SMEDDS [10 (c)] reveal liquid SMEDDS adsorbed onto Syloid particles, with partially covered syloid particles due to promoted adsorption through physical mixing. Crystalline structures of PGZ are absent in P-SMEDDS micrographs, indicating the drug is fully dissolved in liquid SMEDDS before adsorption onto syloid 244 FP.

Outcome of solidification on globule size, PI and ZP

Optimized PGZ L-SMEDDS in water had a mean globule size of 78 ± 14.12 nm, while powder SMEDDS showed 170.5 ± 7.12 nm (Figure 11). The increase in globule size in P-SMEDDS was attributed to bimodal distribution from Syloid 244 FP. Solid SMEDDS samples allowed large syloid 244 FP particles to sediment before measuring droplet size in the remaining microemulsion. ZP distribution is presented in Figure 12.

Development and Evaluation of Tablet SMEDDS (T-SMEDDS) of PGZ

Table 9 illustrates the composition of the PGZ tablet from P-SMEDDS

Evaluation of PGZ T-SMEDDS Blend

Micromeritic characteristics

Flow characteristics were assessed by calculating the angle of repose, TD, BD, CI, and HR. The results (Table 10) indicated a favorable angle of repose for PGZ P-SMEDDS at 33º 33' ± 3º, with CI and HR both classified as "Good" at 5.84 ± 0.93 and below 1.06, respectively.

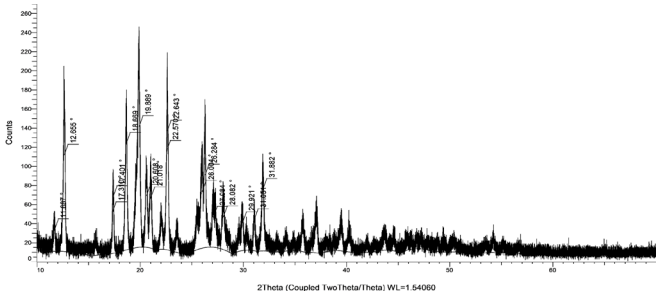

Figure 9(a): XRD of plain PGZ

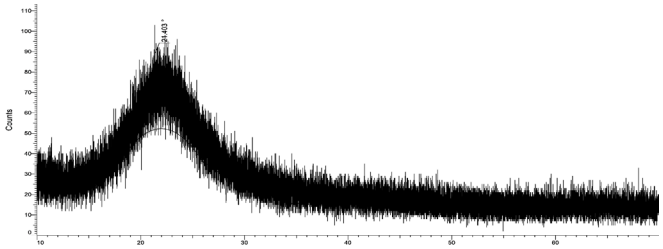

Figure 9(b): XRD of plain Syloid 244 FP

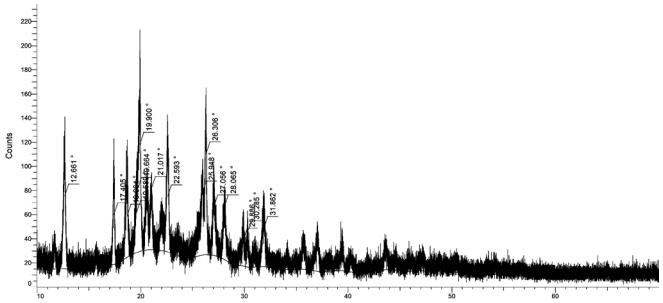

Figure 9(c): XRD of physical blend of PGZ and Syloid 244 FP

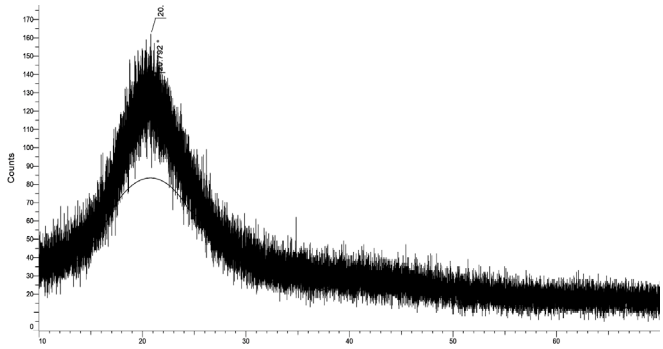

Figure 9(d): X-ray diffractogram of PGZ P-SMEDDS

Evaluation of T-SMEDDS

Physical characteristics of tablet

The parameters assessed for T-SMEDDS of PGZ indicated satisfactory results. Tablet weight variation fell within acceptable limits, with no deviation exceeding 5% w/w. The tablets exhibited sufficient hardness (4.5 kg/cm^2). Disintegration time for six tablets averaged 5 minutes and 45 seconds, meeting the specified requirements. The T-SMEDDS of PGZ also passed the friability test with a result less than 1%.

