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Research Article

Micromeritics and *In-vivo* Bioavailability Study for PEG400 and Labrasol Based Liquisolid Compacts of Tacrolimus

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Abstract

The objective of this study is to enhance flowability, compressibility and oral bioavailability of tacrolimus using the liquisolid technique. Tacrolimus primarily functions as an immunosuppressant. The primary obstacles for developing effective formulations for this compound are its limited aqueous solubility and low bioavailability, reported to be 25%. To address this, we formulated cinacalcet HCl liquisolid compacts with PEG 400 and labrasol as the non-volatile solvents, sylysia 350 as the carrier material, and aerosil as the coating material. Our comprehensive analysis included Differential Scanning Calorimetry (DSC), Powder X-ray Diffraction (P-XRD), kawakita analysis, quality control tests and pharmacokinetic study. The results indicated improved flowability, compressibity, no drug-excipient interaction and tacrolimus presence in the porous carrier in a dissolved state. Notably, selected formulation (L6) exhibited enhanced dissolution rate, disintegrating in less than 3 min with significant improvement in oral bioavailability. Overall, the liquisolid approach holds promise for developing a stable and scalable solid dosage form with improved flowability, compressibility and oral bioavailability.

Keywords: Kawakita analysis; Sylysia 350; Dissolution rate; Pharmacokinetic study

Introduction

Poorly water-soluble drugs exhibit slow dissolution rates, which pose a significant challenge in formulating oral pharmaceutical dosage forms [1]. Enhancing solubility and dissolution rate is crucial for improving drug absorption along the intestinal tract [2]. Various approaches have been explored to address this issue, including solid dispersions inclusion complexation, particle size reduction, salt formation, co-crystallization, co-solvency, spray-drying techniques, lyophilisation, micronization and microwave for improving rate of dissolution [3-12].

The liquisolid approach, devised by Spireas and their team, offers a strategy to increase the dissolution rate of poorly water-soluble pharmaceuticals [13]. The technique involves incorporating poorly water-soluble pharmaceuticals into a non-volatile solvent that is miscible with water, either in dissolved or suspended form. This mixture can then be transformed into a flowable, compressible, non-adherent powder [14]. The process involves using a porous carrier and a coating material. A dry powder is produced by covering the wet porous coating material with fine particles [15].

Tacrolimus primarily functions as an immunosuppressant [16]. Classified as a BCS Class II drug, it exhibits low water miscibility but readily permeates biological membranes, characterized by high log P values [17]. The primary obstacles for developing effective formulations for this compound are its limited aqueous solubility and low bioavailability, reported to be 25% [18]. This study aims to enhance flowability, compressibility, dissolution properties, and oral absorption tacrolimus using the liquisolid approach.

Materials

A gift sample of Tacrolimus was obtained from DRL, Hyderabad, India. A gift sample of Sylysia 350 was obtained from Fuji Sylysia, Japan. Labrasol came as complimentary sample from Gattefosse India Ltd. PEG600 and aerosol was sourced from Himedia, India.

Methods

Pre-formulation study

Solubility study: Following the standard protocol, the saturation solubility of tacrolimus was examined in a range of non-volatile liquid vehicles, as shown in Figure 1 [14]. These non-volatile liquids were saturated with tacrolimus,

which were then stirred for 48 h at room temperature. The solutions were then filtered, centrifuged, and processed to UV Visible spectrophotometric examination 287 nm.

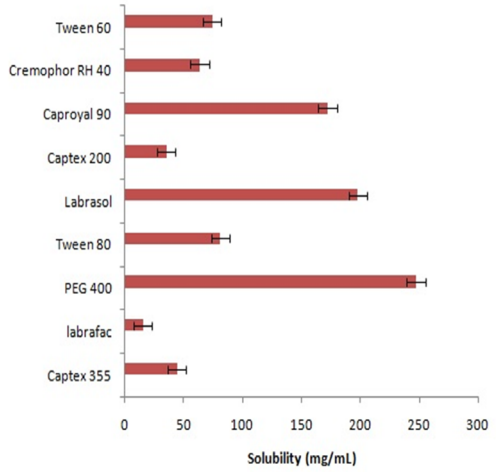

Figure 1: Saturation solubility of tacrolimus in non-volatile solvents

Determination of loading factor: To determine the maximum liquid load capacity sylysia 350 and aerosol were selected as porous carrier and coating material respectively at an R value of 20. To these admixtures of porous carrier and coating material (10 g), increasing amounts of non-volatile liquids PEG400 and labrasol were added. After mixing for 3 minutes, the mixture was kept overnight and the angle of repose was determined. The admixture showing angle of repose 25° was selected [19].

