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# DEVELOPMENT OF A SELF MICRO-EMULSIFYING TABLET OF CYCLOSPORINE- A BY THE LIQUISOLID COMPACT TECHNIQUE

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## ABSTRACT

**Purpose:** The aim of this study was to enhance the dissolution rate of Cyclosporine A, a poorly water-soluble drug by developing a self micro-emulsifying (SME) tablet formulation by using the liquisolid compact technique. A liquisolid system is formed by converting a liquid formulation into a dry, free-flowing and compressible powder mixture with selected carrier material and coating material. This technique has industrial applications for low dose insoluble drugs.

**Method and Results:** The solubility of Cyclosporine A (BCS Class Ⅱ drug), as a model drug in this study, was determined in several oils, surfactants and co-surfactants using an HPLC method. The self micro-emulsifying system of Cyclosporine A was constructed by using Maisine 35-1 and Lauroglycol FCC (1:1, w/w, oil phase), PEG-35 Castor Oil (surfactant) and PEG 400 (co-surfactant). The ratio of these components in the formulation was 20:50:30 (w/w) and optimized by a pseudo ternary phase diagram. The droplet size of the optimized liquid with drug was 32.9±0.1nm. The stability experiment results showed the model drug in the micro-emulsifying system was stable under storage at 60℃ for a period of 10 days. Microcrystalline Cellulose (Avicel PH 101 and Avicel PH 102) and Magnesium Aluminometasilicate (Neusilin® S1) were selected as the carrier material and coating material respectively for preparing the liquisolid compact. The flowability and compactability of different liquid loading factors ($L_f$) and the ratio (R) of coating material to carrier material were evaluated using several parameters. A liquid loading factor $L_f$ =0.67 and an R=0.6 were optimal for preparation of the liquisolid compact. The obtained powder mixture had good flowability (Hausner's Ratio=1.243, Carr's Index=19.565) and good compactability (Hardness=5.18±0.33kp, Tensile Strength=0.47±0.03Mpa). The dissolution profiles of the self micro-emulsifying tablets were determined in three different media (Simulated Gastric Fluids (SGF) pH 1.2, Distilled Water (DI) and Simulated Intestinal Fluids (SIF) pH 6.8±0.1). The dissolution results showed that the dissolution rate of SME tablets was much higher when compared to the conventional tablets prepared by direct compression.

**Conclusion:** In this study, the self micro-emulsifying formulation exhibited acceptable flowability and compressibility and the liquisolid tablets displayed significant improvement in dissolution profiles compared to the conventional tablets.

**INTRODUCTION:** Approximately 40% of newly developed, beneficial drug candidates have poor water solubility and their oral delivery is frequently associated with low dose proportionality, low oral bioavailability, and high intra- and inter-subject variability [1]. Different formulation strategies are employed to overcome these problems including the use of pH adjustment, co-solvents, micro-emulsion, self emulsification, polymeric modification, drug complexation, particle size reduction, the pro-drug approach, surfactants, lipids, permeation enhancers, salt formation, cyclodextrins, nanoparticles, solid solutions and solid dispersions [1, 2].

Self micro-emulsifying drug delivery systems (SMEDDS) are isotropic systems that consist of a mixture of drugs, oils, surfactants and co-surfactants [3]. In recent years, SMEDDS have developed into a satisfactory way to improve the solubility and adsorption of poorly water-soluble drugs in oral dosage forms [4-8]. Micro-emulsions with a droplet size in a range of 10~100 nm can be formed by gentle mixing of these ingredients in aqueous media [9]. There are several marketed oral drugs whose dissolution and absorption have been enhanced by SMEDDS [10-13]. Sandimmun Neoral (CsA-NEO), a self micro-emulsifying capsule of cyclosporine A produced by Norvatis, has been approved by FDA. This SMEDDS product includes three different dosage strenghts (25, 50 and 100 mg) in soft gelatin capsule forms which have some disadvantages, such as the oil system can interact with the shell of the capsule, the drug liquid can leak from the capsule, etc.

The liquisolid system is a powdered form of a liquid drug formed by blending the liquid drug formulation with selected carrier material and coating material to form dry looking, non-adherent, free-flowing and readily compressible powdered mixtures [14]. Various grades of cellulose, starch, lactose etc., can be used as the carrier material, whereas very fine particle size silica powders and magnesium aluminum silicate powders may be used as the coating materials.

According to reports in the literature, a great number of water insoluble liquid and solid drugs have been formulated into liquisolid systems using this technique to improve the physicochemical properties, such as Furosemide [15], Piroxicam [16], Prednisolone [17], Carbamazepine [18], Propranolol hydrochloride [19], Hydrochlorothiazide [20], Famotidine [21], Indomethacin [22], Hydrocortisone [23] and Naproxen [24]. Better dissolution and absorption of an orally administered poorly water-soluble drug can be achieved when the drug is in solution form [25].