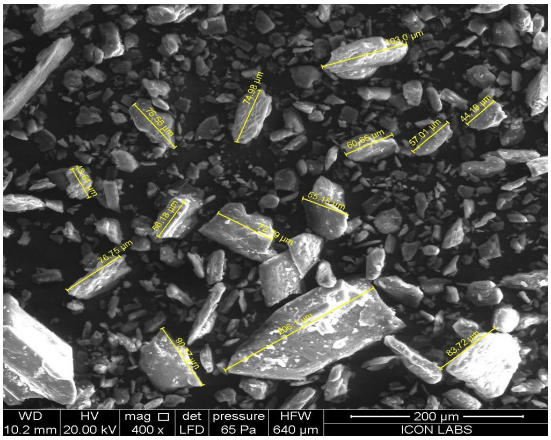

Figure 10(a): SEM images of plain PGZ

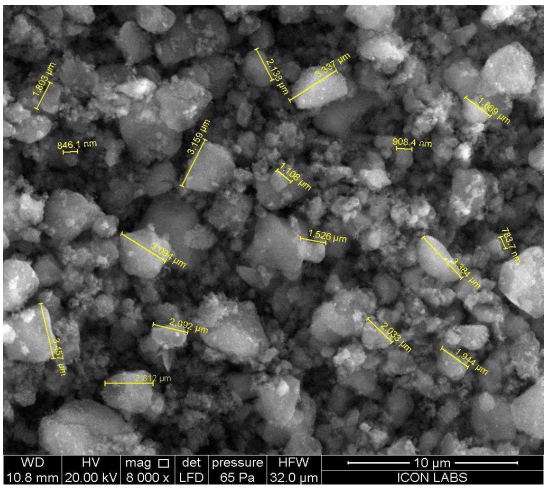

Figure 10(b): SEM images of plain syloid 244 FP

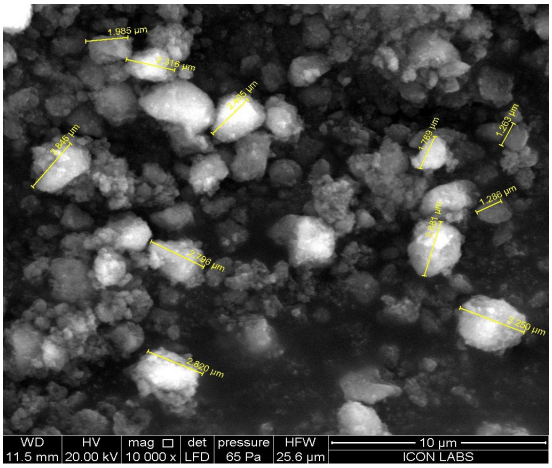

Figure 10(c): SEM images of PGZ P-SMEDDS

Drug content

The drug content of PGZ T-SMEDDS was calculated to be 102.52 ± 2.56%, suggesting a consistent and uniform distribution of PGZ-loaded T-SMEDDS within the tablet excipients.