$$Lf = \frac{Weight\ of\ the\ liquid\ corresponding\ to\ 25^0}{Weight\ of\ the\ carrier}$$

Preparation of liquisolid powder: Two non-volatile solvents, namely PEG400 and labrasol were chosen for preparing liquisolid compacts due to their higher solubilisation capacity to dissolve tacrolimus. The drug was dissolved separately in these selected solvents in different drug loading percentages (2.5% to 15%) and vortexed for 10 minutes (Table 1). Subsequently, the necessary quantity of sylysia 350 and aerosol (20:1 ratio) was incorporated as carrier and coating agents.

Table 1: Composition of liquisolid powder of tacrolimus

Formulation code	Non-volatile Solvent (mL)	Tacrolimus (% W/V)	Carrier coating ratio (R)	Lf	Tacrolimus (mg)	Practical weight of liquid medication (W)	Quantity of carrier Q in g (Q=W/Lf)	Quantity of coating (q) in g q=Q/R	Total weight (g)	Amount Equivalent to 5 mg of Tacrolimus
L1	PEG 400 (5 mL	2.5	20	3.425	125	5.462	1.592	0.079	7.133	285.32
L2		5			250	5.587	1.631	0.081	7.299	145.98
L3		7.5			375	5.712	1.668	0.083	7.463	99.51
L4		10			500	5.837	1.704	0.085	7.626	76.26
L5		12.5			625	5.962	1.74	0.087	7.789	62.31
L6		15			750	6.087	1.772	0.088	7.947	52.98
L7	Labrasol (5 mL)	2.5		2.937	125	5.22	1.777	0.088	7.085	283.4
L8		5			250	5.345	1.819	0.09	7.254	145.08
L9		7.5			375	5.47	1.862	0.093	7.425	99
L10		10			500	5.595	1.905	0.095	7.595	75.95
L11		12.5			625	5.72	1.947	0.099	7.766	62.12
L12		15			750	5.845	1.99	0.099	7.835	52.23

Characterization

Flowability: The micromeritic properties of all formulations (L1 to L12) were comprehensively evaluated using established methodologies. These included the determination of Carr's index, angle of repose, and Hausner's ratio to assess powder flowability characteristics [20].

Kawakita analysis: A 100 ml glass measuring cylinder was taken and filled with 10 g of tacrolimus and 10 g of tacrolimus loaded liquisolid formulation Initial bulk volume was designated as V0 and tapped volume after N number of tappings designated as V [21].

$$\frac{N}{C} = \frac{N}{a} + \frac{1}{ab}$$

Compatibility is represented by "a," while cohesiveness is expressed as the reciprocal of "b." The degree of volume reduction, denoted by "C," is calculated using the original volume (V_0) and tapped volume (V) according to the following equation:

C=(Vo-V)/Vo

Graphical representation of N/C against the number of taps (N) yielded a linear relationship, from which the numerical values of constants a and 1/b were determined. (N=0, 50, 100, 150, and 200).

Preparation of liquisolid tablets

Liquisolid formulations L5, L6, L10, L11 and L12 were selected for tableting as these powders exhibited desirable flowability and compressibility. Sodium starch glycolate and talc were subsequently introduced and mixed for 5 minutes (Table 2). This liquisolid powder was then directly compressed into tablet of 6 mm diameter using a Minipress-II, Karnavati, Ahmedabad.

Quality control tests

Table 2: Composition of liquisolid tablets (batch size 50 tablets per formulation)

Formulation code	Liquisolid powder equivalent to 5 mg of tacrolimus	Sodium starch glycolate (mg)	Lactose (mg)	Total weight/Tablet (mg)
L5	63	3	34	100
L6	53	3	44	100
L10	76	3	21	100
L11	62	3	35	100
L12	53	3	44	100

Quality control assessments were conducted on the liquisolid tablets (L5, L6, L10, L11, and L12) according to standard procedure [22].