In a liquisolid system, the drug is maintained in a solubilized liquid state allowing improved dissolution, but this liquid is converted to a solid granulation suitable for compression [26-30]. Liquisolid compacts containing poorly water-soluble drugs are expected to display enhanced dissolution characteristics and also improved oral bioavailability.

Cyclosporine A (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 [31]. The aim of this study was to increase the dissolution rate of Cyclosporine A by incorporating a SME formulation in a liquisolid compact. Their pre-compression and post-compression parameters were evaluated. And the dissolution profiles in different media were also studied.

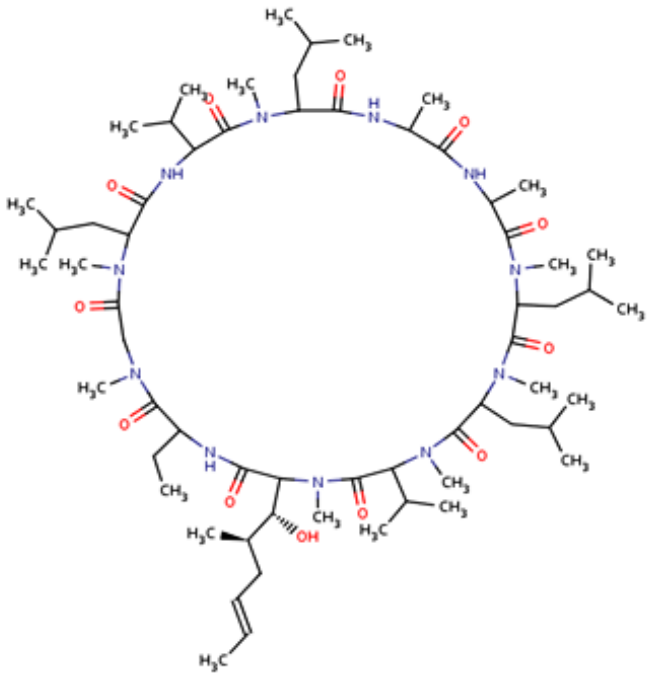

**FIG. 1: CYCLOSPORINE- A STRUCTURE**

## MATERIALS AND EXPERIMENTAL METHODS

**Materials:** Cyclosporine- A (Cys A) used as a model drug was bought from LC Laboratories® (Woburn, USA). Maisine 35-1(Glyceryl Monolinoleate, HLB=4), Lauroglycol FCC (Propylene Glycol Laurate, HLB=4) used as oil phase was supplied from Gattefosse Ltd (France). Cremophor® ELP (PEG-35 Castor oil) used as surfactant was supplied from BASF Corporation (Germany). PEG-400 (Polyethylene glycol) used as co-surfactant was supplied from Dow Chemical Company (USA). Microcrystalline Cellulose (Avicel PH 101, Avicel PH 102 and Acicel 105) used as carrier material was supplied from FMC Biopolymer Corporation (USA). Magnesium Aluminometasilicate (Neusilin® S1, Neusilin® US2, Neusilin® FH2) used as coating material was supplied from Fuji Ltd (Japan). Amorphous Fumed Silica (CAB-O-SIL® M-5P) was supplied from CABOT Corporation (USA). Precipitated Silicium Dioxide (Zeopharm 80) was supplied from J.M. Huber Corporation (USA).

Synthetic Amorphous Precipitated Silica was supplied from Degussa-Hüls Corporation (Germany). Silicified Microcrystalline Cellulose (PROSOLV® SMCC 50 and PROSOLV® SMCC 90) was supplied from JRS Pharmma LP (Germany). Croscarmellose Sodium (Ac-Di-Sol®) from FMC Corporation (USA), Sodium Starch Glycolate (SSG) was supplied from Penwest Pharmaceuticals Co. (USA). Crospovidone (Kollidon® CL) was supplied from BASF Corporation (Germany). Magnesium Stearate was from Prolabo (France). 316 NF Fast Flo® Lactose from Foremost® Farms (USA).All other chemicals used were analytical reagent grade and used as received without further purification. Double-distilled water was used throughout the study.

**Experimental:**

**Solubility studies:** The solubility of Cyclosporine A was determined in different oils, surfactants and co-surfactants, including: Carpryol 90 (Propylene Glycol Monocaprylate, HLB=6), Lauroglyol 90 (Propylene glycol monolaurate, HLB=5), Lauroglycol FCC (Propylene Glycol Laurate, HLB=4), Maisine 35-1, Peceol (Glyceryl mono-oleate, HLB=3), Labrafac Lipophile WL 1349 (Medium chain triglycerides, HLB=2), Span 80, PEG-400, Labrafil M 1994CS (Oleoyl macrogolglycerides (polyoxylglycerides), HLB=2), PEG-35 Castor oil, PEG-40 Hydrogenate Castor Oil, Propylene Glycol, Labrasol (Caprylocaproyl Macrogolglycerides (Polyoxylglycerides), HLB=14). Cyclosporine A was mixed in 10ml test tubes with such amounts of each of the above solvents in order to produce supersaturated solutions. The mixtures were shaken at constant vibration (Environ Shaker, Lab-Line, USA) under ambient temperature for 7 days for equilibrium. The obtained suspensions were centrifuged at 10,000 rpm for 10 minutes. Then an accurately weighed quantity of supernatant was further diluted with methanol and analyzed using an HPLC method for its drug content.

