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Research Article

Formulation and Evaluattion of Self-Micro Emulsifying Drug Delivery System of Cyclosporine Softgels for Improving Oral Bioavailability

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ABSTRACT

Objective: Cyclosporine is a neutral cyclic non-ribosomal peptide composed of 11 amino acids that was first isolated from the fungal extract of Tolypocladium inflatum in 1973. Cyclosporine is a one of the calcineurin inhibitors, is an immunosuppressant widely used to prevent organ rejection after transplantation. Cyclosporine is a BCS class II drug and is bioavailability around 20-40% due to its poor solubility. Self-micro emulsifying drug delivery system (SMEDDS) of Cycosporine will be developed to improve drug solubility in physical conditions and oral bioavailability. Methods: The purpose of the present study is to develop a self-micro emulsifying drug delivery system (SMEDDS) of Cyclosporine softgelatin capsules (100mg) by rotary die process. The nine formulations F1 to F9 were formulated using Capmul MCM as an oil phase, polysorbate 80 as a surfactant and propylene glycol as a co-surfactant in various ratio. Cyclosporine was added very slowly into the glyceryl monocaprylate caprate (Capmul MCM oil) and it was well mixed at the RPM of 700±15 for 30 minutes and Polysorbate 80 (surfactant) and propylene glycol (co-surfactant) was added into the mixture under continues mixing and it was well mixed at RPM of 700±15 for 2 hrs. The nine formulation was prepared and evaluated the pre and post encapsulation parameters of Cyclopsorine SMEDDS formulation, viz., description, pH, Phase separation study, weight per ml, flow character, viscosity, emulsification time, percentage transmittance, thermodynamic stability studies, drug content, loss on drying, weight variation, Dimension, disintegration, *in vitro* release were investigated.

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INTRODUCTION

The pharmaceutical term [1] "emulsion" is most time used to indicate preparations prepared for internal use. Emulsions for external use are always given a different title that it focuses may indicate their use, e g. lotion and cream. An emulsion may be defined as a biphasic system consisting of two immiscible liquids, one of which (the dispersed phase) is finely and uniformly dispersed as globules throughout the second phase (the continuous phase). Oral route [2] is the easiest and most convenient way of non-invasive administration. Oral drug delivery systems being the most cost-effective have always lead the worldwide drug delivery market. This oral route may be a problem route for drug molecules which exhibit poor aqueous solubility. When a drug is administered by oral route the first step for it to get absorbed is its solubilization followed by permeation. Approximately [3], 40% of the new drug candidates in development today are water insoluble and associated with poor bioavailability. were various formulation approaches reported to overcome these problems; these include the use of drug nanoparticles, solid dispersions, micronization, lipids, surfactants, complexation with cyclodextrin, and permeation enhancers.Self-micro emulsifying drug delivery systems [4] (SMEDDS) are complex lipid-based drug delivery systems composed of a mixture of oils (lipids), surfactants, and optionally co-surfactants and co-solvents that have great potential for enhancing the drug solubility and oral bioavailability of poorly water-soluble drugs, such as class II and class IV drugs of the biopharmaceutical classification system (BCS). SMEDDS [5] are defined as isotropic mixtures of synthetic or natural oils, solid or liquid surfactants and cosolvents/co-surfactants which upon mild turbulence followed by dilution in aqueous media, such as GI fluids, can form fine oil-in-water (o/w) emulsions or micro emulsions. Cyclosporine[6,7,8,9,10,11] is (BCS Class II, Biopharmaceutical Classification System) is a fat soluble, hydrophobic polypeptide metabolite of fungus *Beauveria nivea* (formerly *Tolypocladium inflatum* Gams).

It is a hydrophobic cyclic peptide built from non-mammalian amino acids with low oral bioavailability, which is one of first line immunosuppressive drugs used to prevent transplant rejection and to treat autoimmune diseases. Cyclosporine is a one of the above-mentioned low solubility active substances that have been used for many years, is a neutral cyclic non-ribosomal peptide composed of 11 amino acids that was first isolated from the fungal extract of Tolypocladium inflatum in 1973.Cyclosporine is a one of the calcineurin inhibitors, is an immunosuppressant widely used to prevent organ rejection after transplantation, just like the other calcineurin inhibitor tacrolimus. Cyclosporine shows its immunosuppressant activity by forming a cyclosporine-cyclophilin complex after binding to cyclophilin, thereby inhibiting T-cell activation and calcineurin phosphatase, which, under normal circumstances, is responsible for activating the transcription of interleukin-2 (IL-2).

MATERIALS AND METHODS

2.1 Materials and chemicals

Cyclosporine was procured as a gift sample from softgel healthcare private limited (Chennai), Capmul MCM oil was bought from AAK India Pvt Ltd (Maharashtra), Polysorbate -80 was bought from Kamlesh Enterprise (Mumbai, India), Propylene glycol was bought from Griver enterprises (Jaipur, India). All chemicals used were of analytical grade.

