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Development and Evaluation of a Solid Self-Microemulsifying Drug Delivery System Containing Cilostazol Using the Spray Drying Technique

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A robust self-emulsifying formulation containing cilostazol was produced by mixing hydrophilic surfactants with oil. Considering cilostazol's limited solubility and bioavailability, it was crucial to employ suitable formulation ingredients and methods to enhance the solubility and rate of dissolution of drug. The self-emulsifying system was developed using Tween 80, Polyethylene glycol 400, and Oleic acid, as determined by preliminary study. The microemulsion zone was identified by constructing pseudoternary phase diagrams. The spray drying process employed a liquid system comprising of an adsorbent (Aerosil 200) in a 1:1 ratio. The system was evaluated for in-vitro dissolution, % drug content, and emulsification time. Characterization of prepared system was done by Fourier transform infrared spectroscopy (FTIR), Differential scanning calorimetry (DSC), Scanning electron microscopy (SEM), Particle size, Zeta potential, and X-ray diffraction (XRD). The improved formulation had a particle size of 243.8 nm, with 96.52% of the drug being entrapped. Moreover, after one hour, it demonstrated a drug release of 98.01%, exceeding that of the pure drug, potentially attributable to the enhanced surfactant content that reduces both dispersion time and particle size. The drug was successfully converted from crystalline state to an amorphous form and was confirmed by XRD. The spray-dried particles exhibited a smoother surface and confirmed by SEM. The DSC thermogram indicated the absence of a melting endotherm in the system, suggesting that the drug was in an amorphous state and evenly dispersed.

Keywords: Aerosil 200; Cilostazol; Pseudoternary phase diagrams; Self Micro-emulsifying Drug Delivery System; Spray drying; Zeta potential.

Oral administration of drugs with poor water solubility accounts for almost 40% of all new drug candidates. When administered orally, these drugs often have poor bioavailability, substantial variability between subjects, and inadequate dosage proportionality. Several formulation strategies are utilized to address these issues; they include lipids, surfactants, micronization, salt formation, cyclodextrins, nanoparticles, solid dispersions, and permeation enhancers.[1] The approaches do have their limitations like particle aggregation, stability, and

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commercial potential. Among the several strategies demonstrated to enhance the bioavailability of partially water-soluble drugs, one involves the utilization of formulations comprising lipids, oils, or surfactants. Self-emulsifying drug delivery systems (SEDDS) formulations have effectively enhanced the oral bioavailability of insoluble drug compounds by keeping the drugs in a dissolved state within tiny oil droplets during their transit through the gastrointestinal tract.[2] Different lipid-based delivery systems include different combinations of oils, surfactants, co-surfactants, and solvents, ranging from basic oil solutions to more complicated mixtures. For the second group of compounds, the most common type of drug delivery system is a self-dispersing system, which goes by acronyms like SEDDS or Self Micro Emulsifying Drug Delivery System (SMEDDS). Although SMEDDS is more commonly used to describe formulations that disperse into transparent colloidal systems, SEDDS and SMEDDS both produce dispersions that are typically stable for months when used in practice.[3]

This study aimed to improve the solubility and dissolution rate of cilostazol, a synthetic phosphodiesterase III inhibitor. Cilostazol is used to alleviate symptoms of intermittent claudication and has antiplatelet and vasodilator effects. It inhibits the aggregation of platelets that is induced by collagen, 5'-adenosine diphosphate (ADP), epinephrine, and arachidonic acid. ilostazol, an antiplatelet drugs, increases endothelial cell function and prevents platelet aggregation. According to the Biopharmaceutic Classification System (BCS), this drug belongs to class II due to its poor aqueous solubility (6 ìg/mL), and high permeability, hence may exhibit poor bioavailability. Various strategies like salt formation, nano-suspensions, inclusion complexes, nano-emulsions, etc. have been employed to improve its bioavailability. Certain formulations demonstrated enhanced absorption and improved bioavailability. However, conventional colloidal systems have several drawbacks, such as globule size, phospholipids or polymers degradation, cytotoxicity, stability concern, outflow of drug and limited cost-effectiveness. In an effort to increase the bioavailability and solubility of drugs, lipid-based vehicles have recently drawn the interest of researchers.[4,5] While SMEDDS provide numerous benefits, limitations such as low drug loading capacity, limited dosage form options, and challenges in handling and storage have prompted the solidification of this system through various methods. The spray drying technique for solidification presents numerous advantages, including scalability and stability.[6,7]

An attempt was undertaken to address these limitations by formulating the drug as a SMEDDS to enhance its solubility and dissolution, potentially leading to an improvement in bioavailability.

MATERIALS AND METHODS

Materials

Cilostazol was obtained as a gift sample from Amsal Pvt Ltd (Gujrat, India). Tween 80 was acquired from SD Fine (Mumbai, India). Oleic acid and PEG 400 were acquired from Thomas Baker in Mumbai, India. Methanol analytical grade (AR) was acquired from Merck (Mumbai, India). Aerosil 200 was acquired from Research Lab Fine Chem Industries in Mumbai, India.