**HPLC Analysis Method [32]:** The content of Cyclosporine A in this study was determined by HPLC analysis. The Cyclosporine A was detected at 210nm. Chromatographic separations were achieved using a Phenomenex® Gemini 5µm $C_{18}$ 110A column (150×4.6mm, 5µm) (USA).The mobile phase used was methanol-acetonitrile (50:900)-water-phosphoric acid (450:0.5) = 80:20, vol/vol). The buffer was degassed by ultrasonication. The oven temperature was 70℃ and the flow rate was 1.0 mL/min. 10µL of sample solution was injected into the HPLC system (Shimadzu LC-10AD vp Liquid Chromatography; SPD-M10A vp Dide Array Detector; CTO-10A vp Column Oven; SIL-10AD vp Auto Injection; DGU-14A Degasser). The linearity of the method was determined in the range of 0.56µg/mL to 1.12 mg/mL ($R^2$ = 0.9993). Analytical repeatability was acceptable (RSD= 0.40%, n= 6). The Cyclosporine A tablet recovery was 100.65% (n= 9).

**Construction of the pseudo ternary phase diagram:** Pseudo ternary phase diagrams were constructed to screen the formation of oil in water. Micro-emulsions were prepared by using Maisine 35-1: Lauroglycol FCC (1:1, w/w) as the oil phase, PEG-35 Castor Oil as the surfactant, and PEG-400 as the co-surfactant. Different ratios of oil, surfactant and co-surfactant were mixed by the vortex mixer for 1 min. Then 200 mg of the mixture was weighed into a test tube and diluted with 10 mL water. The mixed sample was gently stirred and observed against a black background. If turbidity appeared, the samples were considered not to form a micro-emulsion. If clear and transparent or slightly bluish mixtures were visualized after stirring, the samples were considered to have formed a micro-emulsion. The samples were marked as points in the

phase diagram. The effect of drug on the micro-emulsion region was also studied by dissolving drug in a mixture of oil, surfactant and co-surfactant at an appropriate proportion. The same method was used to construct the pseudo ternary phase diagram with drug. The area covered by these points was considered to be the acceptable micro-emulsion region.

**Droplet Size Measurement:** The droplet size of the optimized liquid with drug was measured by Malvern Zetasizer (Malvern Zetasizer-ZS, Malvern Instruments Ltd, UK). Drug was dissolved in a mixture of oil, surfactant and co-surfactant at an appropriate proportion. Then 200 mg of the mixture was weighed and diluted with 10 mL water. The mixed sample was gently stirred to form a clear solution to measure the droplet size.

**The stability of drug in the oil system:** Drug was dissolved in a mixture of oil, surfactant and co-surfactant at an appropriate proportion. The mixture was transferred into a sealed glass bottle and stored in an oven at 60℃ for 10 days. The contents of the drug were measured using the above HPLC method at 0 day, 5th day and 10th day respectively.

**Adsorption experiment:** The property of excipients selected as carrier material or coating material is that they should not adsorb drug when the drug is released in aqueous media. The extent of drug adsorption on excipients in water was determined by dissolving drug in a mixture of oil, surfactant and co-surfactant at an appropriate proportion. Then 200mg of the mixture was weighed and diluted with 10 mL water. The mixed sample was gently stirred to form a clear solution. A weighed amount of excipient was put into the above solution and shaken at constant vibration under ambient temperature overnight. The solution obtained was filtered through a Millipore filter (0.45μm).Then the filtered solution was analyzed using the HPLC method to measure the drug content and compared to drug without excipient.

**Evaluation of flowability and compressibility of liquisolid powders:** The oil system components of the micro-emulsion including the drug, surfactant and co-surfactant were optimized from the ternary phase diagram. The obtained mixtures were mixed with carrier material and coating material in order to form acceptable free flowing and compressible powdered forms. The evaluation of flowability and compressibility of the powdered forms with different liquid loading factors ($L_f$) and coating ratios (R) was studied. The liquid loading factor and coating ratio can be calculated by equation 1 and 2 [33].