In vitro dissolution test

Liquisolid tablets (L5, L6, L10, L11 and L12) and pure drug tacrolimus underwent dissolution testing. The study employed USP type II paddle equipment operating at 50 rpm, using 0.1 N HCl as the dissolution medium for a span of 2 h. The dissolution profiles were analyzed to determine key parameters such as Q30, Q45, average dissolution time, and the correlation to the Hixson-Crowell cube root model [23].

DSC study

Accurately weighed samples of tacrolimus, powdered samples of liquisolid tablets (L6, and L12) were enclosed in sealed aluminum pans and subjected to thermal analysis with heating rate 100°C/min upto a temperature of 220°C.

P-XRD study

Powder X-ray diffraction patterns were obtained for both tacrolimus and powdered samples of liquisolid tablets (L6 and L12) within the 2° to 70° 2θ angular range.

Stability study

The stability characteristics of formulation L6 were assessed under accelerated conditions (40°C ± 2°C/75% ± 5% relative humidity) over a 6-month period. The study protocol adhered to the ICH Q1A (R2) guidelines. Liquisolid tablet integrity was evaluated by measuring drug content, disintegration time, and dissolution at 30 min mark [24].

Pharmacokinetic study

Twelve male albino rabbits with a body weight of 2 kg were carefully selected for this study. Group 1 (6 rabbits) received the tacrolimus liquisolid tablet (L6) as the test substance, while Group 2 (6 rabbits) was administered the standard aqueous suspension of tacrolimus. The dose for rabbit was calculated as 0.46 mg (=0.5 mg). An amount equivalent to 0.5 mg dose was given orally using a Ryle's tube. Blood samples (0.5 mL) were drawn from the marginal ear vein of male rabbits at specific time points (0 hours, 0.5 hours, 2 hours, 6 hours, 12 hours and 24 hours) with a 24-gauge needle and collected in eppendorf tubes. Pharmacokinetic parameters including C_{max}, T_{max}, and AUC were calculated. The study was conducted with IAEC (160) approval. UFLC was performed using a reported method on a 250 mm × 4.6 mm i.d 0.5 µm particle, C18 column with 85:15 (V/V) acetonitrile: Phosphate buffer pH 4.0 (1 mM) as mobile phase at a flow rate of 1 ml/min using PDA detection at 198 nm [25].

Results and Discussion

Solubility study

Tacrolimus was most soluble in PEG 400, reaching a concentration of 247 mg/mL, whereas labrasol achieved a solubility of 198 mg/mL (Figure 1). PEG400 and labrasol were selected for further studies. Both PEG400 and labrasol enhances solubility by forming micelles or emulsions. These non-volatile solvents can encapsulate lipophilic drugs within its micellar structures, effectively increasing their solubility in aqueous media [26].

Liquid loading factor

The flowable liquid retention potential values for admixture of sylysia 350 and aerosol (R=20) were 3.425 and 2.937 for PEG 400 and labrasol, respectively. The adsorption capacity of Sylysia 350 is approximately 310 mL per 100 grams. It has a high specific surface area of 300 m^2/g, making it effective for adsorbing a significant proportion of drugs or other substances [27].

Preparation of liquisolid compact

Liquisolid powders were formulated using a mixing technique. The chosen method is scalable and adaptable. Tacrolimus exhibited complete solubility in both PEG400 and Labrasol. An increase in drug loading (2.5% to 15%) as well as sylysia 350 content within the liquisolid formulation resulted in improved flowability, thereby enhancing its suitability for tablet compression.

Flowability

Flowability assessments indicated that pure tacrolimus exhibited suboptimal flow properties. Conversely, liquisolid formulations (L5, L6, L10, L11 and L12) demonstrated favorable tableting characteristics because of higher proportion of sylysia 350 and higher drug loading irrespective of variations in non-volatile solvent (Table 3). The improved flowability of the liquisolid formulations is likely due to the adsorptive and compressible properties

inherent to sylysia 350 [28]. Additionally, the presence of an aerosol coating on the wet surface of the porous carrier contributes to the improved flowability [29].