Method

Screening of Oils, Surfactants, and Cosurfactants

The drug was dissolved in 5 mL of oil, 5 mL of surfactant and co-surfactant mixture in separate 10 mL stoppered vials. In order to achieve equilibrium, the liquids were combined using a vortex mixer. Then, the vials were shaken using an orbital shaker at a temperature of 37°C ± 1°C for 48 hours at 100 rpm.[8]

Construction of Pseudo-ternary Phase Diagram

The microemulsion zone and the possibility of creating microemulsions with different oil and surfactant-cosurfactant combinations, such as Oleic acid, Tween 80, and PEG 400, were determined through the development of pseudo-ternary phase diagrams using a water titration technique. Surfactant to cosurfactant ratios of 1:1, 2:1, and 3:1 were selected and mixes were prepared according to these ratios. Weight ratios of 90:10, 80:20, 70:30, 60:40, 50:50, 40:60, 30:70, 20:80, and 10:90 were used to blend the surfactant-cosurfactant combinations with the oil phase. The mixture was stirred with a magnetic stirrer as water was added gradually until a uniform solution or dispersion was achieved. We checked the system's physical condition after each increment. As soon as the solution became a bit cloudy or turbid, we knew

the titration was complete. We kept track of how much water was needed to make the solution turbid. Lastly, phase diagrams have been generated using the CHEMIX software (trial version 3.5).[8,9]

Formulation of Liquid Self-Microemulsifying Drug Delivery System (L-SMEDDS)

Based on solubility experiments and ternary phase diagram analysis, the oil to surfactant-cosurfactant ratios for L-SMEDDS formulation were established, as indicated in Table 1. The oleic acid, Tween 80 and PEG 400 was used as the oil phase, surfactant, and co-surfactant, respectively. After adding ciprostazol to the oil phase, vortexing vigorously for 10 min was performed. After that, the mixture was vortexed for a further 15 minafter the surfactant and co-surfactant were added. To aid dissolution of cilostazol, the mixture was then heated for 10 min in a water bath kept at 40 ± 2°C. The mixture was heated and then allowed to cool to room temperature before being used again. Visual examination, self-emulsifying property assessment, and in vitro drug release tests were used to evaluate the L-SMEDDS.10,11

Spray drying of prepared L-SMEDDS

The solid SMEDDS were prepared utilizing a lab-scale spray dryer (Labultima LU 222). Aerosil 200, an inert carrier, was dispersed in 100 mL of methanol and stirred using a magnetic stirrer to form a suspension. A liquid SMEDDS, with a SMEDDS to carrier ratio of 2:1, was integrated into the suspension and continuously stirred at 40°C until a clear and homogeneous suspension was obtained. The suspension underwent spray drying utilizing a peristaltic pump with a nozzle diameter of 0.7 mm, under specified conditions: a feed flow rate of 2 mL/min, an inlet temperature of 60°C, an outlet temperature of 50°C, a cooling temperature of 45°C, an air pressure of 6.5 kg/cm², an aspirator flow rate of 50 Nm³/h, and a vacuum level of 90 mm of Wc. The resulting powder was collected and stored in a desiccator for subsequent use.[12]

Evaluation of Solid-SMEDDS (S-SMEDDS)[13,14]

Percent practical yield

By using following equation, percent practical yield of spray-dried particles was determined.

$$\%\ practical\ yield = \frac{Weigt\ of\ spray\ dried\ formulation\ obtained}{weigt\ of\ liquid\ SMEDDS+Aerosil\ 200} \times 100$$

...(1)

Angle of repose

The static funnel method was used to measure the angle of repose for the S-SMEDDS formulation. A 5 g sample of S-SMEDDS that had been accurately weighed was let fall out of the funnel onto a surface. The funnel was raised to the point where it almost brushed the top of the S-SMEDDS pile. The resulting cone's height and diameter were then measured, and the angle of repose was computed using the equation that follows:

$$\theta = tan^{-1}(h/r)$$

...(2)

Where, h and r are the height and radius of the powder cone respectively. The experiment was performed in triplicate to ensure accuracy.

Carr's index (Compressibility index)

An easy way to measure the bulk and tap densities and compaction rate of a powder is with the Carr's index. The given equation was used to determine it.

$$Carr's\ Index = \frac{Tapped\ density - bulk\ density}{Tapped\ density} \times 100$$

...(3)

The apparent bulk density (BD) was determined by pouring the powder into a graduated cylinder and measuring the volume. The density, expressed in g/mL, was calculated using the following formula:

$$BD = \frac{M}{V_0}$$

The mass of the powder is represented by M, while its bulk volume is represented by V€ . To get the tapped density (TD), a digital bulk density instrument (Metalab Mumbai, India) was used to tap the cylinder. We recorded the volume after 100 taps until we reached a constant level. The tapped density, expressed in g/mL, was then determined using this final volume.

$$TD = \frac{M}{V_t}$$

The mass of the powder is represented by M, while its bulk volume is represented by V_t. To make sure each composition was accurate and reliable, it was tested three times.

Hausner's ratio

The flow characteristics of a powder are quantitatively reflected by Hausner's ratio. The following equation was used in the computation.

$$Hausner's\ ratio = \frac{TD}{BD}$$

Hausner's ratio value below 1.25 is desirable for optimal flow of powder.