It is clear that no single and simple test method can adequately characterize the flow properties of pharmaceutical powder. Therefore, different flow parameters were employed. In this study, the flowability of the obtained mixtures was evaluated by measuring the angle of repose and determining the bulk densities and tap densities (Vanderkamp® Tap Density Tester, Vankel Industries, Inc. USA) used to calculate both the Hausner's ratio and the Carr's index. Tablet hardness was determined on tablets compressed at 1.5m ton for 3 seconds on a Carver Press (Single Punch Carver Laboratory Press, Fred S. Carver. Inc. USA). The tensile strength of the tablets was calculated by equation 7 [34].

**EQUATIONS FOR CALCULATIONS**

| | | |
|---|---|---|
| 1 | Loading factor=Amount of liquid/Amount of carrier material | $Lf=W/Q$ |
| 2 | Coating ratio=Amount of coating material/Amount of carrier material | $R=q/Q$ |
| 3 | Bulk density=Mass/Poured volume | $\sigma b=M/V_0$ |
| 4 | Tap density=Mass/Tapped volume | $\sigma t=M/V_f$ |
| 5 | Carr's index=100*(Tap density-bulk density)/Tap density | $C=100*(\sigma t-\sigma b)/\sigma t$ |
| 6 | Hausner's ratio=Tap density/ Bulk density | $H=\sigma t/\sigma b$ |
| 7 | Tensile strength=2* Hardness/[π*Diameter of tablet (D)*Thickness of tablet (l)] | $TS=2H/\pi DI$ |

**Choice of Disintegrants:** Disintegration is an integral part and prerequisite for dissolution for oral formulations. Different superdisintegrants, including Ac-Di-Sol®, SSG and Kollidon® CL, were selected to measure the disintegration time of the SME tablets. And the amount of the selected superdisintegrant was also optimized. Disintegration times were measured in 900 mL DI water at 37℃.

**Preparation of Liquisolid tablets:** The oil system was prepared by mixing Maisine 35-1: Lauroglycol FCC (1:1, w/w) and PEG-35 Castor Oil with PEG-400. Cyclosporine A was then dissolved in the mixture, followed by gentle mixing and heating. Wet granules were prepared by mixing the above liquid solution with Avicel PH 101 as carrier material and 4% Ac-Di-Sol® added as an internal disintegrant.

Then Avicel PH102 was added to form wet particles. Wet particles were then admixed with Neusilin S1 to form a free flowing powder. Finally, 4% Ac-Di-Sol® was added externally as disintegrant along with 0.5% magnesium stearate as a lubricant. The powder mixture was compressed into tablets on a Carver Press.

**Quality control tests of Cyclosporine- A liquisolid compact powders and tablets:** In this study, the flowability of the liquisolid compact powders and the tablet weight (Denver A-160 Electric Balance, Denver Instrument Company, USA), tablet thickness (Micrometer, M&W. Ltd, Sheffild; England), tablet hardness (Tablet Hardness tester, Pharmatest, Type PTB 301, Germany), tablet friability, tablet disintegration time (QC-21 Disintegration Test System, Hanson Research Corporation, USA) and drug content uniformity of the tablets were attributes used to evaluate the quality of the liquisolid tablets.

***In-vitro* release of Cyclosporine A from liquisolid tablets:** Dissolution studies were conducted on the prepared Cyclosporine- A liquisolid tablets and conventional tablets according to USP Apparatus Ⅱ (Hanson SR-8 Plus dissolution apparatus, Hanson Research Corporation, USA) at 50 rpm. In all studies, the temperature of the dissolution medium was maintained at 37±0.5℃. 900mL of each media (DI water simulated gastric fluid (SGF) pH1.2 and simulated intestine fluid (SIF) pH 6.8±0.1) was used for the test. Samples were withdrawn at 5, 10, 15, 30, 45, 60, 75, 90 minutes and directly filtered, then injected into the HPLC instrument to measure the content of the drug.

## RESULTS AND DISSCUSSION:

**Solubility studies:** The solubility of Cyclosporine A in the different solvents was studied. The results in **Table 1** were extrapolated to determine the percent w/w of Cyclosporine A in its saturated solution with the solvents under investigation. Cyclosporine A exhibited good solubility in several oil phases, such as Carpryol 90, Lauroglyol 90, Lauroglycol FCC and Maisine 35-1, Labrafac Lipophile WL 1349, Peceol, Labrafil M 1994CS. Good solubility was noted in several surfactants and co-surfactants, such as Propylene Glycol, Labrasol, Span-80, PEG-400 and PEG-35 Castor Oil. However, when Carpryol 90, Lauroglyol 90 and Lauroglycol FCC were selected as oil phase respectively, a micro-emulsion could not be formed. In the study, the mixture of Lauroglycol FCC: Maisine 35-1(1:1, w/w) was selected as the oil phase, PEG-35 castor oil was selected as the surfactant and PEG-400 was selected as the co-surfactant.