Table 3: Micromeritic properties of tacrolimus and its liquisolid powder formulations

Formulation	Angle of repose(°)	Carr's index (%)	Hausner's ratio
Tacrolimus	43 ± 3.1	38.6 ± 2.43	1.62 ± 0.06
L1	41.35 ± 1.56	38.25 ± 2.15	1.49 ± 0.01
L2	40.35 ± 1.48	35.25 ± 1.16	1.45 ± 0.05
L3	38.35 ± 2.14	36.05 ± 1.57	1.43 ± 0.02
L4	41.35 ± 2.14	43.05 ± 1.57	1.67 ± 0.02
L5	24.19 ±0.55	28.28 ± 1.84	1.35 ± 0.01
L6	23.78 ± 1.59	28.28 ± 1.84	1.35 ± 0.01
L7	42.16 ± 1.05	41.64 ± 1.02	1.69 ± 0.04
L8	43.75 ± 1.98	40.75 ± 1.03	1.48 ± 0.05
L9	41.35 ± 2.54	40.12 ± 1.01	1.41 ± 0.03
L10	21.12 ± 2.14	20.12 ± 2.01	1.21 ± 0.03
L11	20.12 ± 2.18	21.13 ± 1.01	1.12 ± 0.03
L12	20.36 ± 1.05	23.35 ± 2.01	1.17 ± 0.01
*Mean ± SD, n=6			

Kawakita analysis

Liquisolid formulations with higher drug loading demonstrated superior flowability compared to Tacrolimus, as indicated by lower 'a' values, a measure of compactability. Additionally, these formulations exhibited reduced cohesiveness, as evidenced by lower '1/b' values, when compared to Tacrolimus (Table 4).

Table 4: Kawakita analysis of liquisolid Formulation

Formulation	Compactibility (a)	Cohesiveness (1/b)	Coefficient of determination (r2)
Tacrolimus	0.72	37.74	0.983
L1	0.46	27.12	0.961
L2	0.48	28.31	0.973
L3	0.36	27.25	0.988
L4	0.25	21.25	0.964
L5	0.17	18.14	0.987
L6	0.14	17.23	0.997
L7	0.57	25.85	0.997
L8	0.46	24.34	0.995
L9	0.32	22.55	0.996
L10	0.21	17.16	0.998
L11	0.16	18.09	0.992
L12	0.13	17.15	0.993

Quality control tests for liquisolid tablets

All liquisolid tablets demonstrated drug content surpassing 96% confirming homogeneous mixing of the drug within the excipients matrix. All formulations exhibited weight variations that complied with the ± 10% acceptance criterion, indicative of satisfactory flow properties. All the selected tablets disintegrated within 4 min suggesting appropriate proportion of disintegrating agent i.e. sodium starch glycolate. Hardness of all the tablet formulations were nearer to 5 kg/cm^2 which is within the acceptable range (Table 5).

Table 5: Quality control tests for liquisolid tablets

Formulations	Drug content* (%)	Weight variation** (mg)	Friability** (%)	Hardness*** (Kg/cm^2)	Disintegration time*** (min)
L5	97 ± 3.8	100 ± 7	0.3 ± 0.01	5.2 ± 0.12	4 ± 1.6
L6	99 ± 1.1	100 ± 8	0.4 ± 0.02	5.1 ± 0.15	2.5 ± 1.3
L10	96 ± 1.5	100 ± 3	0.1 ± 0.05	5.3 ± 0.13	3.5 ± 1.2
L11	97 ± 3.2	100 ± 5	0.4 ± 0.04	5.6 ± 0.17	2.4 ± 1.05
L12	98 ± 1.9	100 ± 6	0.5 ± 0.05	5.1 ± 0.13	2.3 ± 1.5
*Mean ± SD, n=10, **Mean ± SD, n=20, ***Mean ± SD, n=6					

In vitro dissolution test

Interestingly, around 20% of tacrolimus dissolved during 2 h of dissolution study (Figure 2). However, liquisolid tablets with PEG400 as non-volatile solvent (L6) exhibited nearly 100% dissolution of tacrolimus in 45 min whereas L5 took 60 min for 100% dissolution. Liquisolid tablets with labrasol as non-volatile solvent (L10, L11 and L12) demonstrated 100% dissolution in 2 h. The higher rate of dissolution for L6 can be ascribed to higher solubility of tacrolimus in PEG400 and higher percentage of drug loading. Significantly, formulations L6 exhibited dissolution rates that were 9 times higher compared to that of tacrolimus when assessed using the Q30 and Q45 parameter (Table