Emulsification Time

In a 250 mL conical flask with 0.1 N HCl, around 0.5 g of produced SMEDDS were added. After that, the flask was placed on a magnetic stirrer running continuously, and the amount of time needed for the emulsification process to finish was noted.[15,16]

In-vitro Drug Release

The USP class II dissolving test device was used to measure the release of cilostazol. A hard gelatin capsule with approximately 5 mg of equivalent powder was used. The investigation was carried out at 37 ± 0.5°C and 50 rpm, using 900 mL of 0.1 N HCl (pH 1.2) and a phosphate buffer (pH 6.8) as the dissolution media. Sample solutions were taken out, filtered, diluted, and measured at 254 nm using a UV spectrophotometer at predetermined intervals. Promptly, fresh dissolving media was added to keep the sink condition. Next, under the identical circumstances, the drug release profile and the pure drug's dissolution profile were contrasted.[2,17,18]

FTIR Study

The Shimadzu IR Affinity-1 FTIR spectrophotometer was employed to acquire the FTIR spectra of cilostazol and S-SEDDS using a KBr disk. The wavenumber range of 4000 to 400cm-1 was used to scan and record all spectra.[19,20]

DSC study

The drug's purity and thermal behavior were assessed using a DSC study (Hitachi High Tech Science Corporation, Japan). The drug and the S-SEDDS formulation were both accurately measured and sealed in aluminum pan, with each sample weighing 2-5 mg. The samples were initially maintained at a predetermined temperature for 5 min. Subsequently, they were elevated from 25°C to 300°C at a rate of 10°C/min, while an inert nitrogen gas was continuously supplied at a rate of 20 mL/min.[21, 22]

Globule Size and Zeta Potential

The Malvern Zetasizer (Nano ZS90, Malvern, UK) was used to measure the globule size and size distribution. To make a homogenous dispersion, around 1.0 g of the sample was thoroughly mixed with double-distilled water. The zeta potential, size distribution, and mean diameter of this combination were then determined by placing it in the photocell of the Zetasizer.[9]

SEM analysis

The particle size, shape, and surface structure of both the pure drug and the optimized formulation were analyzed using SEM (Quanta 200, Netherlands) in conjunction with an image analysis system (Software xT: Microscope Control; Source Tungsten Filament). The samples were mounted on brass stubs using double-sided adhesive tape and then coated with platinum under vacuum at 15 kV.[2,23]

XRD study

The solid state of pure drug and cilostazol in S-SMEDDS was analyzed using PXRD measurements conducted with an X-ray diffractometer (Model D2 Phaser, Bruker, Germany). The tests were conducted at ambient temperature using monochromatic Cu Ká-radiation at 10mA and at 30kV, covering a 2è range of 5 to 80° with a constant scanning speed of 5°/min. The examined specimens were densely arranged into the hollow space of an aluminum sample holder utilizing a glass slide.[10]

RESULTS AND DISCUSSION

Evaluation of Liquid SMEDDS

Oil plays a vital role in the L-SMEDDS formulation because it can dissolve lipophilic drugs and facilitate self-emulsification. Surfactants and co-surfactants are equally important. he drug must dissolve well enough in the oil for effective emulsification. The drug exhibited significantly greater solubility in oleic acid compared to other oils and was also soluble in Tween 80 and PEG 400. As a result, they were selected for the L-SMEDDS formulation, with findings presented in Table 2.

Table 1. Formulation batches of liquid SMEDDS in mg

Batches	Drug (mg)	Oil (mg)	Surfactant-co-surfactant (mg)	Total quantity (mg)
L1	5	150	700	855
L2	5	200	700	905
L3	5	100	800	905
L4	5	200	800	1005
L5	5	150	800	955
L6	5	100	750	855
L7	5	150	750	905
L8	5	200	750	955
L9	5	100	700	805

Table 2. Solubility of drug in different oils, surfactants, and co-surfactants

Oils	Solubility (mg/ml)	Surfactant	Solubility (mg/ml)	Co-surfactant	Solubility (mg/ml)
Oleic acid	0.112	Labrafil M 2125	0.091	Peceol	0.099
Olive oil	0.100	Captex 200P	0.032	PEG 200	0.095
Arachis oil	0.100	Tween 80	0.096	PEG 400	0.119
Til oil	0.106	Tween 20	0.094		
Soyabean oil	0.103	Cremophor EL	0.086		
Sunflower oil	0.103	Cremophore RH40	0.085		

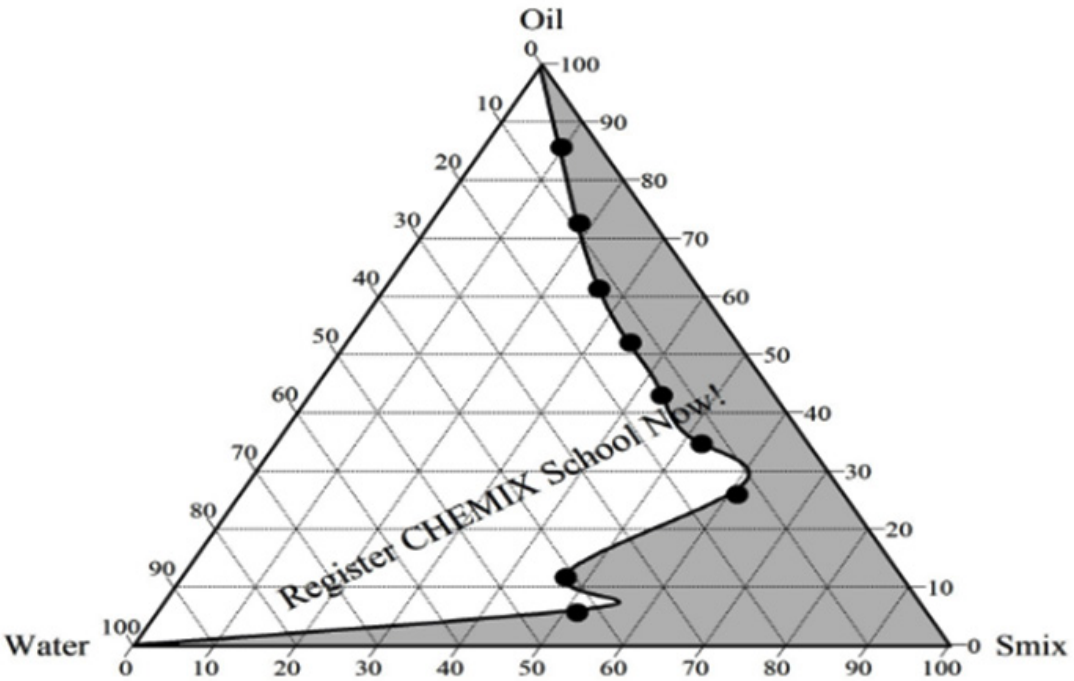

Fig.1. Pseudo-ternary phase diagram with different oils, surfactants and co-surfactants