2.2 PREFORMULATION STUDIES

2.2.1 UV- Spectroscopic Analysis of Cyclosporine [12]

2.2.1.1 Preparation of Standard Stock Solution Using Methanol

The standard stock solution was prepared by dissolving 25 mg of Cyclosporine with methanol and the solution was sonicated for 2-3 min to dissolve drug. The volume was then made up to 100 ml with methanol.

2.2.1.2 Preparation of Working Standard Solution

To prepare working standard solutions 1,2,3,4 and 5 ml of the standard stock solution were diluted to 25 ml with methanol. The absorbance was measured at 287 nm using UV- spectrophotometer (Shimadzu analytical Model-UV 1800).

2.2.1.3 Preparation of Working Standard Solution

To prepare working standard solutions 1,2,3,4 and 5 ml of the standard stock solution were diluted to 25 ml with pH 6.8 buffer. The absorbance was measured at 287 nm using UV- spectrophotometer (Shimadzu analytical Model-UV 1800).

2.2.1.4 Preparation of Working Standard Solution

To prepare working standard solutions 1,2,3,4 and 5 ml were diluted to 25 ml with 0.1N HCL. The absorbance was measured at 287 nm using UV- spectrophotometer (Shimadzu analytical Model-UV 1800).

2.2.2 Solubility studies

The solubility [13] of Cyclosporine in various oils (Capmul MCM oil, MCT oil, capryl oil), surfactants (Tween 20, Tween 80, Cremophor RH 40) and cosurfactants (PEG-400, Propylene Glycerol, Transcutol R) was determined as follows. Cyclosporine (10 mg) was added to a vial containing above selected vehicles (10 ml of each). After sealing, the vials were kept in sonicator and the mixture was heated at 40°C in a water bath to facilitate the solubilization. Mixing of system was performed using cyclomixer. Mixture was shaken in mechanical shaker at 25°C for 48 h. After reaching equilibrium, each vial was centrifuged at 3000 rpm for 5 min, and excess insoluble Cyclosporine was discarded by filtration using Whatman filter paper.

2.2.2.1 Estimation of drug from oil, surfactant and cosurfactant

1 ml of the above filtrate was transferred into a 100 ml volumetric flask and diluted with methanol / pH 6.8 buffer sufficiently and the free drug concentration of Cyclosporine in suitable vehicle was quantified by UV spectroscopy at 287 nm.

2.2.3 Drug-excipient compatibility studies

2.2.3.1 FT-IR studies

FTIR is a basic approach for detecting differences in drug-excipient combinations. The loss of an absorption peak, a reduction in peak strength or the emergence of a new peak all indicate the presence of interactions between API and the excipient under investigation. Fourier transform infrared (FTIR) spectroscopy was used to identify the functional groups and chemical interactions between the drug and the excipients used in the formulation. Mixture was blended with KBr powder and compressed into pellets 4000–400 cm-1 spectral range was used to the scanning.

2.3 PREPARATION OF SMEDDS CYCLOSPORINE

Cyclosporine was added very slowly into the glyceryl monocaprylo caprate (Capmul MCM oil) oil base under continues mixing at emulsifying stirrer and it was well mixed at the RPM of 700±15 for 30 minutes as the product temperature was maintained at 45±5°C.Polysorbate 80 (surfactant) and propylene glycol (co-surfactant) was added into the mixture under continues mixing using emulsifying stirrer and it was well mixed at RPM of 700±15 for 2 hrs

2.4 ROTARY DIE PROCESS

Gelatin was allowed to flow into a spreader box through a gelatin tank. Then this gelatin was spread on cooling drum 16°C which rotated. This lead to the formation of a solid gel ribbon.Through hopper tank the inner region materials i.e., fill materials was allowed to reach wedge region, where it was present in between two die rollers.Inside die cavities, fill substances was injected through wedge where two gelatin ribbons (left and right) pass into the rolling system. Simultaneously, the machine provided the gelatin ribbon as the wedge injected the fill material. Two halves of gelatin were connected by sealing process.Online capsules were directly connected to the tumble dryer, the tumble dryer removed about $1/4^{th}$ of the water amounts present in the capsules (30-40mins).

2.5 PRE-ENCAPSULATION PARAMETERS

2.5.1 Weight per ml

BP defines it as the weight in grams of a 1 ml volume of liquid in air at 20 °C. A measuring cylinder was meticulously cleaned and dried. The sample was tarred and filled to a 10 ml capacity. The reading was noted following dividing the observed weight by 10.

2.5.2 Flow character

All filling liquids must [14] be able to flow by gravity and have a temperature of 35°C or less. One of the key

characteristics that is crucial for the optimization of the liquid filling formulation for soft gels is viscosity. The viscosity of the system was determined using Brookfield viscometer (Japan) DV-E using spindle RV-16 at 5 rpm at 25±0.

2.5.3 Phase separation and stability test [15]

20 ml of distilled water was taken in a beaker its temperature was maintained at 37°C. To this 1 ml of the formulation of Cyclosporine liquid SMEDDS was added by agitation. This was kept aside for 24 h. Then the formulation was visually assessed for any phase separation.

