Tacrolimus Loaded Liquisolid Compacted Tablets: Fabrication and Characterization for Improvement in Oral Bioavailability

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Abstract

The primary objective of this investigation was to improve the oral bioavailability of a selected poorly water-soluble drug tacrolimus by developing Liquisolid (LS) compacted tablets. LS compact formulations were prepared using 3 different non-volatile solvents PEG600, Capryol 90 and labrasol. Neusillin US2 and aerosil were used on the porous carrier and coating material respectively for all nine formulations. The selected LS3, LS 5, and LS 9 were compressed into tablets using cross carmellose sodium as disintegrants. The formulations were evaluated for content uniformity, friability, hardness, disintegration test, *in vitro* drug release studies, and *in vivo* pharmacokinetic studies. The drug-excipient compatibility study by FTIR and DSC investigation revealed no potential interaction. The optimized formulation LS3 exhibited an improved dissolution rate with disintegration in less than 10 min. Pharmacokinetic study for the optimized liquisolid formulation LS3 exhibited 5 folds improvement in oral bioavailability.

Keywords

Tacrolimus, Liquid load factor, Liquisolid Tablets, Dissolution rate, Bioavailability

INTRODUCTION

Solubility is one of the greatest obstacles for the majority of drugs especially the BCS II and BCS IV categories of drugs for developing a suitable dosage form (1). The poorly water-soluble drugs have a slow rate of drug dissolution and ultimately have poor oral bioavailability (2). The different solubility and dissolution enhancement methods available are solid dispersions (3), Complexation with β- cyclodextrin (4), micronization (5) and spray-drying technique (6).

Liquisolid is one of the most promising techniques used to improve the solubility and dissolution rate of poorly water-soluble drugs (7-9). This technique is based on the conversion of poorly water-soluble drugs in a nonvolatile solvent either in solution or suspension form into suitable free-flowing and compressible powders (10). Practically, the solution or suspension of

selected drug in non-volatile solvent is blended with porous carrier coating material until the free-flowing and compressible powder is obtained. Based on the solubility of the drug, the selection of nonvolatile solvents is performed. The most frequently used nonvolatile solvents for the preparation of LS compacts include polyethyleneglycol (PEG), propylene glycol, polysorbate 80, glycerol, Tweens, and spans (11). Carrier materials are selected based on their liquid-holding capacity, flow-ability, and compressibility. The most commonly used carriers in LS formulations are microcrystalline cellulose, Sylysia, Neusillin US2 etc. Lu Mei *et al*, developed the liquisolid technique to improve the dissolution properties of water-insoluble drugs (12). The required flowability as well as compressibility of Liquisolid systems, mainly depends on two factors i.e. liquid load factor (Lf) and excipients ratio (R). Lf simply represents the required amount of vehicles in the formulation. It may also be defined as the ratio of the weight of the liquid drug and the weight of the carrier material. R (Excipients ratio) represents the weight ratio of carrier material and coating material used for the preparation of LS compacts. The mathematical relationship of Lf and R is given as follows.

$$Lf = Ø + Ø\,(1/R)$$

Where Ø represents the liquid retention potential (flowable) of the carrier and $Ø$ represents the liquid retention potential (flowable) of the coating material.

This method was already reported to augment the solubility and dissolution rate of many drugs such as naproxen (13), famotidine (14), carbamazepine (15), piroxicam (16), indomethacin (17), hydrocortisone (18) and prednisolone (19). Tacrolimus is generally used for the suppression of the immune system. It is prescribed for patients after organ transplantation like kidneys, lungs, and heart to prevent allograft rejection (20). Tacrolimus belongs to class II of the Biopharmaceutics Classification System with low solubility and high permeability i.e. insoluble in water with high log p values (21). The absorption and oral bioavailability of Tacrolimus is very poor i.e. 25 % approximately (22). Duaa J. Al-Tamimi et al prepared and characterized tacrolimus-loaded solid self-microemulsion for improving oral bioavailability (23). Y Wang et al. prepared and characterized Tacrolimus amorphous nanosuspensions to improve dissolution rate and oral bioavailability (22). Kang JH et al prepared and evaluated tacrolimus-loaded thermosensitive solid lipid nanoparticles to enhance dermal penetrability (21) whereas, the current investigation was focused to improve solubility and oral bioavailability of Tacrolimus, by developing Liquisolid compacted tablets. The aim of this investigation is to increase the rate of dissolution and oral bioavailability of Tacrolimus via the liquisolid technique. PEG600, labrasol, and caproyl 90 were selected as the non-volatile liquid vehicle. Neusilin US2 and aerosil 200 were used as carrier and coating materials respectively to produce powders with acceptable flow properties which were compacted into tablets.

MATERIALS AND METHODS

Materials

Tacrolimus was received as a gift sample from Dr. Reddy's Laboratories Ltd, Hyderabad, India. Neusilin US2 was also received as a gift sample from Fuji chemical industries co Ltd, Mumbai, India. Avicel PH 102 and Aerosil 200 were purchased from HI Media Pvt Ltd, Mumbai, India.

PEG 600 was procured from Himedia Labs. Capryol 90 and Labrasol were received as gift samples from Gattefosse India Pvt. Ltd. Mumbai. All other materials and reagents used were of analytical grade.

Methods

Selection of non-volatile solvent

An excess amount of tacrolimus was transferred to a 5 ml volumetric flask containing 1 ml of different non-volatile solvents such as PEG 600, Capryol 90, Labrasol, Tween 80, Captax 200, and PEG 200. The saturated solutions were shaken for 72 h in a water bath shaker at room temperature (24). Then the above mixtures were centrifuged at 8000 rpm for 15 minutes. After centrifugation, 0.1 ml of supernatant was taken using the micropipette to another 10 ml of the volumetric flask, then the volume was made up of 10 ml by adding methanol and analyzed spectrophotometrically at λ max 287 nm.