Pseudo Ternary Phase Diagram

The area of microemulsion formulation expanded as the ratio of Smix rose, as this led to an increase in the emulsification of oil. Figure 1 shows a boundary that marks the microemulsion zone, where clear and transparent formulations were produced. The phase research revealed that the microemulsion area was maximized when the surfactant to co-surfactant ratio was 2:1, in comparison to other ratios. The

Table 3. Flow properties of S-SMEDDS

Batch spray drying technique	Bulk Density (g/ml)	Tap Density (g/ml)	Carr's Index (g/ml)	Hausner's ratio	Angle of Repose (°)
1:1	0.2635±0.15	0.3122±0.17	15.60±2.45	1.18±0.12	29.35±3.15

Table 4. *in vitro* drug release of S-SMEDDS in different media

Time (min)	Distilled water (%CDR)*	0.1 N HCl (%CDR)*	Phosphate buffer pH 6.8 (%CDR)*
10	56.08±2.36	79.88±2.36	73.78±2.46
20	63.37±1.57	82.15±2.63	78.15±2.69
30	77.97±2.34	87.13±2.89	83.48±3.26
40	89.17±2.12	90.75±3.27	91.26±3.78
50	95.00±3.68	93.02±3.53	95.13±2.45
60	96.46±2.71	98.01±4.12	97.07±2.76