2.5.4 Emulsification time

The SMEDDS formulation [16] (0.1 ml) was introduced into 100 ml of 0.1 N HCl under action of propeller stirrer at constant speed of 100 rpm at 37±5 °C temperature. Emulsification time was measured by visual observation.

2.5.5 Percentage Transmittance

The SMEDDS formulation [16] (0.1 ml) was introduced into 100 ml of 0.1 N HCl under action of propeller stirrer at constant speed of 100 rpm at 37±5 °C temperature. Percent transmittance was measured at 387 nm through UV spectrophotometer (Shimadzu analytical Model-UV 1800).

2.5.6 THERMODYNAMIC STABILITY STUDIES

2.5.6.1 Heating cooling cycle

Formulations F1 to F9 were subjected to Six cycles [16] of heating and cooling between refrigerator temperatures 4℃ and 45℃ (Blue star biomedical freezer model DW-YL) with storage at each temperature for 48 h was studied. These formulations were stable at this temperature and were subjected to centrifugation test.

2.5.6.2 Centrifugation test

Formulations F1 to F9 were centrifuged [16] at 3500 rpm for 30 min (Remi-12C, Japan) These formulations did not show any phase separation and were taken for freeze thaw stress test.

2.5.6.3 Freeze thaw cycle

All formulations F1 to F9 were subjected to three freeze thaw cycles [16] between -21℃ and +25℃ (Blue star biomedical freezer model DW-YL) with storage at each temperature for 48 hours were done.

2.5.6.4 Robustness to dilution

These systems [17] were diluted with excess of water, standard phosphate buffer (pH 6.8) and 0.1 N HCL (900 ml) and were stored for 12 h. No precipitation or phase separation were said ‘robust to dilution’.

2.6 POST- ENCAPSULATION PARAMETERS

2.6.1 Drug content

The fill mass was evaluated for the content of drug present in each capsule after encapsulation.

2.6.1.1 Preparation of standard solution

50 mg of Cyclosporine was accurately weighed and transferred into a 50 ml volumetric flask and dissolved in methanol.2ml of above solution was pipetted into 100 ml volumetric flask then dilute to volume with methanol and mixed well.

2.6.1.2 Preparation of sample solution

Weighed accurately and transferred 10 capsules into 500 ml volumetric flask, To this was add about 350 ml of methanol and sonicated for 60 minutes with intermittent shaking. flask was cooled to room temperature and diluted to volume with methanol and mixed well.The solution was filtered through 0.45µm PTFE filter.Pipette 1.2ml of above sample solution into 100ml volumetric flask then diluted to volume with methanol and mixed well.

2.6.2 Disintegration test

Medium: WATER

Six capsules were taken in six tubes of the basket and 800 ml of water was taken as a medium. A detachable stainless steel sieve wire was attached to the surface of the basket-rack assembly's lower plate. Distilled water at 37 ± 2℃ was used as the immersion fluid to operate the equipment. The time taken for the disintegration of capsules was noted.

2.6.3 Loss on drying of capsule shells

An appropriate clean, dry cutting tool, such as scissors or a razor-sharp open blade, was used to cut open and open 10 capsules, and the contents were completely removed by washing with isopropyl alcohol. The occluded solvent was allowed to evaporate from the shells at room temperature over a period of about 30 minutes. Clean glass-stoppered, shallow weighing bottle was dried at 105℃ for 30 minutes. It was cooled to room temperature (about 30 minutes) in a desiccator and then weighed accurately (W1g). 1 gm of capsule shell was transferred to the bottle. It was closed and then weighed accurately (W2g). The test specimen was then distributed as equally as possible to a depth of about 5 mm by giving the device a little sideways shake. Bottle was placed in the oven, by removing the stopper. The sample was dried at 105℃ for 2 hrs. The temperature of drying did not vary by more than ±2℃. It was then placed in a suitable desiccator and allowed to cool for 30 mins to room temperature and then weighed accurately (W3g).

$$\%\text{Loss on drying} = \frac{(W2g - W3g)}{(W2g - W1g)} \times 100$$

2.6.4 *In-vitro* drug release studies

Dissolution is considered as a tool for predicting rate of absorption and bioavailability of the drugs administered by orally. In vitro dissolution studies was conducted using 900mL of 0.1 N HCL as dissolution medium using USP type II (paddle method) dissolution apparatus. A temperature of 37 ± 0.5°C and a rotation speed of 100 rpm was maintained. Capsule was placed in each dissolution vessel and dissolution studies was performed. Samples of 5 ml was withdrawn at predetermined time intervals over a period 1h, passed through a 0.45µm nylon membrane. Then the sample removed was replaced with the same volume of fresh dissolution medium in order to maintain constant dissolution medium. The filtered samples was suitably diluted and analysed at 287 nm using UV-Visible spectrophotometer. Dissolution experiments were be conducted in triplicate. The cumulative drug release was calculated.