Selection of carrier and coating materials

To select carrier and coating material for all the non-volatile solvents, carr's index was determined for a mixture of non-volatile solvents and porous carriers. In the initial phase two carrier materials i.e. Avicel PH 102 and Neusilin US2 were selected with aerosil as coating material. In this study, 0.5 g of the carrier was kept in a china disc. An increasing amount of non-volatile solvent i.e. 0.5 ml, 1 ml, 1.5 ml, 2 ml, and 2.5 ml were added and mixed. Carr's index for each of the mixtures was determined to select a porous carrier.

Preparation of LS Powder for Tacrolimus

As the API tacrolimus exhibited good solubility in PEG 600, Labrasol and Capryol-90 compared to the other non-volatile solvents, a total of 9 liquisolid formulations were fabricated by dissolving Tacrolimus in selected non-volatile solvents at 3 concentration levels i.e. 5%, 10% and 15% W/V. The drug solution was mixed with calculated quantities of Neusilin US2 and Aerosil PH102 mixture to get a freely flowable powder as shown in Table 1.

Characterization of LS powder

Powder Flowability

The fabricated LS powders were subjected to evaluation of flowability and compressibility before being compressed into tablets (25). These include the measurement of the angle of repose, Carr's index, and Hausner's ratio. The traditional fixed funnel method was employed to determine the angle of repose. The bulk density and tapped density were determined using USP Bulk Density Apparatus. After obtaining bulk density and tapped density, Carr's index and Hausner's ratio were determined by using the following formula.

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

$$Hausner's\ Ratio = \frac{Tapped\ density}{bulk\ density}$$

Drug content

An amount equivalent to 5 mg of tacrolimus for each LS powder formulation was calculated & diluted in 5 ml of methanol followed by sonication for 5 minutes. Then it was filtered, diluted, and analyzed spectrophotometrically at 287 nm.

In vitro dissolution studies

The different Liquisolid compact formulations i.e. LS 1, LS 2, LS 3, LS 4, LS 5, LS 6, LS 7, LS 8, and LS 9 were subjected to *In-Vitro* dissolution studies by employing USP dissolution apparatus II. 0.1 N hydrochloric acid (900ml) was used as dissolution medium at a temperature of 37 ^{0}C with 50 rpm. Five mL samples were withdrawn at different sampling points of 15, 30, 45, 60, 90, and 120 min. and the withdrawn sample was replaced with an equal volume of the dissolution medium. The percent drug dissolved in each withdrawn sample was determined using UV-Visible Spectrophotometer (Model UV-1800, Shimadzu) at 287 nm.

Fourier transform infrared (FT-IR) spectroscopy

FT-IR studies were performed for the following samples such as pure drug tacrolimus LS formulation LS 3, LS 5, and LS 9 respectively. Potassium bromide was used for making pellets before the FT-IR study.

Differential scanning calorimetry (DSC)

DSC study was performed for the pure drug tacrolimus, LS formulations with non-volatile solvents PEG 600, Caproyl 90 & Labrasol. An empty aluminum pan was used for DSC measurement.

Preparation of LS Compacted Tablets

Tablets were prepared by taking an amount of LS formulation equivalent to 5 mg of Tacrolimus as API, Cross carmellose sodium as a disintegrant, and Neusiilin US2 as diluents to make a tablet of weight 100 mg. The direct compression method was used to prepare the tablets using a multi-station rotary compression machine with flat circular punches of 6 mm diameter. The LS 3, LS 5, and LS 9 formulations were formulated as a tablet with composition as presented in Table 4

Quality control tests for LS Compacted Tablets

Drug content, hardness, disintegration, weight variation, friability tests and *In-vitro* dissolution tests were performed for LS compacted tablets of tacrolimus (25). The drug content was determined by triturating 10 tablets in a mortar and pestle and then percent drug content was determined in UV spectroscopy by sonicating the sample in methanolic solution followed by filtration and dilution. The hardness of tablets was measured by using a portable digital tablet hardness tester. The hardness of 20 tablets was measured and the average hardness was calculated. 1 tablet was placed in every six cylinders. The basket rack was kept in a 1000 ml vessel with 900 ml disintegration medium maintaining temperature at 37 ^{o}C±2^{o}C and the basket rack assembly was allowed to oscillate and DT was determined on observation of each fragment of tablets crossing the sieve in each cylinder. 10 randomly selected units of tablets in each formulation were taken and weighed and subjected to a friability test using a Roche friabilator set at 25 rpm for 4 minutes then the tablets were taken out and weighed again and the % friability

was calculated using the following formula. In-vitro dissolution studies were performed for LS compacted tablets of formulation LS3, LS5 and LS9 in 0.1 N HCl for 2 h.

X-Ray Diffraction Studies

The crystallinity of Tacrolimus, and Tacrolimus-loaded LS 3 powder, were assessed by X-ray powder diffraction technique.

Pharmacokinetic study

Grouping of animals and treatment

12 no. of male albino rabbits weighing 2 kg each were screened and segregated into 2 groups each having 6 animals. One group is administered with an optimized liquisolid formulation of Tacrolimus i.e. formulation of L3 as test and another group were administered with an aqueous suspension of Tacrolimus as standard.

Dose calculation

The formula for dose calculation for each rabbit was presented as follows.

The total dose in mg (in humans) × 0.07 (factor for each 2 kg weight of rabbit)

= (5×0.07 ×2)/1.5 = 0.46 mg of 2 kg rabbit

The total dose of Tacrolimus for each rabbit was rounded off to 0.5 mg.