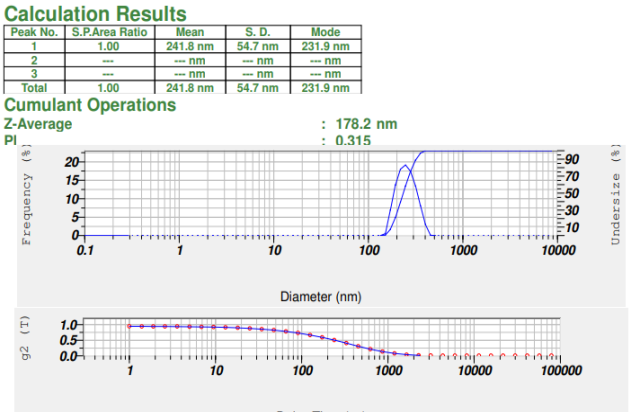

Figure 11: Globule size distribution and PDI of batch in water

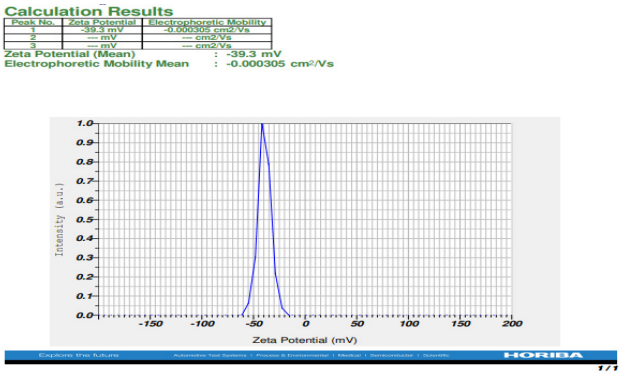

Figure 12: ZP distribution of batch in SGF

Table 9: Composition of optimized PGZ Tablet-SMEDDS

Ingredients	*Amount/tablet (mg)*	*% w/w*
PGZ P-SMEDDS	1380.00	76.67
Magnesium stearate	36.00	2.00
Talc	36.00	2.00
MCC	348.00	19.33
Weight (mg)	1800	100 .00

Table 10: Flow characteristics of PGZ T-SMEDDS blend

Parameter	*PGZ P-SMEDDS*
Angle of Repose	33º 33' ± 3º
BD *(g/mL)	0.4556 ± 0.319
TD*(g/mL)	0.4822 ± 0.126
CI*(%)	5.84 ± 0.933
HR*	1.06

* Values are expressed as mean ± SD (n= 3), BD-bulk density, TD-Tapped Density

In-vitro dissolution study of PGZ T-SMEDDS tablet

Figure 13 indicates that at the initial stage tablets require time to disintegrate and hence there, is slow dissolution of the drug was seen. However, once the tablet gets completely disintegrated, fast dissolution of drug was seen from the self-emulsifying

Table 11: *In-vivo* study results

Pharmacokinetic parameters	*Units*	*Group A- Plain PGZ API*	*Group B- Marketed 15 mg tablets*	*Group C- SMEDDS 15 mg tablets*
t1/2	h	2.32 ± 0.22	2.11 ± 0.22	1.34 ± 0.11
Tmax	h	4 ± 0.32	4 ± 0.22	4 ± 0.20
Cmax	µg/mL	1.31 ± 0.12	3.77 ± 0.42	6.62 ± 0.32
AUC 0-t	µg/mL*h	6.04 ± 0.82	16.83 ± 1.55	27.83 ± 2.72
AUC 0-inf_obs	µg/mL*h	8.48 ± 1.42	20.08 ± 3.69	29.85 ± 2.49

