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RESEARCH ARTICLE

Improvement of dissolution rate of tacrolimus by solid dispersion technique

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Abstract Tacrolimus has a poor solubility in water ranging from 4 to 12 μg mL^{-1}. The mean bioavailability is ~21 %.The present study was carried out with a view to enhance the dissolution rate of poorly water-soluble drug tacrolimus using Gelucire 44/14® and Gelucire 50/13® as carriers and lactose monohydrate as an adsorbent. A combination of melt and adsorption techniques was employed for the preparation of solid dispersions (SD) to make final product easy for handling. Phase solubility study was conducted to evaluate the effect of carriers on aqueous solubility of tacrolimus. In order to elucidate the mechanism of dissolution enhancement, solid state characteristics were investigated using Fourier transform infrared spectroscopy, differential scanning calorimetry and powder X-ray diffraction. Mathematical modeling of in vitro dissolution data indicated the best fitting with Korsemeyer–Peppas model and the drug release kinetics primarily as Fickian/anomalous diffusion. All prepared solid dispersions showed dissolution improvement compared to pure drug, with Gelucire 50/13® as the superior carrier over Gelucire 44/14®. Almost similar dissolution profile was obtained as a function of storage time; this can be explained by no change in XRD and DSC pattern after 45 days storage period.

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Introduction

In large part, the success of solid organ transplantation lies in the appropriate utilization of immunosuppressive medications. Tacrolimus (Fig. 1), a lipophilic 23-member macrolide lactone isolated from *Streptomyces tsukubaensis* (molecular weight of 803.5 Da), is an important immunosuppressant widely used in transplant patients, but with a narrow therapeutic window. The half-life of tacrolimus in human is 8.7–11.3 h. (Spencer et al. 1997; Venkataramanan et al. 1995; Kershner and Fitzsimmons 1996). Absorption of tacrolimus has been shown to be highly variable between individuals. After oral administration, the drug is generally absorbed with mean time of peak concentrations of 1.5–2 h. However, in some patients, the drug may be absorbed over a prolonged absorption period, resulting in a more flat absorption profile (Duijnhoven et al. 1998).The mean bioavailability is ~21 %, although there is large intersubject variability.

To improve bioavailability and clinical efficacy of poorly water soluble lipophilic drugs numerous techniques have been used (Bhattacharyya et al. 1993). Among various approaches, most popular approaches are the incorporation of the drugs into inert lipidic vehicles such as oils, surfactant dispersions, self-emulsifying formulations (Gershanik and Benita 2000) and the preparation of solid dispersions based on cyclodextrin inclusion complexes (Kimura et al. 1997), polyvinylpyrrolidone (Tantishaiyakul et al. 1999), and polyethylene glycols 4000 and 6000 (Baykara and Yuksel 1991). Gelucire® excipients have been used in the formulation of semi-solid dispersions (Baykara and Yuksel 1991;

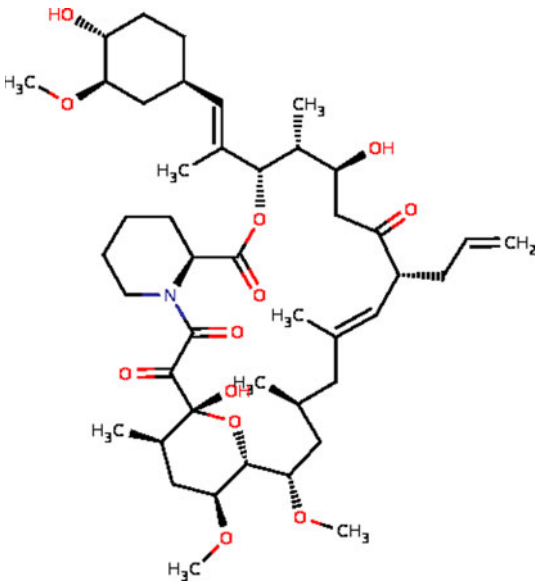

Fig. 1 Structure of Tacrolimus

Gattefosse 1999; Crison et al. 1997). They are solid waxy materials that are amphiphilic in character and identified by two values: their melting points and their hydrophilic–lipophilic balance (HLB) values. Gelucires® are saturated polyglycolized glycerides consisting of mono-, di-, and triglycerides and of mono- and di-fatty acid esters of polyethylene glycol. The nature and proportion of each component are specific to a given grade of Gelucire® (European Pharmacopoeia 2002). Gelucire 44/14® is a semi-solid excipient from this group, while Gelucire 50/13® is a solid pellet. Melting point of Gelucire 44/14® and Gelucire 50/13® is 44 and 50 °C respectively.