**TABLE 1: SOLUBILITY OF CYCLOSPORINE A IN DIFFERENT SOLVENTS**

| Solvent | Solubility(mg/g) |
|---|---|
| Carpryol 90 | 536.0±3.6 |
| Lauroglyol 90 | 502.9±2.3 |
| Lauroglycol Fcc | 477.8±1.5 |
| Progylene Glycol | 424.1±3.7 |
| Maisine 35-1 | 360.4±2.0 |
| Labrasol | 370.2±2.5 |
| Labrafac Lipophile WL 1349 | 276.4±0.4 |
| Span-80 | 140.2±11.7 |
| PEG-400 | 263.9±5.1 |
| Peceol | 221.1±1.4 |
| PEG-35 castor oil | 165.5±1.8 |
| Labrafil M 1994 CS | 145.2±4.3 |

**Pseudo-ternary Phase Diagram:** Two pseudo-ternary phase diagrams of the investigated oil system with drug and without drug are presented in **Figure 2**. Formation of micro-emulsion systems (the shaded area) was observed at room temperature. The phase study revealed that if the proportion of oil was less than 15%, the drug can not dissolve completely in the oil mixture, if the proportion of oil was more than 25%, the micro-emulsion could not be formed. And when the proportion of surfactant was less than 45%, the micro-emulsion also could not be formed. PEG-400 selected as co-surfactant was less viscous than the oils and the surfactant and could contribute to dispersion. The micro-emulsion region shrunk after addition of the drug. Based on this result, the optimum micro-emulsion formulation consisted of Lauroglycol FCC: Maisine 35-1 (1:1, w/w) (20%), PEG-35 castor oil (50%) and PEG-400 (30%). According to the solubility results of Cyclosporine A in these solvents, 1 to 6 was selected

as the ratio between the drug and the mixture. The specification of the liquisolid tablet we studied was 25 mg of Cyclosporine A per tablet.

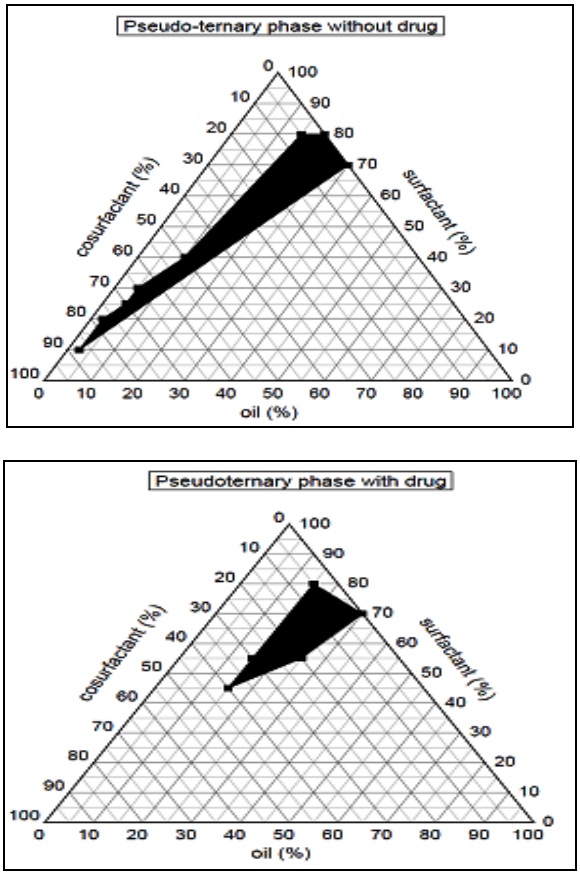


**FIG. 2: PSEUDO-TERNARY PHASE DIAGRAMS OF THE MIXTURE LAUROGLYCOL FCC: MAISINE 35-1 (1:1, w/w), PEG-35 CASTOR OIL, PEG-400 AND WATER**

**Droplet Size Measurement:** The droplet size of the optimized liquid with drug was 32.9±0.1nm which was in the micro-emulsion droplet size range of 10~100 nm. The results showed that the optimized liquid formulation can be formed into micro-emulsion by gentle mixing in water.

**Drug stability in the Oil System:** No significant variations of the drug content were observed in the oil system solution at 5th day (99.8%) or 10th day (99.2%) at 60°C when compared to the drug content at 0 day (100.0%).

**Adsorption Studies:** The absorption of drug by different excipients in the micro-emulsion formulations was studied. The results in **Table 2** indicate that several excipients (Prosolv 90, $SiO_2$, Neusilin US2 and Neusilin FH2) could adsorb the drug in the micro-emulsion formulations. These results were considered to be related to the cyclic structure of the drug, which was easy to be adsorbed. Therefore, these excipients could not be selected as carrier or coating materials. Avicel PH 101 and Avicel PH 102 were selected as carrier materials. Neusilin S1 was selected as coating material.