*n=03

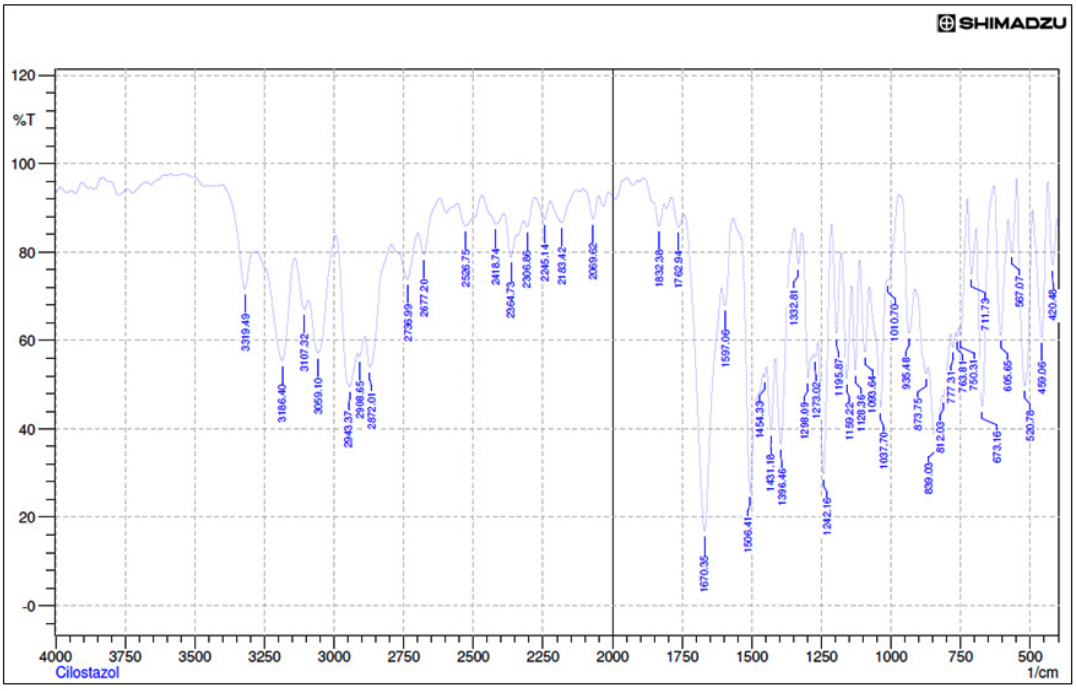

Fig. 2. FT-IR Spectrum of cilostazol

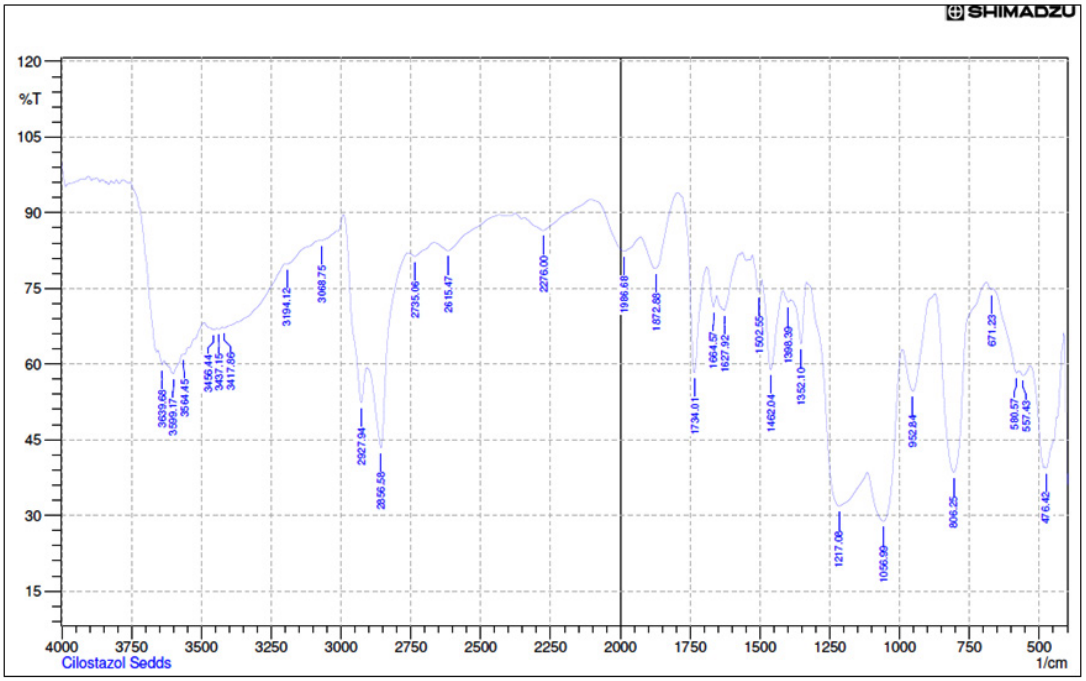

Fig. 3. FT-IR Spectrum of S-SMEDDS

Results

			Size (d.nm):	% Intensity:	St Dev (d.n...
Z-Average (d.nm):	243.8	Peak 1:	155.6	100.0	39.16
PdI:	0.513	Peak 2:	0.000	0.0	0.000
Intercept:	0.938	Peak 3:	0.000	0.0	0.000

Result quality : Refer to quality report

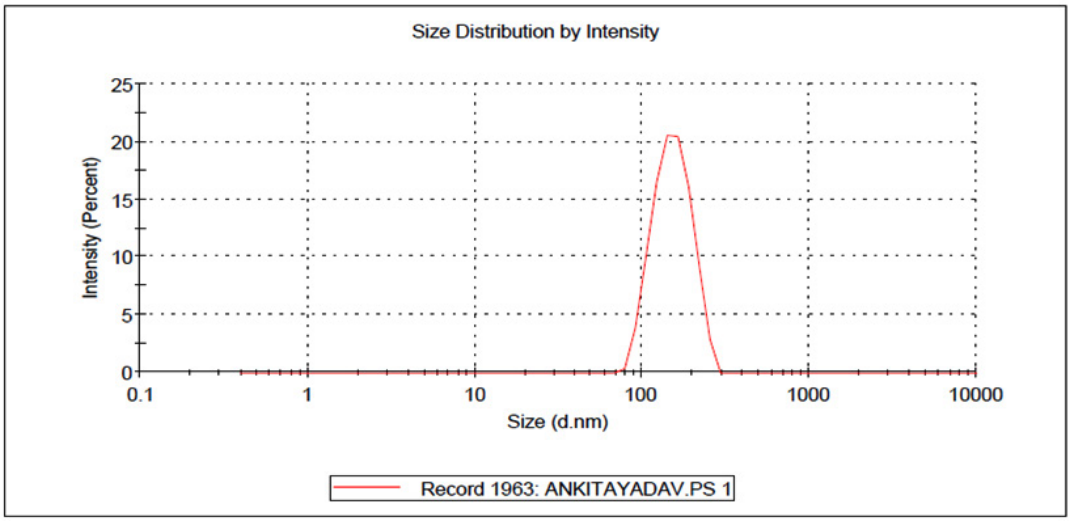

Fig. 4. Particle size of S-SMEDDS

L-SMEDDS exhibited transparency and had a homogeneous, single-phase liquid appearance when examined against light for visual clarity. The absence of any un-dissolved drugs or other solid ingredient implies the formulation is optically clear. The formulations exhibited stability and did not exhibit phase separation after heating, chilling, and centrifugation. Moreover, the formulation was found to be unaffected by dilution with water and 0.1N HCl (pH 1.2), which confirms its ability to maintain its effectiveness even when diluted. The formulation's self emulsifying capacity varies depending on the concentration of Smix. It was observed that, with increase in concentration of Smix, emulsification time reduced and found to be within 40 to 52 sec. The drug concentration of all formulations was in acceptable range (L2, 96.85%).

Evaluation of S-SMEDDS

Spray drying was used to dry all of the previously created liquid formulations after they were adsorbed on a carrier. The % practical yield is good in the case of spray drying, according to reports. A % practical yield between 78.14% and 85.68% was recorded. The S2 batch produced the highest yield. All of the formulations demonstrated rapid emulsification, and the drug content ranged from 88.96 to 96.52% which was in acceptable range. The time required for emulsification was measured. Formulation S2 emulsified rapidly (in 42 seconds), however Formulation S5 needed more time (54 seconds) than the others.

Flow properties of the powder

The carr's index, Hausner's ratio and angle of repose are shown in table 3 and the values signified that prepared S-SMEDDS exhibit good flow properties.