Table 6: *In-vitro* release kinetic study

Parameters	Tacrolimus	L5	L6	L10	L11	L12
Q30 (%)	8.1 ± 0.03	68 ± 0.5	77 ± 1.2	26 ±	27 ± 1.2	32 ± 1.1
Q45 (%)	11.4 ± 0.04	85 ± 3.5	100 ± 2.5	44 ± 5.5	48 ± 2.5	51 ± 1.6
MDT (min)	45 ± 02	24 ± 0.6	23 ± 0.8	31 ± 1.1	31.2 ± 1.3	30.5 ± 0.8
Hixson Crowell's (r^2)	0.879	0.987	0.998	0.976	0.991	0.994
Mean ± SD, n=6						

6). Liquisolid tablet L6 exhibited the shortest Mean Dissolution Time (MDT) among all formulations tested, indicating enhanced dissolution efficacy relative to pure tacrolimus [30].

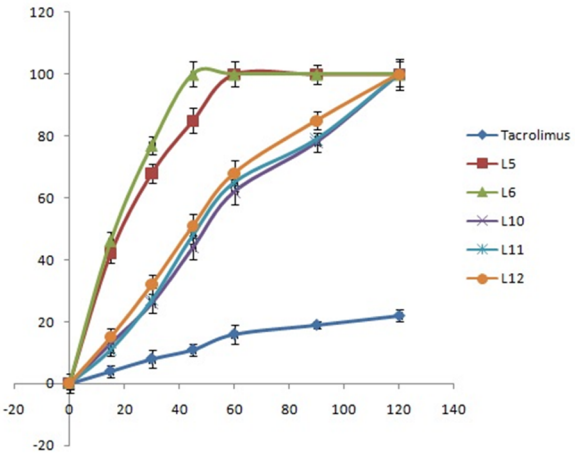

Figure 2: *In-vitro* dissolution profile for liquisolid tablets

DSC study

An evident endothermic peak resulting from drug melting is visible in the thermogram of pure Tacrolimus (123°C). The presence of a strong endothermic peak and a narrow melting range confirms the crystalline form of Tacrolimus (Figure 3). The DSC for both PEG400 and labrasol based liquisolid formulation did not manifest any melting peak which can be ascribed to the presence of Tacrolimus is liquid form i.e. dissolved or molecular state.

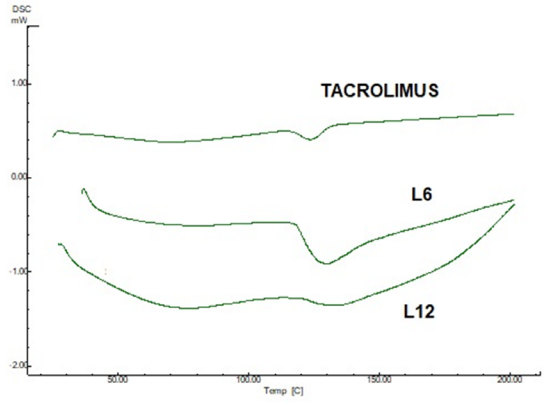

Figure 3: DSC thermogram for tacrolimus, L6 and L12

P-XRD study

P-XRD diffractogram for tacrolimus suggests that it is a crystalline drug as it has shown peaks at 2ɵ angles of 10°, 11°, 14.1°, 17°, 18.96°, 19.924° (Figure 4). The diffractograms for powdered samples of both liquisolid tablets (L5 and L12) completely disappeared i.e. no peaks were observed at any of the 2° angles. This complete absence of peaks for PEG400 and labrasol based liquisolid formulations can be imputed to the presence of tacrolimus in solubilised (molecular) form.