The major reported mechanism for improved solubility or dissolution rate was conversion of a crystalline drug into a higher energy state, e.g. the amorphous state. Thermodynamically, this high-energy state is metastable and can, in the course of time, be reconverted into the stable crystalline state (Yoshioka et al. 1995). As a consequence, the biopharmaceutical performance will be affected. Researchers (Damian et al. 2002) reported that Gelucire® solid dispersion is not stable on storage due to change in carrier structure during storage period. Moreover Gelucire® is waxy, semisolid in nature which makes its use difficult due to difficult in handling.

In this study we tried to develop tacrolimus solid dispersion in Gelucire 44/14® and Gelcuire 50/13® along with adsorbent lactose monohydrate with a view that adsorbent will prevent re-crystallization of drug or carrier on storage and make dispersion stable for longer time. Also adsorbent will improve sticky nature of solid dispersion. In order to evaluate the feasibility of this approach, tacrolimus solubility and dissolution studies were performed. Mathematical model has been used for investigating mechanism of drug release from prepared solid dispersions. Solid-state characterization based on FT-IR spectroscopy, DSC and powder X-ray diffraction were carried out to investigate the mechanisms of carrier dissolution enhancement.

Materials and methods

Materials

Tacrolimus was gifted from Alembic Ltd. Pharma Vadodara, India. Gelucires 44/14® and Gelucire 50/13® were kindly gifted from Gattefosse, India. High-performance liquid chromatography (HPLC) grade Acetonitrile was purchased from RFCL limited, New Delhi, India.

Reversed phase high performance liquid chromatography (RP-HPLC)

Quantification of drug was carried out using reversed phase HPLC (Young Lin 9160 photodiode array detector, Seoul, South Korea). The mobile phase used was 100 % acetonitrile. The effluent was monitored with PDA detector at 213.0 nm and total run time is 15 min. Retention time was around 5 min at a flow rate of 0.9 mL min^{-1}. 20 µL prepared solution (all standard solution were prepared in 100 % acetonitrile) were injected into HPLC containing column LiChrospher® 100 RP-18 (5 µm), 4/120 mm. A calibration curve was constructed from tacrolimus concentrations ranging between 5 and 250 µg/mL, which yielded a linear correlation ($r^2 = 0.9978$).

Phase-solubility studies

Solubility measurements were performed in triplicate using the method reported by Higuchi and Connors (Higuchi and Connors 1965). An excess amount of tacrolimus was added to the aqueous solutions of each carrier in distilled water containing increasing concentrations of the individual carrier (i.e., 1, 2, 3, 4 and 5 %). The flasks were sealed and shaken at 37 °C for 48 h in a thermostatically controlled orbital shaker and the samples were filtered through a 0.45 µm membrane filter. The filtrate was suitably diluted and analyzed by HPLC method as described above.

The ΔG°tr value provides information about whether the treatment is favourable or unfavourable for drug solubilization in an aqueous medium. Negative Gibbs-free energy values indicate improved dissolution. The values of Gibbs free energy of transfer, ΔG°tr, of tacrolimus from plain distilled water to aqueous solution of the carriers were calculated according to the following relationship:

$$\Delta G^{\circ}tr = -2.303\ RT\ (\log S_o/S_s),$$

where S_0 and S_s are the molar solubility of tacrolimus in different % w/v aqueous solution of the carrier and in the plain water, respectively. R is the general gas constant while T is absolute temperature (Paulo 2001).