**TABLE 2: THE ADSORPTION RESULTS OF DIFFERENT EXCIPIENTS AND CYCLOSPORINE A**

| Samples | Drug content (%) in the suspensions |
|---|---|
| Drug without excipients | 100.00 |
| Drug+ Avicel PH 101 | 101.95 |
| Drug+ Avicel PH 102 | 100.35 |
| Drug+ Avicel PH 105 | 96.65 |
| Drug+ Silicified microcrystalline cellulose (Prosolv® 90) | 78.81 |
| Drug+ Silicified microcrystalline cellulose (Prosolv® 50) | 82.63 |
| Drug+ Silicon Dioxide（Synthetic Amorphous Precipitated Silica） | 17.01 |
| Drug+ Silicon Dioxide (CaB-O-SiL, Amprphous Fumed Silica) | 12.68 |
| Drug+ Silicon Dioxide (Zeopharm 80, Precipitated Silicium Dioxide) | 26.6 |
| Drug+ Magnesium Aluminometasilicate (Neusilin® S1) | 102.98 |
| Drug+ Magnesium Aluminometasilicate (Neusilin® US2) | 87.98 |
| Drug+ Magnesium Aluminometasilicate (Neusilin® FH2) | 94.56 |

**Evaluation of flowability and compressibility of Liquisolid Powders:** The angle of repose (θ) is a characteristic related to inter-particulate friction or resistance to movement between particles. Lower angle of repose values indicate a less cohesive powder mixture. The range of Carr's index between 15 and 30 is considered acceptable for flowability. Hausner's ratio is related to the inter particle friction. Hausner's

ratios less than 1.34 are acceptable. Formula composition of liquisolid powders evaluated for flowability and compressibility are listed in **Table 3**. The flowability and compactability results are listed in **Table 4**. In order to have higher drug loading, the liquid loading factor $L_f$ = 0.67 and coating ratio=0.6 were selected to prepare the liquisolid compacts.

**TABLET 3: FORMULA COMPOSITIONS OF LIQUISOLID POWDER (%w/w)**

| Component | LS-1 | LS-2 | LS-3 | LS-4 | LS-5 | LS-6 | LS-7 |
|---|---|---|---|---|---|---|---|
| Oil system (drug: liquid =1:6) | 33.3 | 25.1 | 29.5 | 30.9 | 20.0 | 23.8 | 25.0 |
| Avicel PH 101 | 33.3 | 37.4 | 44.1 | 46.1 | 40.0 | 47.6 | 50.0 |
| Neusilin S1 | 33.3 | 37.4 | 26.4 | 23.0 | 40.0 | 28.6 | 25.0 |
| Tablet Weight (mg) | 525.0 | 697.0 | 592.5 | 566.5 | 875.0 | 735.0 | 700.0 |

**TABLE 4: FLOWABILITY AND COMPRESSIBILITY OF LIQUISOLID POWDERS**

| Liquisolid Powder | Loading Factor | Coating Ratio | Angle of Repose (θ) | Densities (g/cm$^3$) | |
|---|---|---|---|---|---|
| | | | | Bulk Density | Tap Density |
| LS-1 | 1.0 | 1.0 | 37.777 | 0.465 | 0.620 |
| LS-2 | 0.67 | 1.0 | 36.175 | 0.449 | 0.574 |
| **LS-3** | **0.67** | **0.6** | **39.938** | **0.460** | **0.579** |
| LS-4 | 0.67 | 0.5 | 43.222 | 0.418 | 0.540 |
| LS-5 | 0.5 | 1.0 | 33.418 | 0.435 | 0.593 |
| LS-6 | 0.5 | 0.6 | 35.418 | 0.427 | 0.582 |
| LS-7 | 0.5 | 0.5 | 39.119 | 0.446 | 0.590 |

| Liquisolid Powder | Loading Factor | Coating Ratio | Hausner's Ratio | Carr's Index | Tablet Hardness (kp, n=3) | Tablet Tensile Strength (Mpa, n=3) |
|---|---|---|---|---|---|---|
| LS-1 | 1.0 | 1.0 | 1.333 | 25.000 | 5.17±0.03 | 0.57±0.0003 |
| LS-2 | 0.67 | 1.0 | 1.278 | 21.739 | 18.34±0.36 | 1.69±0.05 |
| **LS-3** | **0.67** | **0.6** | **1.257** | **20.455** | **5.69±0.23** | **0.56±0.02** |
| LS-4 | 0.67 | 0.5 | 1.294 | 22.727 | 3.60±0.11 | 0.36±0.01 |
| LS-5 | 0.5 | 1.0 | 1.364 | 26.667 | 33.20±0.36 | 2.54±0.03 |
| LS-6 | 0.5 | 0.6 | 1.364 | 26.667 | 15.50±0.43 | 1.32±0.03 |
| LS-7 | 0.5 | 0.5 | 1.324 | 24.444 | 10.73±0.07 | 0.94±0.01 |

**Disintegrant selection studies:** Formula LS-3 was modified using various disintegrants which were added either internally and/or externally to optimize disintegration time of the tablet. In order to compare the disintegration time of the tablets added different type and different amount of disintegrants, the weight of the tablet was fixed to 650mg. The results in **Table 5** showed the superdisintegrant Ac-Di-Sol® provides faster disintegration time compared to that of the other two superdisintegrants. 8% Ac-Di-Sol® (4% internal, 4% external) was selected as the optimum disintegrant amount.