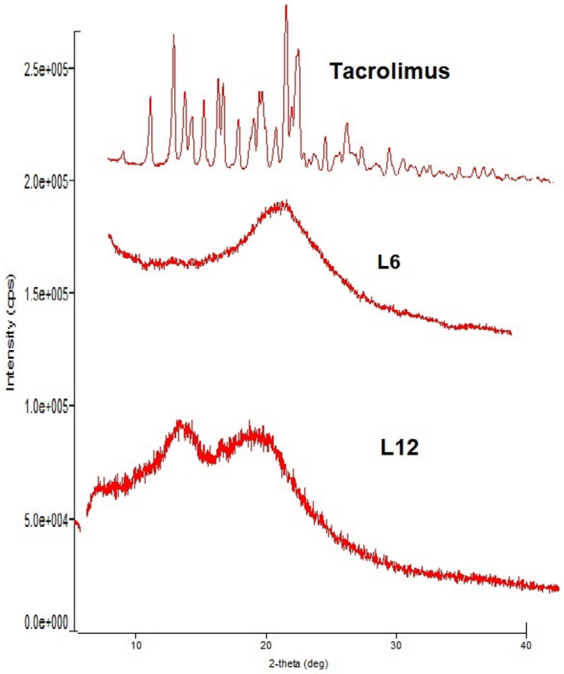

Figure 4: P-XRD for tacrolimus, L6 and L12

Stability study

Liquisolid tablets (L6) did not exhibit any significant change in quality control parameters during 6 months of stability study (ICH) guidelines (Table 7).

Table 7: Stability data liquisolid tablet (L6)

Time (months)	Drug content (% w/w)	Disintegration time (min)	Drug release at 30 min (%)
0	99 ± 1.1	2.5 ± 1.3	77 ± 1.2
1	99.1 ±1.7	2.4 ± .03	76 ± 0.5
2	98.1 ± 4.85	2.8 ± 0.5	78 ± 0.5
3	98.6 ± 4.82	2.1 ± 0.4	74 ± 0.5
6	98.2 ± 3.56	2.4 ± 0.5	75 ± 0.5
Mean ± SD, n=6			

Pharmacokinetic study

The pharmacokinetic study findings for aqueous suspension of tacrolimus and liquisolid tablet (L6) suggest that PEG400 based liquisolid tablet (L6) exhibited faster dissolution and rapid absorption as ascertained from the decrease of T_{max} from 6 h to 2 h (Figure 5) (Table 8). The intensity of action for liquisolid tablet (L6) was nearly 4.5 time more as evidenced from C_{max} values. The AUC (area under the curve) values are higher for liquisolid tablet which suggests that oral bioavailabilty was increased by 4.4 fold [31].

Table 8: Pharmacokinetic parameters

PK parameters	Aqueous suspension of tacrolimus	Liquisolid tablet (L6)
C_{max} (µg/ml)	67.2 ± 6.5	301.8 ± 4.2
T_{max} (h)	6 ± 0.3	2 ± 0.2
AUC (µg.h/ml)	775.29 ± 32.17	3461.92 ± 56.81
Mean ± SD, n=6	6	6

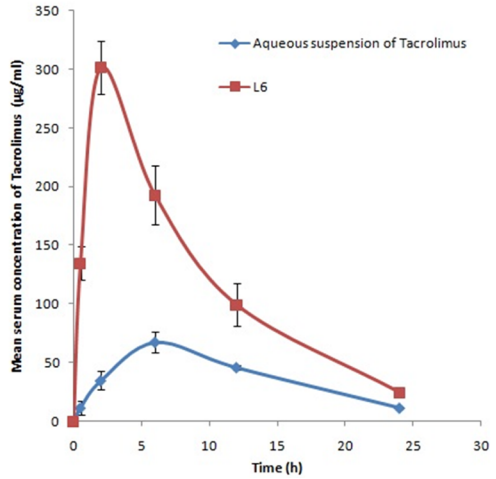

Figure 5: Serum drug concentration versus Time curve for aqueous suspension of tacrolimus and L6

Conclusion

Non-volatile solvents PEG400 and Labrasol were successfully employed in the creation of liquisolid formulations Notably, the PEG400-based liquisolid formulation demonstrated significant improvements in solubility and dissolution rate. he porous support material, Sylysia 350, coated with Aerosil (R=20), demonstrated exceptional liquid adsorption properties. These liquisolid formulations also displayed desirable flowability for tablet processing. These liquisolid formulations exhibited excellent flow properties, making them suitable for direct compression into tablets. Among them, formulation L6 exhibited higher dissolution, disintegration in 2.5 min. Furthermore, the pharmacokinetic study revealed a 4.4 fold enhancement in oral bioavailability for liquisolid formulation L6. Thus, the successful application of the liquisolid technique can enhance both dissolution rate and oral bioavailability of tacrolimus.

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Conflict of Interest

We declare that, we all authors have no conflict of interest.

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