In-vitro drug release of S-SMEDDS

The results of the in vitro drug release study indicated that increasing the amount of surfactant slightly enhanced drug release, whereas a higher quantity of adsorbent led to a reduction in %CDR. The optimized batch demonstrated the highest drug release. This optimal self-emulsification may be attributed to the amount of oil used. Additionally, as the surfactant concentration raises, the proportion of oil increases, resulting in smaller droplet sizes. This creates a larger surface area for interaction with the dissolution media, facilitating maximum release. The cumulative drug release percentages over 60 minutes for all formulations are shown in Table 4.[12]

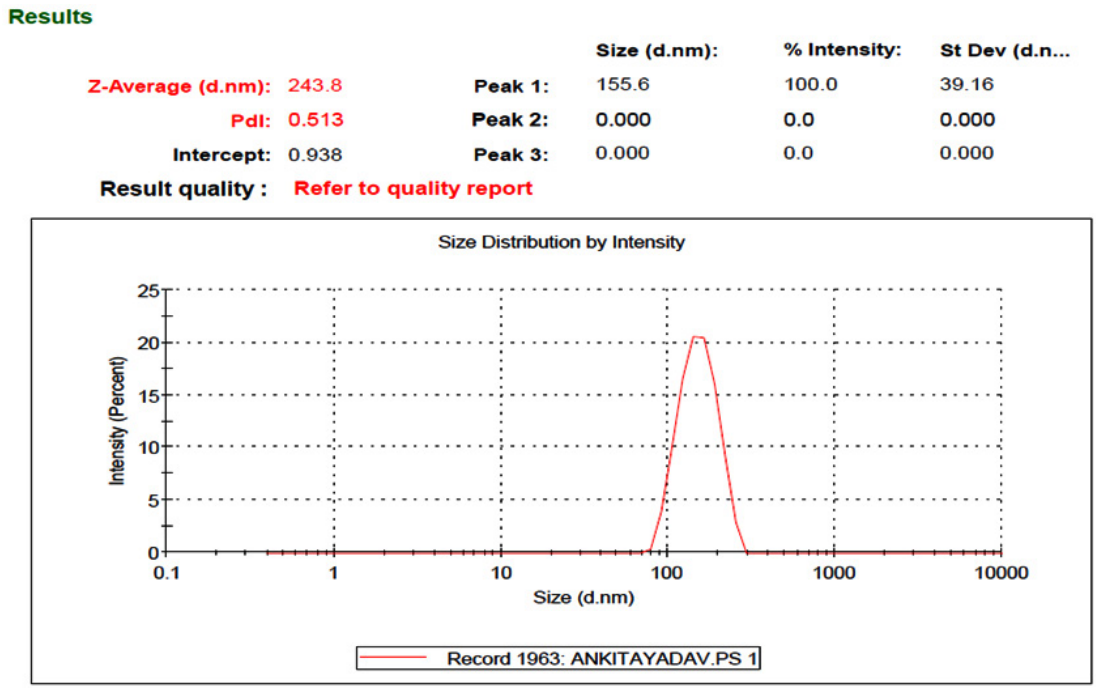

Fig. 5. Zeta potential of S-SMEDDS

FTIR Study

The IR spectra of cilostazol were recorded and analyzed for functional groups and observed peaks. The results were compared to the findings in the FTIR study, and the intensity of the prominent peaks of the drug was determined. These peaks include an N-H stretch at 3186.40 cm^{-1}, a C-H stretch at 2942.33 cm^{-1}, and a -NH-C=0 stretch at 1670.35 cm-1. The analysis verifies that the drug sample given is indeed cilostazol.

The FT-IR spectrum of the solid formulation displayed the spectra of both the drug and the excipients utilized is shown in figure 3. The intensity of distinct peak values, mentioned above had been remained unchanged with slight change in intensity and shifting of wave number. A new broad peak of hydroxyl group (-OH) observed between 3650-3150 cm-1 is of that of PEG 400. The primary amine group of drug merges in to

Table 5. Stability study of S-SMEDDS formulation

Temperature	Parameter	Initial	After 3 Months
45 ± 2°C	% Drug content	96.52±2.12%	95.32±1.58 %
75% RH ± 5	Dispersion time (sec)	54±2 sec	52±3 sec
	Emulsification time(sec)	42±3 sec	45±3 sec