Drug administration

0.5 mg of pure drug powder dispersed in 3ml of water was administered to 6 rabbits. 3 ml of formulation LS3 (containing 0.5 mg of drug) was administered to 6 rabbits. Pure drug and optimized Liquisolid formulation (LS3) were administered simultaneously to the animals with the help of wood and a feed tube (Ryle's tube). The marginal ear vein was punctured by using needle no. 24 at regular intervals and 1 mL of blood was collected in an Eppendorf tube each time.

Blood sampling

After administration of the dose to rabbits, 0.5 mL blood was withdrawn from the marginal ear vein of the rabbit and transferred into Eppendorf tubes at different sampling points of 0, 0.5, 2, 6, 12, and 24 h. The serum was collected from the blood keeping the Eppendorf tubes undisturbed in a slanting position for 30 min to allow coagulation followed by centrifugation at room temperature for 30 min at 5000 rpm. The supernatant layer was collected by employing a micropipette. The study was conducted with the approval of the Animal Care Committee, Institutional Animals Ethics Committee (IAEC)/CPCSEA with a protocol approval number 160.

Estimation of the drug in rabbit serum

The standard curve of Tacrolimus was carried out in blood serum by solvent extraction method with diethyl ether. The peak area of different concentrations at λ_{max} of 198 nm was measured. The linearity was seen in the concentration range of 100-100000 µg/mL. This calibration curve was utilized to calculate the amount of tacrolimus present in the *in-vivo* samples collected at different time intervals.

The important pharmacokinetic parameters i.e. AUC (area under the curve), Cmax (peak plasma conc.), Tmax (peak time) was estimated from the serum conc. versus time plot. The elimination rate constants (k) for aqueous suspension of pure drug and LS formulation (LS3) were

determined from the semi-logarithmic plot of serum conc. versus time plot. The elimination rate constant (k) was calculated from the terminal linear portion of the curve.

RESULTS AND DISCUSSION

Selection of non-volatile solvent

The saturation solubility study for the pure drug tacrolimus was performed in different non-volatile solvents. Three solvents in which tacrolimus showed higher solubility were selected for further formulation. The selected solvents were as follows PEG 600 (207.5 mg/ml), Caproyl 90 (182.4 mg/ml), and Labrasol (172.6 mg/ml) as presented in Figure 1. On preliminary screening for solubility of Tacrolimus in different nonvolatile solvents, PEG 600, Capryol 90, and labrasol were found to be the most suitable ones as the drug is more soluble in these solvents.

Selection of carrier and coating materials

In order to select carriers and coating for all the non-volatile solvents, Carr's index was determined for each non-volatile solvent and porous carrier. In the initial phase 2 carrier materials, i.e. Avicel PH 102 and Neusilin US2 were selected, whereas, aerosil was taken as coating material. In this study, 0.5 g of the carrier was taken in a china disc to that increasing amount of non-volatile solvent i.e. 0.5 ml, 1 ml, 1.5 ml, 2 ml, and 2.5 ml was added and mixed separately. Carr's index for each of the mixtures was determined to select a porous carrier. Initially, Avicel PH 102 and Neusilin US2 were screened for selection as carrier materials. From the above study, it was observed that the Combination of Avicel PH 102 and Aerosil were not successful in converting the non-volatile liquid vehicle PEG 600, capryol 90, and labrasol into free-flowing powder. It exhibited very poor flowability when 0.5 ml of nonvolatile solvents (PEG 600, capryol 90, and labrasol) was added to 0.5 g of a mixture of Avicel PH 102 and aerosol (20:1). Subsequent increase in the proportion of nonvolatile solvents resulted in the formation of non- flowable sticky powders. The increased amount of non-volatile solvents was added to 0.5 g of neusillin US2 and mixed for 2 min. It was observed that Neusillin US2 (0.5 g) can convert 2 mL of PEG 600, 1.5 mL of capryol 90, and 1.5 mL of labrasol into free-flowing powder. Those concentrations were selected for the determination of the liquid load factor.

Characterization of LS Powder for Tacrolimus

Powder flowability

The angle of repose, Carr's index, and Hauser’s ratio were presented in Table 2. It was observed that the pure drug powder of tacrolimus was very poorly flowable and compresiible. Among three PEG600 based LS formulations (LS1, LS2 and LS3), it was observed that LS3 exhibited desirable flowability and compressibility for processing into tablet dosage form as the angle of repose, Carr’s index and hausner’s ratio were within the theoretical range. Similarly in case of caproyl 90 based LS formulations (LS, LS5 and LS6) and labrasol based LS formulations (LS7, LS8 and LS9), it was observed that LS5 and LS9 exhibited desirable flowability and compressibility. All the evaluated parameters were found to be under the standard range of specifications.

Drug Content

The values of drug content are presented in table 3. All nine LS formulations exhibited more than 90% drug content. This high drug content can be ascribed to the proper selection of non-volatile solvents, carrier material, coating material, and optimum mixing time.

In vitro dissolution studies

In vitro dissolution study for pure drug tacrolimus suggests a very poor dissolution rate i.e only 11% of drug dissolution in 1 h of dissolution study. Among all the LS formulations, a higher dissolution rate was observed for PEG 600-based LS formulations. Formulation LS 3 exhibited the highest dissolution rate i.e around 17, 13, and 9 fold increase in dissolution rate compared to the pure drug sample of tacrolimus. LS formulations prepared with other nonvolatile solvents caryol 90 and labrasol also exhibited improvement in dissolution rate but comparatively, it was less than PEG 600-based formulation. The data are presented in table 3.