2.6.5 STABILITY STUDIES

For all the pharmaceutical dosage form it is important to determine the stability of the dosage form this will include storage at exaggerated temperature conditions, with necessary extrapolations to ensure the product will, over its designed shelf life, provide medication for absorption at the same rate as when originally formulated. Specification which is list of tests, reference to the analytical procedures and proposed acceptance criteria including the concept of different acceptable criteria for release and shelf-life specifications are addressed in ICH guidelines. The capsules of the best formulation are to be tested for stability for 2 months in accelerated test conditions. The capsules will be exposed to 40±2℃ and 75±5% RH conditions for 2 months. The capsules will be observed for change in physical appearance, moisture content, assay values, impurities and dissolution values at end of first and second month. Thus, the stability of the best formulation will be determined.

3 RESULTS AND DISCUSSION

3.1 STANDARD CALIBRATION CURVE OF CYCLOSPORINE

Table 1: Concentration of Cyclosporine in Methanol

Concentration (µg/ml)	Absorbance
10	0.322
20	0.688
30	0.865
40	1.153
50	1.465

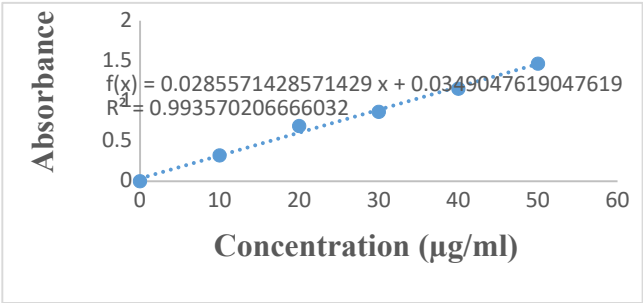

Figure 1: Calibration Curve of Cyclosporine in Methanol

Table 2: Concentration of Cyclosporine in pH 6.8 Buffer

Concentration (µg/ml)	Absorbance
10	0.313
20	0.615
30	0.889
40	1.166
50	1.53

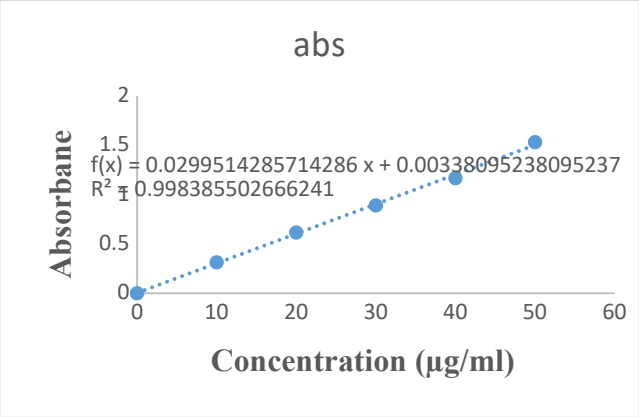

Figure 2: Calibration Curve of Cyclosporine in pH 6.8 Buffer

Table 3: Concentration of Cyclosporine in 0.1 N HCL

Concentration (µg/ml)	Absorbance
10	0.296
20	0.597
30	0.916
40	1.264
50	1.584

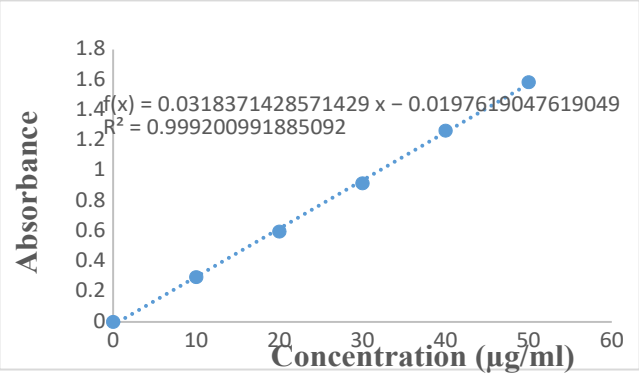

Figure 3: Calibration Curve of Cyclosporine in 0.1N HCL

3.2 DRUG – EXCIPIENT COMPATIBILITY STUDIES

3.2.1 CYCLOSPORINE

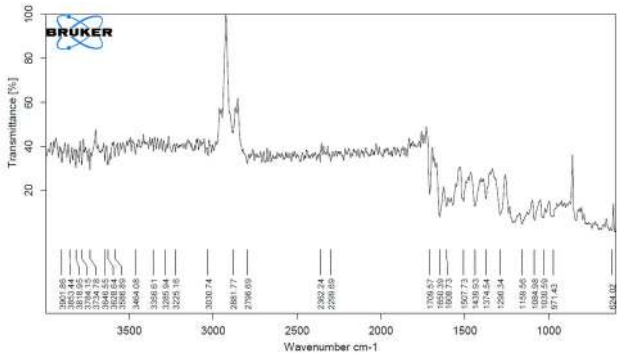

Figure 4: Interpretation of Cyclosporine

3.2.2 CYCLOSPORINE + CAPMUL MCM OIL

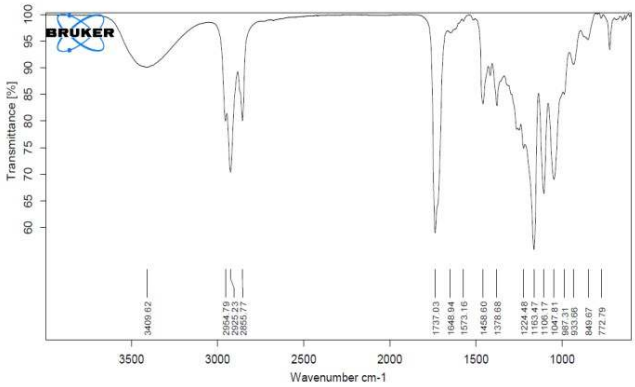

Figure 5: Interpretation of Cyclosporine + Capmul MCM Oil

3.2.3 CYCLOSPORINE +POLYSORBATE 80

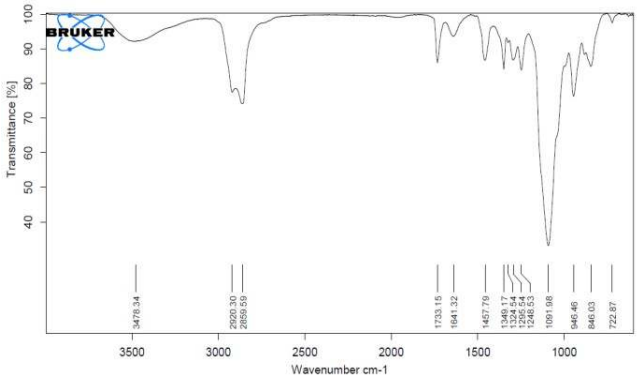

Figure 6: Interpretation of Cyclosporine + Polysorbate 80

3.2.4 CYCLOSPORINE + PROPYLENE GLYCOL

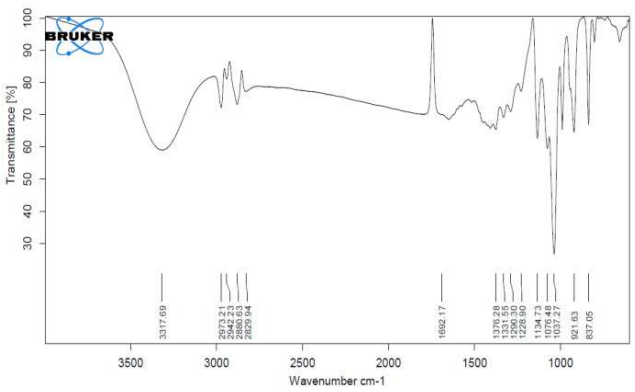

Figure 7: Interpretation of Cyclosporine + Propylene Glycol