**TABLE 5: DISINTEGRANTS EFFECT ON DISINTEGRATION TIME OF TABLETS PREPARED FROM BASIC FORMULA LS-3**

| Disintegrant | Weight (mg) | Hardness (kp) | Disintegration Time(min) |
|---|---|---|---|
| 5% Disintegrant (n=6) | | | |
| Ac-Di-Sol | 650±0.9 | 4.7±0.2 | 14.1±0.3 |
| Crosspovidone | 652±3.3 | 4.7±0.3 | 21.3±0.3 |
| SSG | 652±4.9 | 4.8±0.1 | 20.5±0.6 |
| Ac-Di-Sol (n=6) | | | |
| 1% (external addition) | 650±1.0 | 5.0±0.2 | 29.0±0.7 |
| 3% (external addition) | 651±1.7 | 5.1±0.2 | 18.7±0.4 |
| 5% (external addition) | 650±0.9 | 4.7±0.2 | 14.1±0.3 |
| 8% (external addition) | 652±2.2 | 5.7±0.3 | 12.1±0.2 |
| 8% (4% internal addition, 4% external addition) | 650±0.7 | 5.1±0.2 | 10.0±0.3 |

**Final optimized formulation:** Based on the ternary phase diagram, adsorption study, powder flowability and compactability results, the final optimum formulation of the SME tablet is listed in **Table 6**. The micro-emulsion oil system consisted of Lauroglycol FCC: Maisine 35-1(1:1, w/w) (20%), PEG-35 castor oil (50%) and PEG-400 (30%).The drug loading was 25mg per tablet with a drug to micro-emulsion oil mixture of

1 to 6. Microcrystalline Cellulose (Avicel PH 101 and Avicel PH 102, Avicel PH 102 added could improve the flowability of the liquisolid compact powders) and Magnesium Aluminometasilicate (Neusilin® S1) were selected as the carrier material and coating material respectively and a liquid loading factor Lf =0.67 and a coating ratio R=0.6 were optimal for preparation of the liquid solid compact.

**TABLE 6: THE FINAL OPTIMUM FORMULATION OF THE SME TABLETS**

| Component | Weight(mg) | Ratio (%) |
|---|---|---|
| Oil system (drug: liquid=1:6) | 175.00 | 26.92 |
| Avicel PH 101 | 200.00 | 30.77 |
| Avicel PH 102 | 59.75 | 9.19 |
| Neusilin S1 | 160.00 | 24.62 |
| Ac-Di-Sol | 52.00 | 8.00 |
| Magnesium Stearate | 3.25 | 0.50 |
| Total | 650.00 | 100.00 |

**Quality control tests of Cyclosporine A liquisolid tablets:** One batch of tablets was prepared by using the final optimized formulation. Related quality parameters of the liquisolid powders and tablets of this batch were measured. Results in **Table 7** indicate the flowability of the final liquisolid compact powders is suitable. Results in **Table 8** indicate tablet weight, thickness, hardness, and content uniformity are acceptable. The disintegration time of the tablet is less than 15 min, which contributes to the observed faster dissolution of the tablets.

**TABLE 7: FLOWABILITY OF THE FINAL LIQUISOLID COMPACT**

| Angle of Repose (θ) | Densities(g/cm$^3$) | | Hausner's Ratio | Carr's Index |
|---|---|---|---|---|
| | Bulk Density | Tap Density | | |
| 39.263 | 0.438 | 0.544 | 1.243 | 19.565 |

**TABLE 8: THE QUALITY CONTROL TESTS OF THE SME TABLET**

| | Tablet 1 | Tablet 2 | Tablet 3 | Tablet 4 | Tablet 5 | Tablet 6 | Average ±SD |
|---|---|---|---|---|---|---|---|
| **Weight (mg)** | 652.00 | 655.00 | 653.00 | 649.00 | 651.00 | 648.00 | 651±2.58 |
| **Thickness (mm)** | 6.15 | 6.20 | 6.14 | 6.19 | 6.17 | 6.18 | 6.17±0.02 |
| **Hardness (kp)** | 5.75 | 4.80 | 4.93 | 5.28 | 5.11 | 5.20 | 5.18±0.33 |
| **Tensile strength (MPa)** | 0.529 | 0.437 | 0.436 | 0.484 | 0.469 | 0.476 | 0.47±0.03 |
| | **Tablet 7** | **Tablet 8** | **Tablet 9** | **Tablet 10** | **Tablet 11** | **Tablet 12** | **Average ±SD** |
| **Disintegration time (min)** | 9.13 | 9.95 | 9.80 | 9.54 | 10.08 | 10.30 | 9.80±0.38 |
| | **Tablet 13** | **Tablet 14** | **Tablet 15** | **Tablet 16** | **Tablet 17** | **Tablet 18** | **Average ±SD** |
| **Drug content (%)** | 99.50 | 99.41 | 98.78 | 100.56 | 101.04 | 99.38 | 99.78±0.85 |