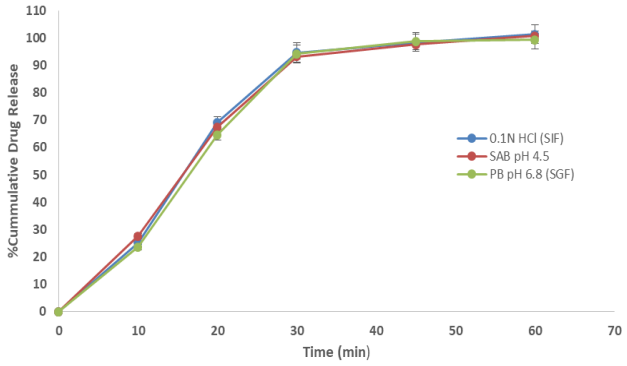

Figure 13: Release study of PGZ T-SMEDDS in numerous media

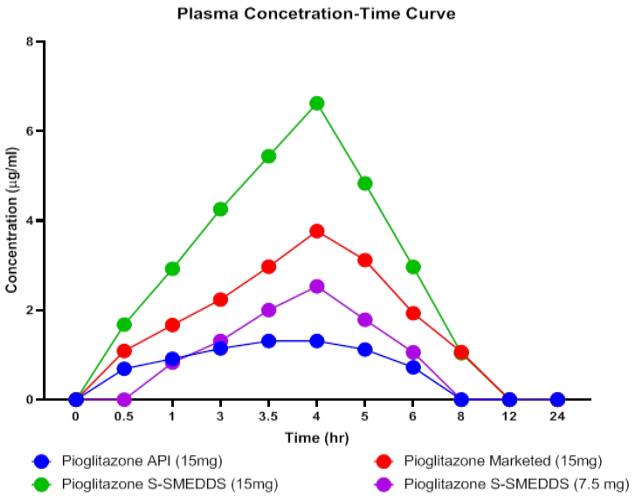

Figure 14: *In-vivo* study results

components as well as the solid carrier. At 45 minutes, more than 95% drug was dissolved in all three-dissolution mediums irrespective of the pH of the medium. These results indicate that as far as the dissolution is concerned, the self-emulsifying tablet formulation of PGZ was found to be very fast dissolving & release was found to be pH independent.

In-vivo study

In a crossover study design, an oral bioequivalence investigation was carried out utilizing healthy wistar rats under fasting conditions. The tablet preparation of S-SMEDDS was compared against both plain API and a marketed product. The pharmacokinetic profiles were depicted in Figure 14. The parameters, including AUC, T1/2, and MRT, for all variants are presented in Table 11. Notably, the tablets formulated with SMEDDS displayed a noteworthy increase in C_{max} and AUC comparison in the direction of both the marketed tablets and plain API. This observed enhancement in these parameters suggests an improvement in solubility and bioavailability for the SMEDDS formulation.

DISCUSSION

The study aimed to improve the solubility and dissolution kinetics of PGZ Hydrochloride, a drug with limited water solubility. The strategy involved creating oral tablets for L-SMEDDS. The process encompassed developing L-SMEDDS and subsequently converting the optimal L-SMEDDS into an S-SMEDDS through syloid (SYL) adsorption. Selected P-SMEDDS formulation underwent comprehensive powder characterization and analytical assessment. The study successfully formulated 32 L-SMEDDS variants, identifying the optimal formulation (PLS12). PLS12 exhibited favorable characteristics, including a droplet size of 75 nm, well below 200 nm, indicating the formation of a nanosized droplet emulsion with uniform distribution. The formulation displayed stability under diverse conditions, achieving maximum drug loading capacity. Solidifying PLS12 into solidified SMEDDS (S-SMEDDS) utilizing Sylloid 244 FP yielded a free-flowing powder without drug interactions. The incorporation of S-SMEDDS in tablets was achieved utilizing varied tableting excipients. The selected tablet batch passed quality control and stability tests, demonstrating favorable mechanical characteristics, disintegration time, and *in-vitro* pharmacodynamics. The tablets exhibited significant potential for improving the water solubility, dissolution profile, and improved bioavailability of PGZ as compared to commercial tablets. The study emphasizes the synergistic impact of SMEDDS and tablets in increasing the solubility and dissolution of PGZ hydrochloride. Successful transition from liquid formulations to solid dosage forms presents a hopeful approach for enhancing poorly water-soluble drugs' overall drug delivery characteristics. The comprehensive characterization and testing conducted provide a strong foundation for further development and potential clinical applications of the proposed drug delivery system.

CONCLUSION

This investigation involved evaluating thirty-two formulations of L-SMEDDS for PGZ. The optimal formulation (PLS12) was determined, comprising 40% Capmul MC8 as oil, 40% Cremophore RH40 as surfactant, and 20% PEG as co-surfactant. PLS12 demonstrated a droplet size of

approximately 75 nm, well below 200 nm, and a polydispersity Index value of 0.47, indicating nanosized droplet emulsion with uniform distribution. The formulation exhibited stability under varied conditions, achieving maximum drug loading. solidifying the optimized L-SMEDDS into S-SMEDDS utilizing Sylloid 244 FP resulted in a free-flowing powder without drug interactions. Incorporating S-SMEDDS into tablets utilizing diverse excipients passed quality control and stability tests. The tablet exhibited a rapid and pH-independent release profile. The combined impact of SMEDDS and tablets synergistically improved the solubility and dissolution of PGZ hydrochloride.

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