3.2.5 **FTIR studies:** The FTIR spectra of the pure drug and the physical mixtures with all the excipients used in the formulation are shown in Fig.4-7. The disappearance of an absorption peak, a reduction of the peal intensity, or the new peaks appearance is indicative of the existence of interactions between the API and the excipient under study. There is no significant change in peak intensities and appearance or disappearance of peaks in spectrum. The original bands of the drug are well preserved and hence the drug and excipients are compatible in nature.

3.3 SOLUBILITY STUDIES

Table 4: Solubility in mg/ml

S NO	Ingredients	Solubility in mg/ml
	oils	
1	Capmul MCM oil	10.03
2	Medium chain triglyceride	5.57
3	Capryl oil	7.42
	Surfactants	
1	Polysorbate 20	6.45
2	Polysorbate 80	7.87
3	Cremophor RH 40	6.27
	Co-surfactants	
1	Propylene glycol	6.55
2	Polyethylene glycol	5.14
3	Transcutol R	3.09

Result of solubility studies on Cyclosporine in various oils, surfactants and co-surfactants are presented in Table 4. Capmul MCM oil showed highest drug solubility (10.03 mg/ml) and no other oil showed comparable solubility and hence only Capmul MCM oil was selected as oil phase for Cyclosporine SMEDDS formulation. Propylene glycol showed highest drug solubility (6.55 mg/ml) and good solubility was also observed in polysorbate 80 (7.87 mg/ml). Hence propylene glycol was selected as cosurfactant and polysorbate 80 was selected as surfactant as solubility of drug was found to be 7.87 mg/ml.

3.4 PRE- ENCAPSULATION PARAMETERS

Table 5: Fill Mass Analysis

S.NO	Formulations	Flow character	Weight/ml	Phase separation study
1.	F1	Satisfactory flow	1.02 g/ml	Phase separation not observed
2.	F2	No flow	1.11 g/ml	Phase separation not observed
3.	F3	Good flow	1.09 g/ml	Phase separation not observed
4.	F4	No flow	1.04 g/ml	Phase separation not observed
5.	F5	Good flow	1.01 g/ml	Phase separation not observed

S.NO	Formulations	Flow character	Weight/ml	Phase separation study
6.	F6	Satisfactory flow	1.07 g/ml	Phase separation not observed
7.	F7	Good flow	0.98 g/ml	Phase separation not observed
8.	F8	Good flow	1.03 g/ml	Phase separation not observed
9.	F9	Good flow	1.09 g/ml	Phase separation not observed

3.4.1 Flow character

The flow character of the fill mass analysis F1 and F6 was found to be satisfactory flow while F2 and F4 was found to have no flow and F3, F5, F7, F8, F9 was found to have good flow. F2 and F4 have less oil in the formulations which could have resulted in poor flow characteristics. The viscosity of all formulation did not seen to significantly affect the flow characteristics.