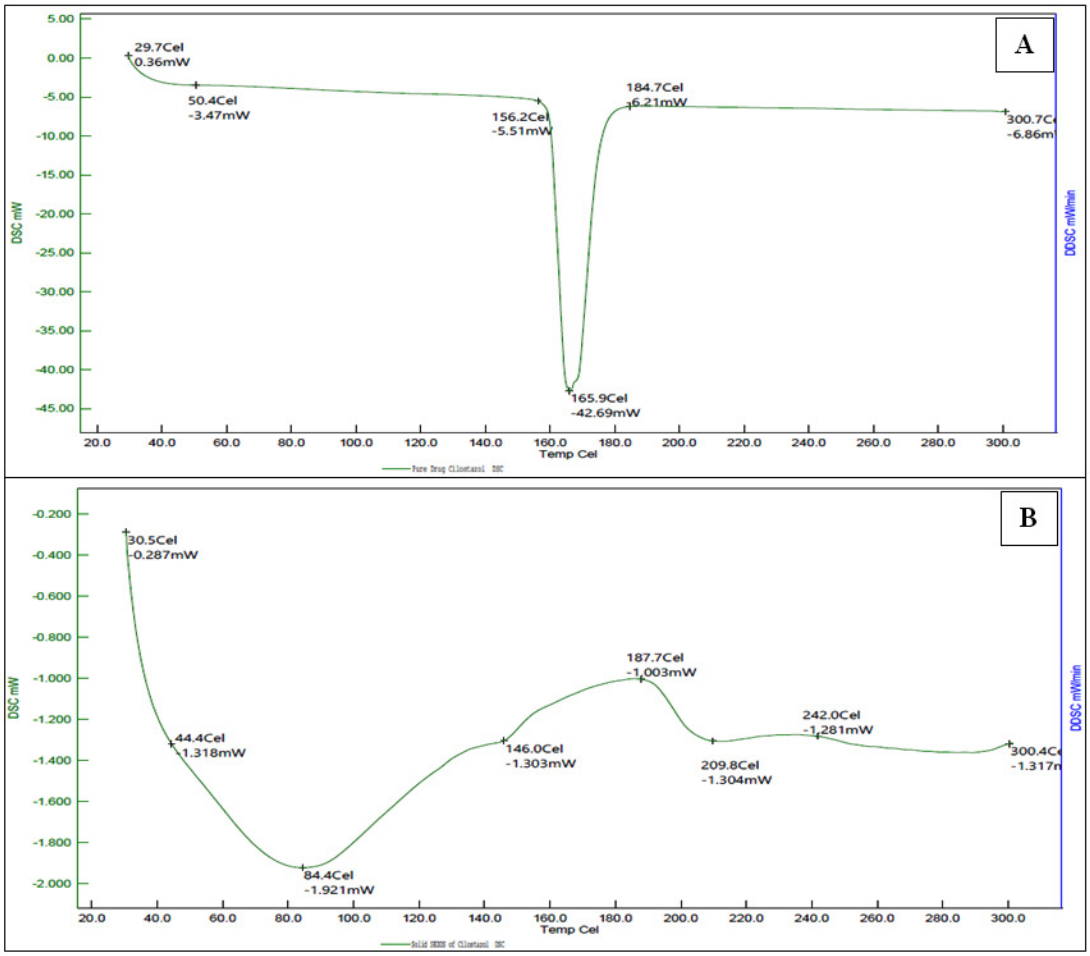

Fig. 6. DSC thermogram of cilostazol (A) and S-SMEDDS (B)

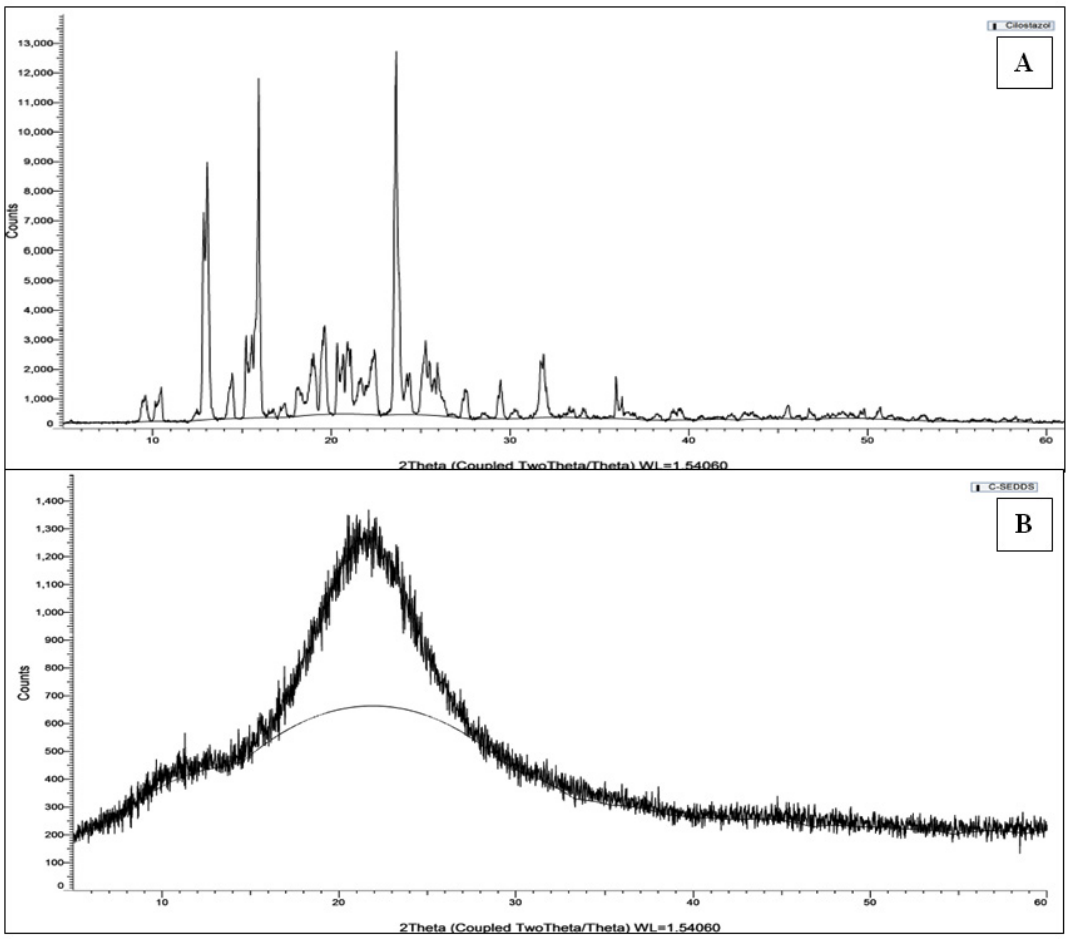

Fig. 7. XRD of cilostazol (A) and S-SMEDDS (B)