Fourier transform infrared (FT-IR) spectroscopy

The FT-IR spectra of tacrolimus exhibited major peaks at 3480 cm-1, 1732 cm-1,1640 cm-1, 1700 cm-1, and 1091 cm-1 due to O - H stretching vibration, C = O (ester and ketone) stretching vibration, and C Ξ O (keto–amide) and C = C stretching vibration, and C – O – C (ether) stretching vibration respectively. In liquid formulation, the majority of the peaks disappeared which can be attributed to the interaction of tacrolimus with a non-volatile solvent and carrier, which might be due to the hydrogen bonding of the drug with the excipient used in liquisolid formulation. The FTIR spectra of Tacrolimus, LS with PEG 600, LS with capryol 90, and LS with labrasol were presented in Figure 2.

Differential scanning calorimetry (DSC)

The pure drug tacrolimus exhibited an endothermic peak at 123^{o} C with onset and end set temperatures of 117.6 C and 129.92 ^{o}C respectively. The LS formulation (PEG 600) showed a slightly shifted peak at 130 ^{o}C. This indicated that there was no interaction between the drug and the excipient. In the case of LS formulation with PEG 600, caproyl 90 and labrasol did not show any peak for melting of tacrolimus. This can be attributed to the presence of the drug in a dissolved state in a liquisolid formulation. The thermal spectra of A. Tacrolimus, B. LS with PEG 600, C. LS with capryol 90, and D. LS with labrasol were presented in Figure 3.

Preparation of Liquisolid Compacted Tablets

LS powders equivalent to 5 mg of tacrolimus for formulations LS3, LS5 and LS9 were weighed and mixed with superdisintegrating agent cross caramellose sodium (3%). Neusillin US2 was added to increase the bulk weight of the tablet.

Quality Control tests for LS tablets

The dissolution curve of LS 3, LS 5, and LS 9 were presented in Figure 4. The LS3, LS5, and LS9 compact tablets were evaluated for hardness, friability, DT, and in vitro dissolution and were presented in Table 5. All the three LS formulations passed the quality control tests for tablets. However formulation LS3 showed lesser disintegration time with highest dissolution rate. Hence LS compacted tablet LS3 was selected for further studies.

X-Ray Diffraction Studies

The P-XRD study for pure drug exhibited peaks at the following 2θ angles i.e. 10^o (31740), 11^o (18606), 14.1^o (17316), 17^o (19302), 18.96^o (42720), 19.924^o (23184). This indicated that tacrolimus was a crystalline drug, whereas, the LS formulation (Caproyl 90) did not exhibit any peak this can be attributed to the presence of the drug in the completely solubilized form in the formulation. The X-RD spectra of Tacrolimus and drug-loaded LS with Capryol 90 were presented in Figure 5.

Pharmacokinetic Study

The pharmacokinetic parameters were presented in Table 6 and the serum drug concentration versus time was presented in Figure 6. A pharmacokinetic study of both the pure drug Tacrolimus and optimized Liquisolid formulation (LS3) was performed by UFLC by measuring serum drug concentration at different time intervals. The T_{max} for Tacrolimus and LS3 compacts were found to be 6 h and 2 h respectively which indicated a faster rate of absorption of the drug from the LS3 as compared to the pure drug. The AUC for LS3 was found to be 3146.923±16.36µg.hr/ml, whereas it was found to be 716.229±11.25µg.hr/ml for Tacrolimus exhibiting that LS3 had better bioavailability as compared to the pure drug of Tacrolimus, almost 5 fold more. The Cmax value for Tacrolimus was observed to be 87.2 (µg/ml) whereas 285.8 µg/ml for LS3. Approximately, 5 fold increase in Cmax value for LS3 showed faster absorption of the drug from the formulation. The elimination rate constants for Tacrolimus and LS3 were found to be 34.3791 and 0.0946 respectively. The pharmacokinetic profile of the optimized LS3 was found to be superior compared to the aqueous suspension of pure drugs, which can be therapeutically and commercially exploited.

CONCLUSION

Liquisolid compacts fabricated by using PEG600 as a non-volatile solvent and neusillin US2 as carrier material and aerosil as coating material have shown the highest dissolution rate. Liquisolid formulations exhibited desirable flowability for processing into a tablet dosage form. Selected formulation LS3 exhibited an increased dissolution rate with disintegration in less than 10 min. A pharmacokinetic study for liquisolid formulation LS3 showed nearly 5 times improvement in oral bioavailability. Hence Liquisolid technique can be used successfully to improve the dissolution rate and oral bioavailability of tacrolimus.

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Ethical Approval:

This research has passes institutional animal ethical committee (IAEC) clearance with number 926/PO/Re/S/06/CPCSEA/160.