3.4.2 Weight per ml

The fill mass of weight/ml was found to be 0.99g/ml to 1.13g/ml.

3.4.5 Phase separation study

The fill mass analysis of phase separation was not found in F1 to F9.

3.4.6 Emulsification time

Table 6: Emulsification Time

S. No	Formulations	Emulsification time (Seconds) ± SD
1	F1	34.54±0.30
2	F2	41.34±0.15
3	F3	43.16±0.37
4	F4	41.47±0.35
5	F5	44.43±0.32
6	F6	31.25±0.18
7	F7	48.28±0.24
8	F8	46.30±0.15
9	F9	44.22±0.10

Where- value expressed as Mean ± SD, (n=3)

The emulsification time for all batches are shown in Table 6. Formulation in batches F1, F2, F3, F4, F5, F7, F8, F9 required time less than a minute which is indicative of micron size of globules. Furthermore, the emulsions of these batches were clear with bluish tinge and stable. Generally, the formulation can be termed microemulsion only if the globule size in less than 300 nm. Batches F2, F3, F4, F5, F7, F8 and F9 showed higher globule size and low clarity.

3.4.7 Percentage transmittance

Table 7: Percentage Transmittance

Sno	Formulations	% Transmittance ±SD
1	F1	94.42±0.21
2	F2	65.36±0.26
3	F3	68.30±0.16
4	F4	55.56±0.21
5	F5	57.26±0.14
6	F6	95.31±0.13
7	F7	60.32±0.20

Sno	Formulations	% Transmittance ±SD
8	F8	64.46±0.26
9	F9	62.44±0.32

Where- value expressed as Mean ± SD, (n=3)

The percentage transmittance for all formulations are shown in Table 7. Percentage transmittance can be used to reflect clarity and micron size of globule. The average transmittance observed of all the prepared batches was around 80% while batches F1 and F6 showed highest (90%) transmittance. From the globule size analysis, it was concluded that batches F1 and F6 has smaller globule size as compared to other batches, as these batches contained only 10% oil. As the concentration of oil increases the globule size increase whereas increasing the amount of surfactant and co-surfactant leads to decrease in globule size

3.4.8 Thermodynamic stability studies

Table 8: Thermodynamic Stability Studies

Formulations	Heating cooling cycle	Centrifugation	Freeze thaw cycle
F1	√	√	√
F2	√	√	√
F3	√	√	√
F4	√	X	√
F5	√	X	X
F6	√	√	√
F7	X	√	X
F8	√	√	√
F9	√	√	√

√ - Formulation passed

X - Formulation failed

Thermodynamic stability study was designed to identify and avoid the unstable systems. SMEDDS are thermodynamically stable systems and are formed at a particular concentration of oil, surfactant and co-surfactant, with no phase separation, creaming or cracking. It is the thermostability, which differentiates microemulsion from emulsions that have kinetic stability and will eventually phase separate. The thermodynamic stability study was performed by conducting three studies like heating cooling cycle, freeze thaw cycle, centrifugation. On the basis of the mentioned three studies, six formulations were selected out of nine formulations and results are shown in Table 8.

On the basis of the thermodynamic stability studies, it was found that 6 formulations were passed and selected for further characterization. Note- F1, F2, F3, F6, F8, and F9 passed thermodynamic stability studies.

3.4.9 Robustness to dilution

Table 9: Robustness to Dilution

Vehicles	F1	F2	F3	F4	F5	F6	F7	F8	F9
Distilled water	√	√	√	√	√	√	√	√	√
0.1N HCL	√	√	√	√	√	√	√	√	√
pH 6.8 Phosphate buffer	√	√	√	√	√	√	√	√	√

Where √- stable formulations

After diluting all formulations with water 0.1N HCL and buffer pH 6.8 and storing for 12 h, it was observed that there was no sign of phase separation or drug precipitation in F1-F9 formulations. Hence, they were 'robust to dilution'.

3.5 POST- ENCAPSULATION PARAMETERS

3.5.1 Drug content

Table 10: Percentage Drug Content of Cyclosporine

S.NO	Formulations	% Drug content
1	F1	97.35±0.36
2	F2	98.40±0.24
3	F3	97.77±0.25
4	F4	99.20±0.22
5	F5	97.54±0.19
6	F6	99.40±0.26
7	F7	98.54±0.33
8	F8	98.32±0.51
9	F9	98.39±0.58

Where- value expressed as Mean ± SD, (n=3)

All the capsules were evaluated for their Drug content. The drug content estimation data for all the formulations were found to be 97.35±0.36 to 99.40.40±0.26. The drug content was uniform in all the capsules formulations indicating uniform distribution of drug. In all the cases the calculated standard deviation values are very low which suggest that, the prepared capsules were uniform in drug content. The prepared capsules of all the formulations were evaluated and results shown in Table 10.