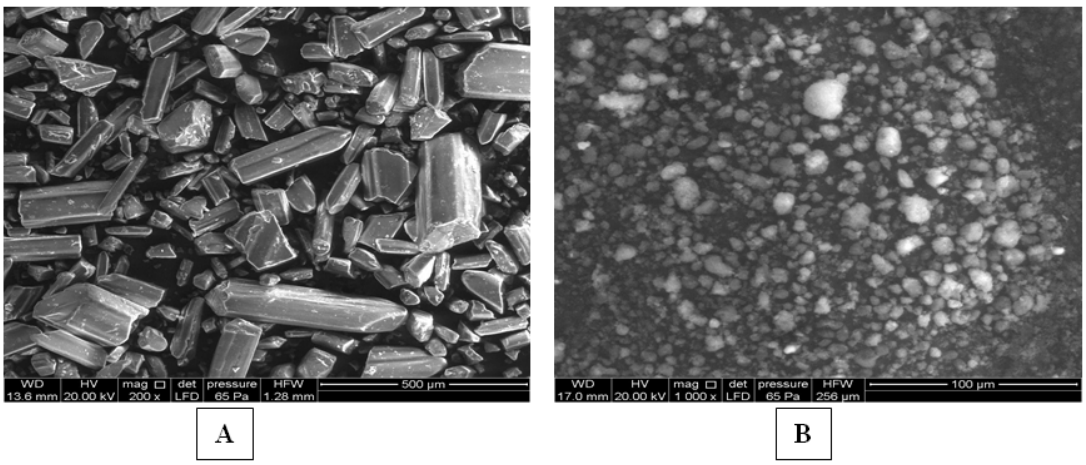

Fig. 8. SEM of cilostazol (A) and S-SMEDDS (B)

broad peak of OH between 3650-3150 cm^{-1}. The -NH-C=O peak slightly shifted to 1662.04 cm^{-1} with reduce intensity. FTIR data shown that, both drug and excipients utilized were present in spray dried S-SMEDDS.

Particle Size and Zeta Potential

The S-SMEDDS exhibited a particle size of 243.8 nm. The polydispersity index (PDI) measured 0.513, indicating the uniformity of droplet sizes in the formulation, as illustrated in Figure 4. The findings demonstrate that the globule diameters are less than 250 nm, thereby confirming the successful synthesis of S-SMEDDS. The PDI is within the 0-1 range, indicating that the optimized formulation demonstrates a uniform distribution and is considered stable.

The optimized solid formulation exhibited a zeta potential value of -10.3 mV, as illustrated in Figure 5. The zeta potential value indicates good long-term stability. The zeta potential values were ranged from -30 to +30mV. Therefore, the optimized formulations exhibited good stability.

DSC study

Figure 6 displays the DSC thermograms of cilostazol and its S-SMEDDS. The formulation lacked the endothermic peak indicative of drug melting. This could be attributed to either the drug being encapsulated, dissolved, or being in an amorphous form.

XRD Study

The XRD analysis of Cilostazol and the improved formulation was documented, as depicted in Figure 7. The physical characteristics of cilostazol and S-SMEDDS were assessed using XRD. The XRD pattern of cilostazol exhibits distinct and well-defined peaks. The X-ray powder diffraction pattern of the pure drugs exhibits crystallinity. The S-SMEDDS did not exhibit any noticeable crystalline peaks. The drug was incorporated in S-SMEDDS, resulting in a decrease in peak intensities. It suggests that the drug's crystalline structure was altered as drug present in dissolve state in the formulation. It can be concluded that the drug's crystalline structure A transformed into an amorphous state when being formulated into S-SMEDDS.

SEM Study

The surface morphology of cilostazol, S-SMEDDS was analyzed using an analytical SEM, as depicted in Figure 8, and indicate drug is present in crystalline form. The SEM image of S-SMEDDS shows that they have a smooth surface, suggesting that the L-SMEDDS is absorbed or coated within the pores of Aerosil 200.

Stability study

A stability investigation was conducted on the optimal formulation for duration of 3 months at a temperature of 40 °C and a relative humidity of 75%. After a period of 3 months, the formulations were analysis to determine the percentage of drug content, emulsification time, and dispersion time (as shown in Table 5).

CONCLUSION

An effective self-emulsifying formulation of cilostazol was successfully developed by combining Oleic acid, Tween 80, and PEG 400. The formulation was then adsorbed onto Aerosil 200 using a spray drier technique. The solidification of the system can address the conventional limitations of L-SMEDDS. The resulting system exhibited a fine particle size and, when dispersed in aqueous environments, displayed a small droplet size. The zeta potential served as a measure of the system's stability. The dissolving profile of both the pure drug and S-SMEDDS clearly demonstrates the significance of this system in the pharmaceutical sector for improving the dissolution of drugs that have low solubility in water. L-SMEDDS, when combined with spray drying, may have potential industrial uses.

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Conflict of Interest

The authors do not have any conflict of interest.

Data Availability Statement

This statement does not apply to this article.

Ethics Statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Author's contribution

Moreshwar Patil: Designing and conducting experiments or data analysis. Handling the submission and correspondence with the journal; Ankita Yadav: Conduct the majority of the research; Rajendra Mogal: Reviewing and editing the manuscript; Mahevish Shaikh: Providing technical assistance; Sulabha Lalsare: Ensuring the research adheres to ethical standards; Sanjay Kshirsagar: Overseeing the research design and methodology.

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