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Conflict of Interest

The authors declare no conflict of interest

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Figures

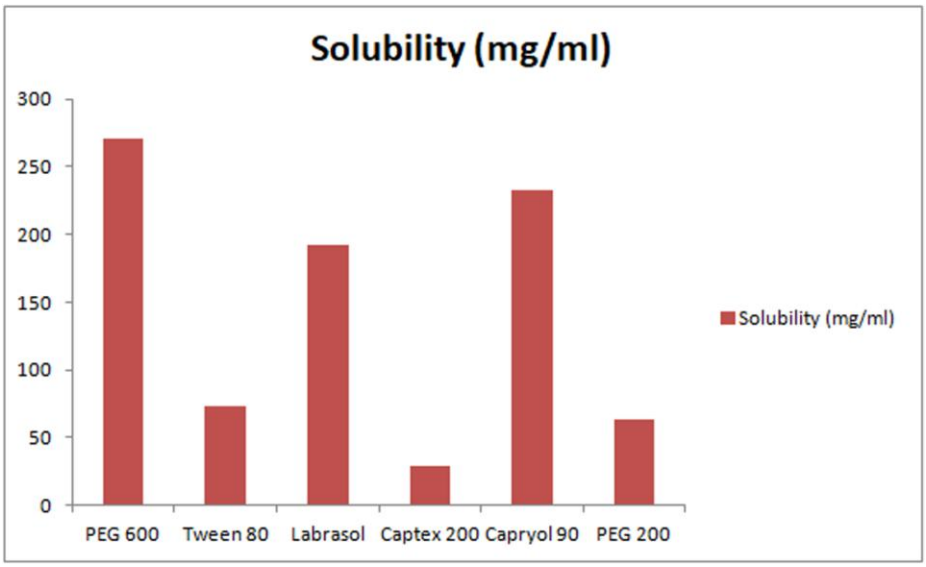

Figure 1: Solubility of Tacrolimus in different non-volatile solvents

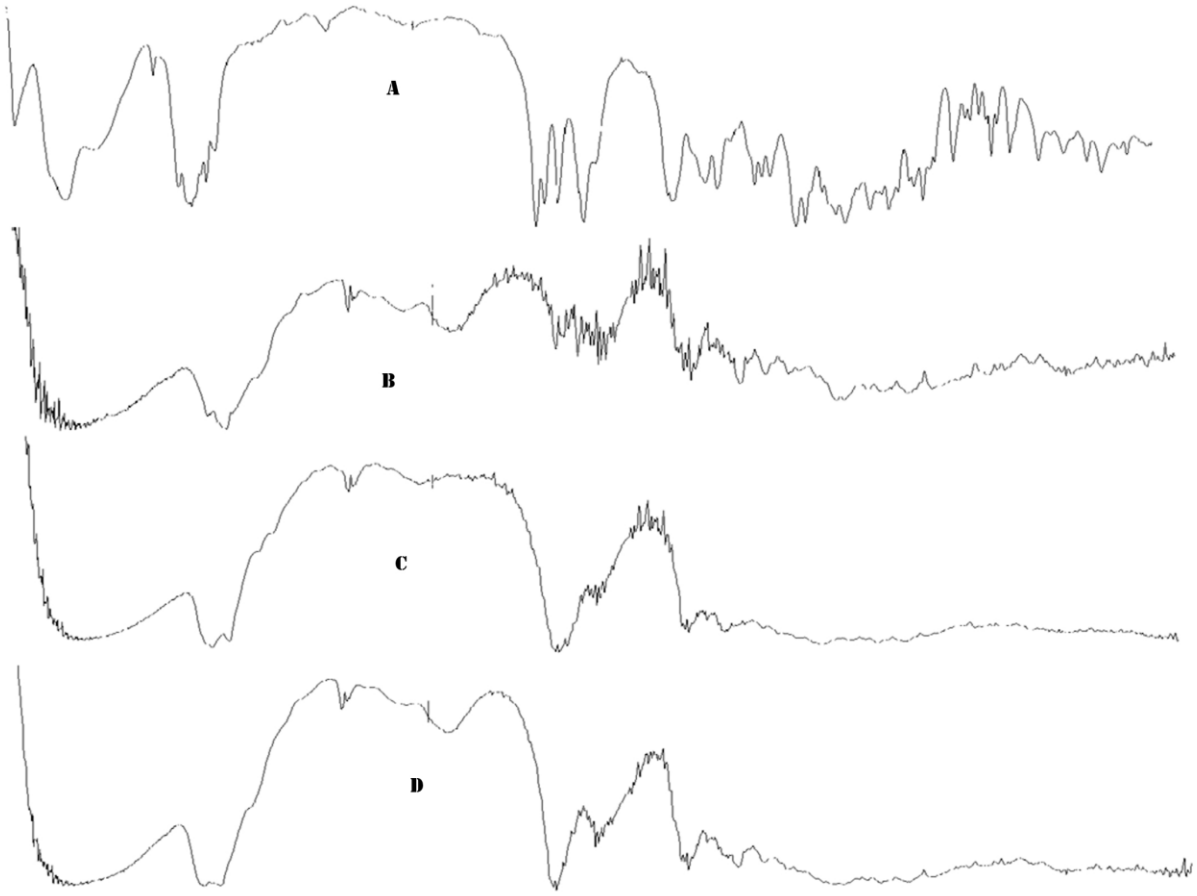

Figure 2: FTIR spectra of A. Tacrolimus, B. LS PEG, C. LS Capryol 90, and D. LS Labrasol.