3.5.2 Disintegration test

Table 11: Disintegration Time for Formulated Cyclosporine Soft Gelatin Capsules

S.NO	Formulations	Disintegration time
1	F1	13 minutes 10 seconds
2	F2	13 minutes 46 seconds
3	F3	14 minutes 05 seconds
4	F4	14 minutes 49 seconds
5	F5	13 minutes 57 seconds
6	F6	13 minutes 06 seconds
7	F7	14 minutes 10 seconds
8	F8	14 minutes 24 seconds
9	F9	13 minutes 32 seconds

The average disintegration time for the capsule to completely dissolve in water was 13 minutes, 10 seconds and it was not more than 30 minutes therefore it passes the disintegration test.

3.5.3 Loss on drying of capsule shells

Table 12: Loss on Drying of Cyclosporine

S.NO	Formulations	% Loss on drying
1	F1	8.98
2	F2	11.43
3	F3	9.05
4	F4	9.78
5	F5	12.87
6	F6	8.54
7	F7	10.53
8	F8	9.67

S.NO	Formulations	% Loss on drying
9	F9	10.24

Specification for LOD of capsule after at 105℃ for 2 hours- 8.0 to 12.0 % w/w. LOD of capsule shell comes under the range 8.0 to 12.0 % w/w, hence passes the test

3.5.4 *In-vitro* dissolution studies

Table 13: Determination of *In-vitro* Dissolution Study of Different Formulations of Cyclosporine Capsules (F1-F3)

Sno	Time (mins)	F1 (%)	F2 (%)	F3 (%)
1	5	2.46	2.07	2.12
2	10	27.12	19.30	25.87
3	15	43.40	39.67	41.04
4	20	70.64	64.66	68.03
5	25	82.33	72.77	79.06
6	30	96.04	79.43	89.54
7	45	96.30	84.03	89.98
8	60	96.34	85.12	90.23

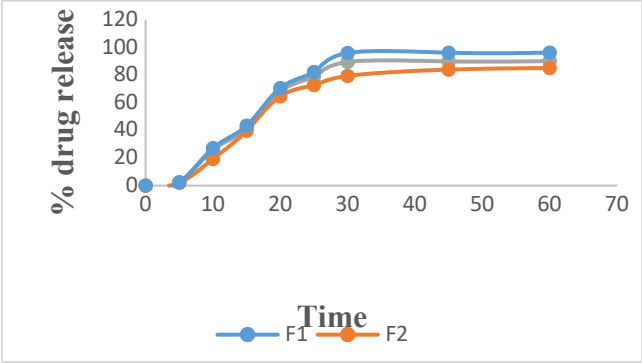

Figure 8: *Invitro* Dissolution Profile of Cyclosporine

Table 14: Determination of *In-vitro* Dissolution Study of Different Formulations of Cyclosporine Capsules (F4-F6)

Sno	Time (mins)	F4 (%)	F5 (%)	F6 (%)
1	5	1.98	2.23	2.736
2	10	19.17	24.98	29.18
3	15	35.53	40.12	46.52
4	20	57.68	70.14	72.66
5	25	68.89	79.43	83.61
6	30	79.97	92.12	98.51
7	45	80.84	92.73	98.81
8	60	82.01	93.02	99.12

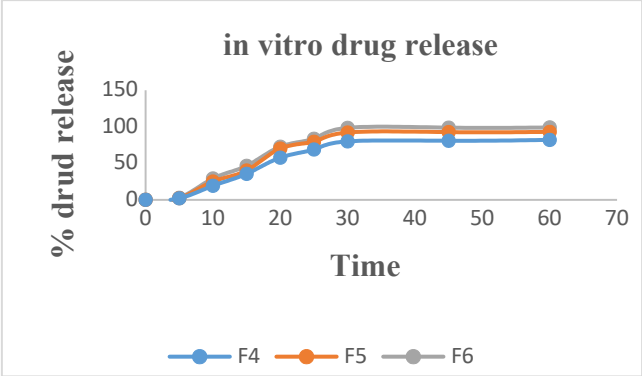

Figure 9: *Invitro* Dissolution Profile of Cyclosporine

Table 15: Determination of *In-vitro* Dissolution Study of Different Formulations of Cyclosporine Capsules (F7-F9)

Sno	Time (mins)	F7 (%)	F8 (%)	F9 (%)
1	5	2.08	1.89	2.12
2	10	19.96	19.32	20.63
3	15	39.32	37.23	41.20
4	20	66.82	62.87	69.34
5	25	75.32	73.03	78.12
6	30	89.51	84.04	91.22
7	45	89.82	85.95	91.71
8	60	90.64	86.04	92.01