***In-vitro* release of the tablets:** The *in-vitro* release of Cyclosporine A from the formulated liquisolid tablets and conventional tablets were performed. The dissolution profiles in three different dissolution mediums, DI water, pH 1.2 simulated gastric fluid (SGF) and pH 6.8±0.1 simulated intestine fluid (SIF), are graphically represented as the percentage drug release versus time plot in **Figure 3**. Compared to the conventional tablets, the drug release rates of the liquisolid tablets in the above three dissolution media exhibit a significant improvement. The results suggest that the SME tablets resulted in spontaneous formation of a micro-emulsion with a small droplet size, which permitted a faster rate of drug release into the aqueous media, than that of the conventional tablet. Thus, this greater availability of dissolved Cyclosporine A from the SME formulation could lead to higher absorption and higher oral bioavailability. A conventional formulation of Cyclosporine A was directly compressed into cylindrical tablets, each containing 25 mg drug. The conventional tablet composition is listed in **Table 9**.

**TABLE 9: CONVENTIONAL TABLET FORMULATION**

| Material | Weight (mg/tablet) | Ratio (%) |
|---|---|---|
| **Cyclosporine A** | 25.00 | 3.85 |
| **Avicel PH 102** | 205.10 | 31.55 |
| **NF 316 Fast Flo Lactose** | 410.15 | 63.10 |
| **Ac-Di-Sol** | 6.50 | 1.00 |
| **Magnesium** | 3.25 | 0.50 |

| | | |
|---|---|---|
| **Stearate** | | |
| **Total Tablet Weight** | 650.00 | 100.00 |

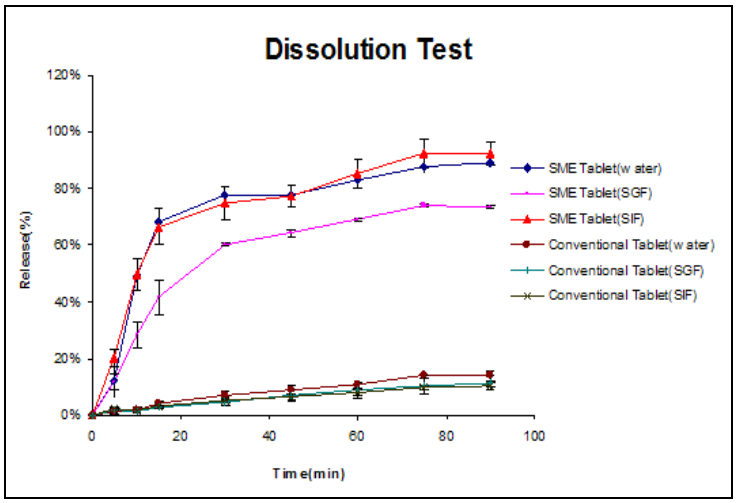


**FIG. 3: DISSOLUTION PROFILE OF CYCLOSPORINE A SME TABLETS AND CONVENTIONAL TABLETS**

**CONCLUSION:** SME formulation consists of oil, surfactant and co-surfactant which were selected on the basis of solubility and emulsification ability for the SME formulation. In this study, the mixture of Lauroglycol FCC: Maisine 35-1 (1: 1, w/w) was selected as the oil phase, PEG-35 Castor Oil was selected as the surfactant and PEG-400 was selected as the co-surfactant. 1 to 6 was selected as the ratio between the drug and the mixture. An Emulsion could not be formed in several oils, such as Carpryol 90, Lauroglyol 90 and Lauroglycol FCC even in which the drug has good solubility.

The self micro-emulsifying Cyclosporine A tablets were prepared by the liquisolid compaction technique. Due to the cyclic structure of Cyclosporine A, some excipients absorbed the drug and could not be selected as carrier material and coating material, e.g., silica powders. The liquisolid tablets were effective in enhancing dissolution of Cyclosporine A, a poorly water-soluble drug. The tablets exhibited good flowability and compactability.

The results showed that the liquisolid compaction technique could be used as a promising alternative technique to improve the solubility and the in-vitro release of Cyclosporine A as a model for poorly water-soluble drugs.

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