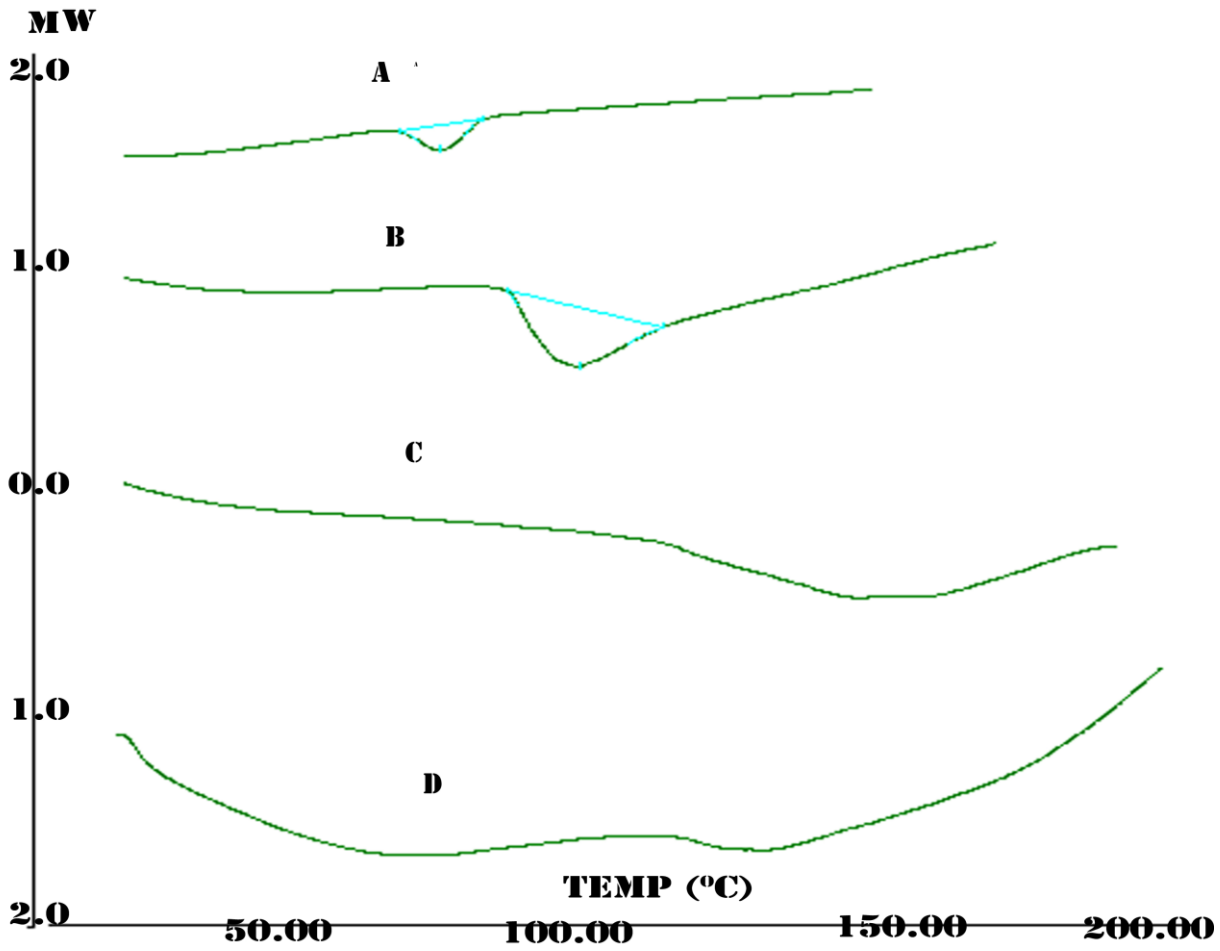

Figure 3: DSC spectra of A. Tacrolimus, B. LS PEG, C. LS Capryol 90, and D. LS Labrasol.