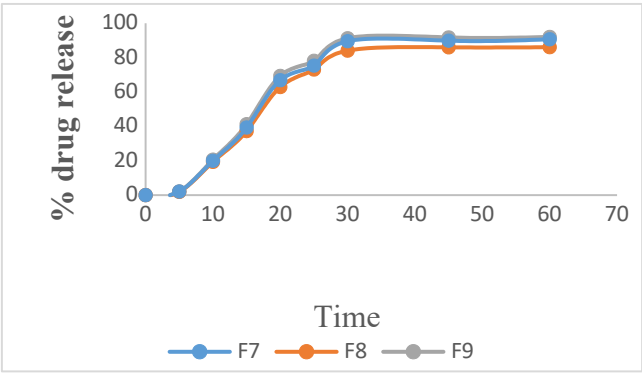

Figure 10: *Invitro* Dissolution Profile of Cyclosporine

3.5.5 *In-vitro* comparison study of Cyclosporine

Table 16: *In vitro* Comparison Study of Cyclosporine

Time(mins)	F6 (%)	Marketed sample (%)
5	2.736	1.52
10	29.18	22.5
15	46.52	42.87
20	72.66	57.46
25	83.61	68.41
30	98.51	72.66
45	98.81	79.59
60	99.12	84.87

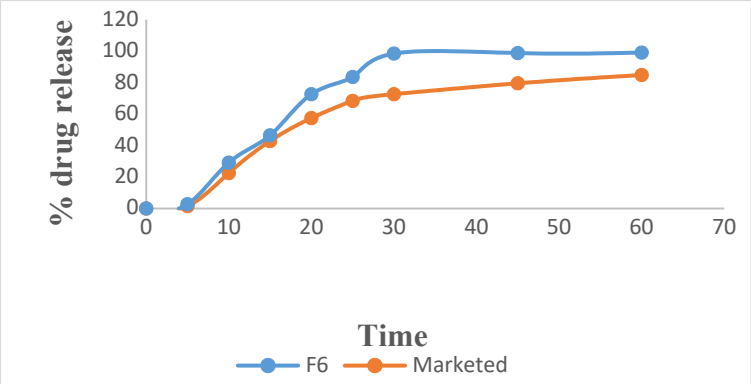

Figure 11: *Invitro* Dissolution Profile of Cyclosporine

In vitro drug release study of Cyclosporine was carried out in 0.1N HCL. The *In-vitro* drug release of Cyclosporine in 0.1 N HCl are given in Table. 13-15 and shown in Fig.8-10. The sample was taken at regular interval in (5min, 10 min, 15 min, 20 mins, 25 mins, 30 mins, 45 mins & 60 mins). Formulation F6 showed highest percentage drug release with 99.12 % of drug at 60 mins. The dissolution profile of F1 was 96.34 % at end of 60 mins. F5, F7, F9 showed 93.02%, 90.64 %, 92.01 % release while comparative dissolution profile was caried out with a marketed softgel capsules of 100 mg cyclosporine, there was significantly increase as compared with F6.

Drug release from the SMEDDS formulation (F6) was found to be significantly higher as compared with that of marketed Cyclosporine capsules. It could be suggested that the SMEDDS formulation resulted in spontaneous formation of a microemulsion with a small droplet size, which permitted a faster rate of drug release into the aqueous phase, much faster than that of marketed Cyclosporine capsules. Thus, this greater availability of dissolved Cyclosporine from the SMEDDS formulation could lead to higher absorption and higher oral bioavailability. The maximum drug release was found to be F6 formulation 99.12% and results were shown in figure 9.

Cyclosporine is a BCS class II drug with bioavailability below 20-40% due to its low solubility. The *invitro* dissolution profile indicates that self-micro emulsifying drug delivery system (SMEDDS) can be used to improve dissolution rate and overall bioavailability.

3.6 Stability studies

The stability studies were carried out for F6 batch under the accelerated Storage condition 40°/75%RH

Table 17: Stability Study of Cyclosporine Capsules Under Storage Condition of 40°/75%RH

Parameters	Initial	1st month	2nd month
Description	Opaque, Peach coloured, oval shaped softgel capsules containing yellow coloured oily mass	Opaque, Peach coloured, oval shaped softgel capsules containing yellow coloured oily mass	Opaque, Peach coloured, oval shaped softgel capsules containing yellow coloured oily mass
Average net weight	480.10 mg	480.6 mg	470.3 mg
Assay	99.40 %	98.67 %	98.3 %
Loss on drying	9.90 % w/w	10.27 % w/w	10.44 % w/w

The optimized formulations were subjected to stability studies for a period of 2 months in order to access their stability. The samples were loaded into humidity chamber at controlled humidity and temperature (40°C/75%/RH). The samples were evaluated description, average net weight, LOD, assay.

CONCLUSION

Cyclosporine is a one of the calcineurin inhibitors, is an immunosuppressant widely used to prevent organ rejection after transplantation. The bioavailability of the Cyclosporine, a BCS class II drug is below 20-40% due to its poor solubility. The poor absorption and low

bioavailability greatly affect the pharmacodynamics effect of Cyclosporine *in vivo*. Self-Micro emulsifying drug delivery system (SMEDDS) is a type of drug delivery system designed to enhanced the oral bioavailability of poorly water-soluble drugs. Hence a self-micro emulsifying drug delivery system (SMEDDS) of Cyclosporine was developed to improve drug solubility in physical conditions and oral bioavailability.

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