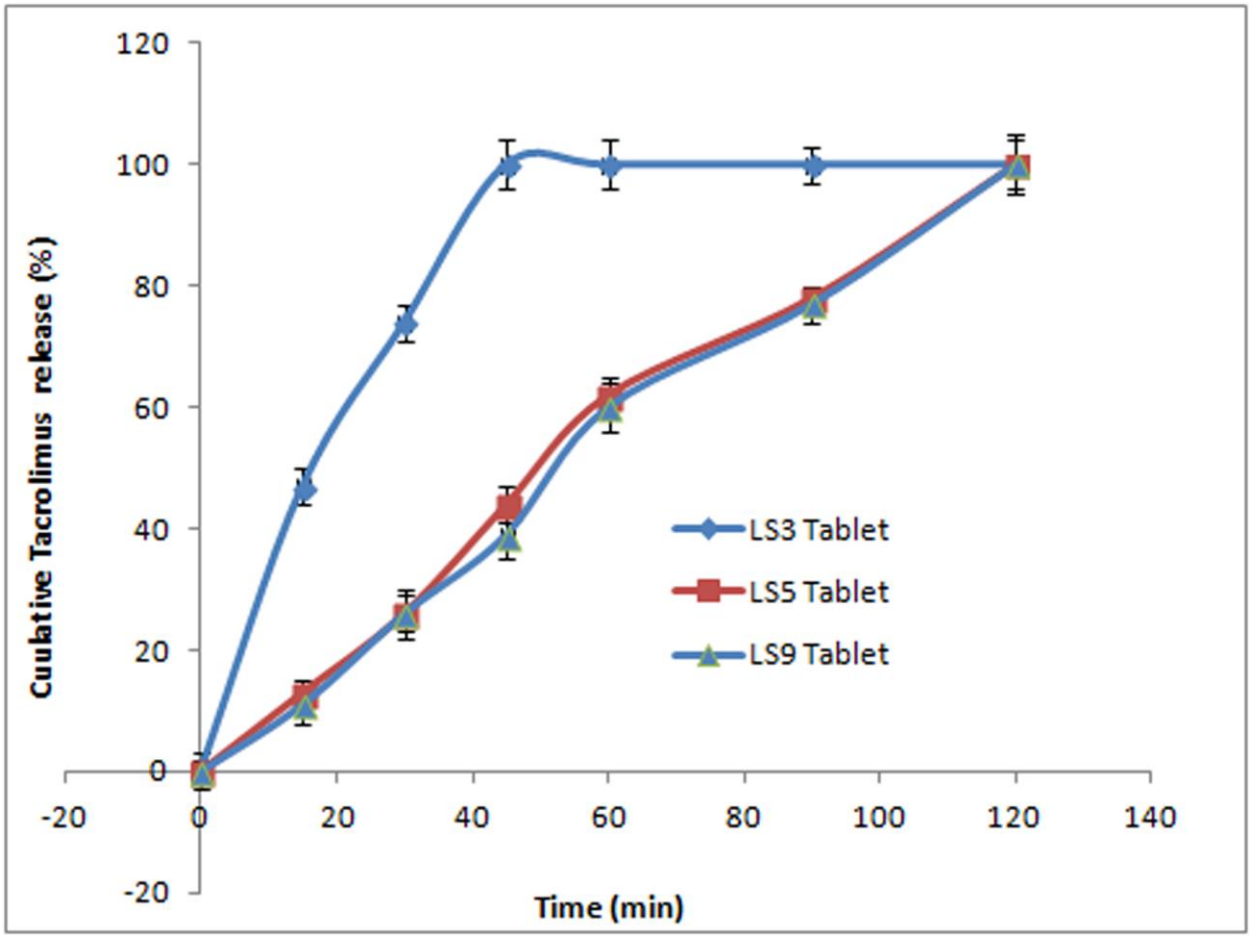

Figure 4: The dissolution curves of LS3, LS5 and LS 9 tablets

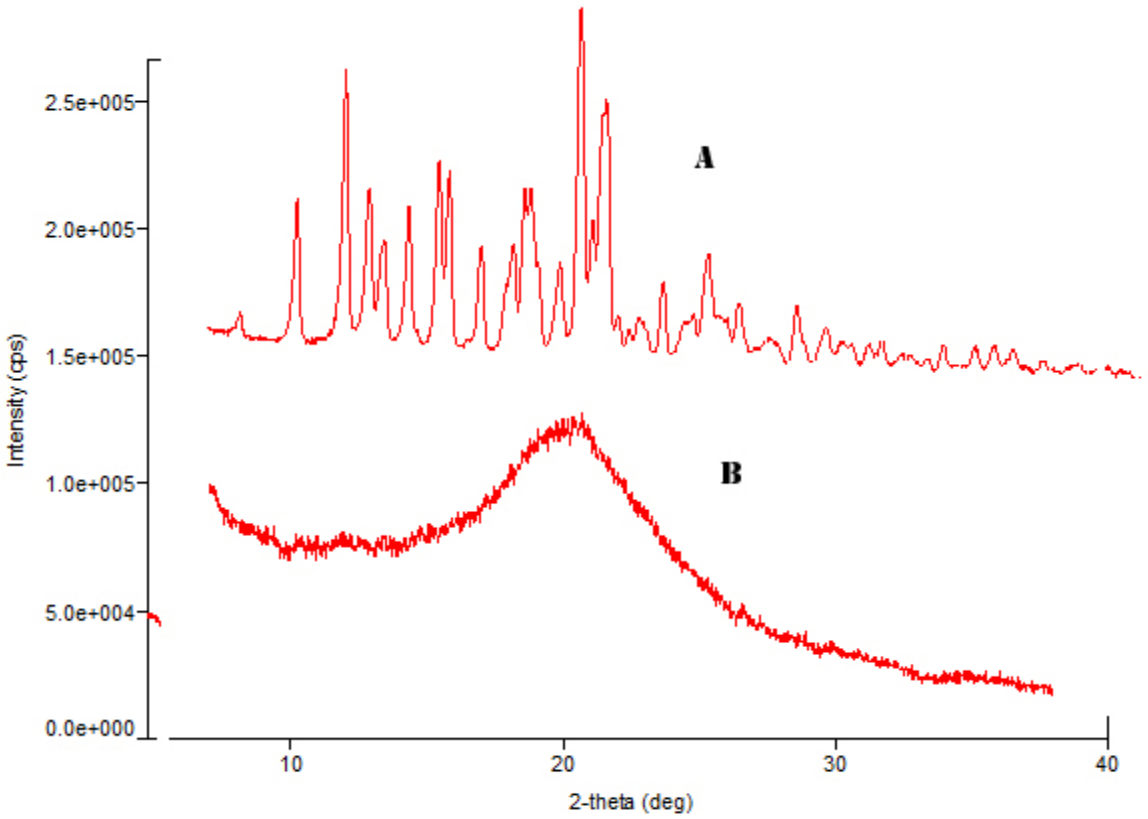

Figure 5: The X-RD spectra of Tacrolimus and Tacrolimus-loaded LS3

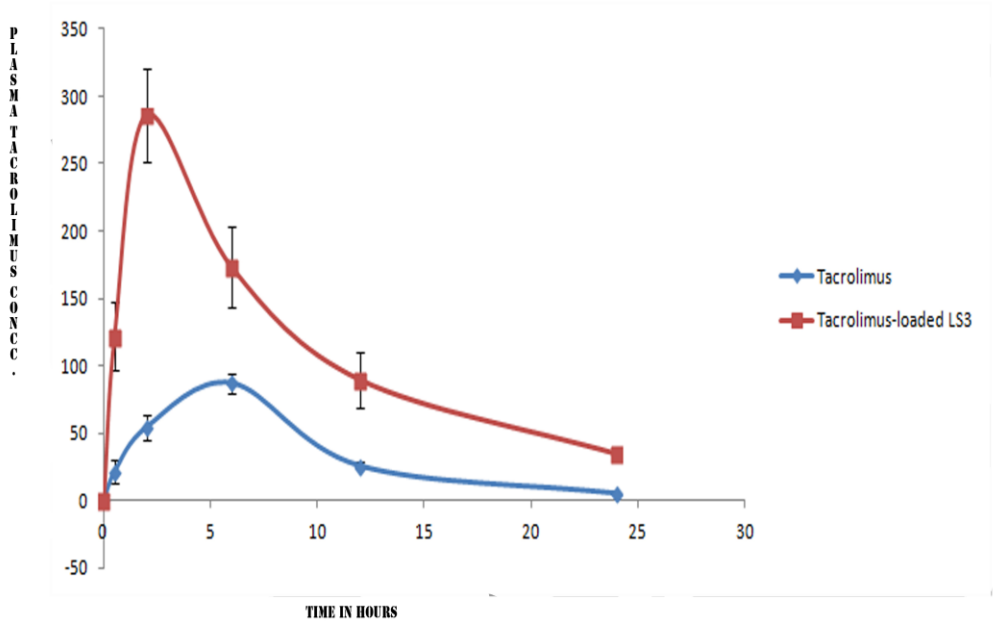

Figure 6: Plasma Tacrolimus conc. versus time curve

Table 1, Composition of Liquisolid Powder formulations

Liquisolid System	Non-volatile Solvent	Drugs Conc.(%) (w/v)	Carrier Coating (R) Ratio	Lf For carrier coating mixture	Tacrolimus (mg)	Liquid Vehicle (ml)	Practical Wt. of Liquid (g)	Wt. of carrier (Neusilin) (g)	Wt. of Coating (Aerosil) (g)	Liquisolid powder equivalent to 5 mg (dose) of Tacrolimous
LS-1	PEG 600	5	20	3.569	250	5	5.596	1.567	0.078	111.92
LS-2	PEG 600	10	20	3.569	500	5	5.854	1.737	0.086	58.54
LS-3	PEG 600	15	20	3.569	750	5	6.105	1.710	0.085	40.7
LS-4	Capryol-90	5	20	2.788	250	5	4.905	1.759	0.087	98.1
LS-5	Capryol-90	10	20	2.788	500	5	5.120	1.836	0.091	51.2
LS-6	Capryol-90	15	20	2.788	750	5	5.330	1.911	0.095	35.53
LS-7	Labrasol	5	20	3.034	250	5	5.378	1.772	0.088	107.56
LS-8	Labrasol	10	20	3.034	500	5	5.730	1.888	0.094	57.3
LS-9	Labrasol	15	20	3.034	750	5	5.795	1.910	0.095	38.63

Table 2, Micromeritic properties of LS powder formulations

Sample codes	Angle of Repose (^{0})	Carr's Index	Hausner's ratio	Inference
Pure drug Tacrolimus	43.25 ± 1.36	38.46 ± 3.54	1.58 ± 0.02	Poor
LS1	41.35 ± 1.56	41.25 ± 2.15	1.65 ± 0.01	poor
LS2	41.35 ± 2.14	43.05 ± 1.57	1.67 ± 0.02	poor
LS3	25.78 ± 1.59	28.28 ± 1.84	1.35 ± 0.01	Good
LS4	42.54 ± 2.21	41.54 ± 1.51	1.76 ± 0.02	poor
LS5	22.25 ± 1.74	25.25 ± 1.56	1.25 ± 0.04	Good
LS6	41.45 ± 2.15	42.35 ± 1.58	1.79 ± 0.03	poor
LS7	43.75 ± 1.98	40.75 ± 1.02	1.69 ± 0.04	poor
LS8	42.95 ± 2.57	41.23 ± 1.05	1.59 ± 0.04	poor
LS9	21.25 ± 2.14	23.35 ± 2.01	1.23 ± 0.02	Good

All results are presented as Mean ± SD, where n=6

Table 3, Quality control tests for LS powders

Liquisolid formulations	**Drug Content (%)***	**Q15 (%)****	**Q30 (%)****	**Q60 (%)****
Pure Drug	**-**	**3** ± 0.02	**6** ± 0.05	**11**± 0.5
LS1	98.25 ± 4.1	20 ± 0.4	32 ± 2.1	68 ± 2.5
LS2	96.35 ± 3.5	27 ± 1.1	41 ± 3.1	100 ± 3.2
LS3	98.5 ± 2.6	51 ± 2.3	78 ± 3.6	100 ± 2.5
LS4	93 ± 3.4	14 ± 1.2	27 ± 2.1	57 ± 2.1
LS5	97.8 ± 4.2	16 ± 1.4	29 ± 2.1	64 ± 3.1
LS6	92.5 ± 3.5	15 ± 1.1	30 ± 1.5	63 ± 2.9
LS7	91.5 ± 3.6	9 ± 0.45	19 ± 0.9	46 ± 2.7
LS8	94.75 ± 4.1	12 ± 0.9	25 ± 0.8	55 ± 2.4
LS9	96.85 ± 3.5	14 ± 0.2	28 ± 1.1	61 ± 2.1

All results are presented as Mean ± SD, where *n=10, ** n = 6

Table 4, Composition of LS Tablets

Composition	LS3	LS5	LS9
LS equivalent to 5 mg of Tacrolimus	40.7	51.2	38.6
Cross carmellose sodium	3	3	3
Neusiilin US2	56.3	45.8	58.4
Total	100	100	100

Table 5, Quality control tests for LS tablets

Tests	**LS3**	**LS5**	**LS9**
Hardness (Kg/cm^2)*	5 ± 0.01	5.5 ± 0.02	5.3 ± 0.05
Thickness (mm)**	3.6 ± 0.5	3.6 ± 0.2	3.6 ± 0.4
Disintegration time (min)*	9 ± 0.05	10 ± 0.06	10 ± 0.05
Friability (%)**	0.52 ± 0.003	0.83 ± 0.002	0.75 ± 0.004
Weight variation (%)***	100 ± 2.54	100 ±3.21	100 ± 2.56
Dissolution (Q60)*	100 ± 3.5	76 ± 3.4	67 ± 2.6

All results are presented as Mean ± SD, Where *n=6, ** n = 10 and ***n = 20

Table 6, Pharmacokinetic parameters for Tacrolimus and its liquisolid formulation

Pharmacokinetic parameters	**Pure drug of Tacrolimus**	**Formulation LS 3**
K_E	34.3791	0.0946
C_{max} (µg/ml)	87.2 ± 2.5	285.8 ± 5.5
t_{max}(hr)	6 ± 0.5	2 ± 0.02
$t_{1/2\ (1)}$	0.02015	7.3217
$AUC_{(0\text{-}t)}$ (ng.hr/L)	716.075 ± 8.5	2782.23 ± 15.5
AUC (t-∞)	0.154 ± 0.002	364.693 ± 15.26
AUC (0-∞)	716.229 ± 11.25	3146.92 ± 16.36

All results are presented as Mean ± SD, where n = 6