Preparation of tacrolimus/Gelucires® binary solid dispersions with adsorbent and corresponding physical mixtures

Solid dispersions were prepared in 1:3, 1:5, and 1:7 (drug/carrier) ratios by a fusion method. Gelucire 44/14® and Gelucire 50/13® were melted at 50 ± 5 °C for 3 min in a porcelain dish on a water bath under stirring, followed by the addition of tacrolimus powder to the to molten carrier and stirring for an additional 5 min until a homogenous dispersion was obtained. Lactose monohydrate was added to the molten mass during cooling (ratio of Gelucire® to lactose was 1:5 for Gelucire 44/14® and 1:3 for Gelucire 50/13®). The prepared solid dispersion were collected, sieved through 40 mesh sieve, and stored at room temperature until subsequent analysis.

In addition, physical mixtures of tacrolimus with Gelucire 44/14® and Gelucire 50/13® along with lactose were prepared by blending them by trituration for 5 min followed by sieving through 40 mesh sieve.

In vitro dissolution studies

Drug release studies were performed on dissolution test apparatus at 37 ± 0.5 °C employing USP apparatus II at 75 rpm. Dissolution media was 500 mL hydroxypropyl cellulose solution (1 in 20,000) in water at pH 4.5 set by phosphoric acid. Dissolution studies were performed on pure drug (5 mg) and the solid dispersions/physical mixtures containing an equivalent amount of the drug. Aliquots of the periodically withdrawn samples (3 mL) were analyzed by HPLC at 213 nm, and were replaced with an equal volume of plain dissolution medium.

DSC analysis

Differential scanning calorimetric (DSC) analyses of the drug, solid dispersion formulation and its corresponding physical mixture were carried out by the differential scanning calorimetry (DSC-60, Shimadzu Corporation, Japan). The samples (about 3–5 mg) were placed in standard aluminum pans and air was used as an atmosphere. All samples were scanned at a temperature ramp speed of 10 °C/min and the heat flow was set from 50 to 300 °C.

XRD analysis

The X-ray diffraction study was carried out to characterize the physical form of tacrolimus in samples of selected batches. Vacuum grease was applied onto the glass slide to stick the sample. The sample was allowed to spread on the glass slide in ~0.5 mm thickness. X-ray powder scattering measurements were carried out with a D2 Phaser diffractometer (X'Pert Model, Phillips, Netherlands) at room temperature using monochromatic CuKa-radiation at 34 mA and at 38 kV over a range of 2θ angles from 5° to 60° with an angular increment of 0.05°/s.

Fourier transform infra red spectroscopy

Fourier transform infrared (FT-IR) spectroscopy was employed to further characterize the possible interactions between the drug and the carrier in the solid state on an FT-IR spectrophotometer (Jasco, FTIR model 6100, Japan) by the conventional KBr pellet method. The spectra were scanned over a frequency range 4,000–400 cm^{-1}.

Mathematical analysis

The in vitro drug release data were fitted to various release kinetic models viz. first-order, Higuchi, Korsemeyer–Peppas and zero-order model employing the following set of equations:

Zero order kinetic models:

$$M_o - M_t = K_o t$$

First-order model:

$$\ln(M_o/Mt) = k_1 t$$

Higuchi model:

$$M_t = Kt^{1/2}$$

Korsemeyr-Peppas model:

$$M_t/M_\infty = kt^n,$$

where, M_o, M_t and M_∞ correspond to the drug amount taken at time equal to zero, dissolved at a particular time, t, and at infinite time, respectively. Various other terms viz. k, k_o, k1, and K refer to the release kinetic constants obtained from the linear curves of Korsemeyer–Peppas, zero-order, first-order, and Higuchi model, respectively (Ahuja et al. 2007).

Stability studies

In order to study the stability of the solid dispersions, the representative samples were placed in airtight containers and stored at 40 °C (75 % RH) for 45 days. After period of 45 days dissolution studies, % drug content, DSC and

XRD were performed to evaluate the physicochemical properties of these dispersions.

Results and discussion

Phase solubility study

Tacrolimus aqueous solubility was observed to be 2 μg/mL; therefore, tacrolimus can be defined as practically insoluble drug according to USP. Phase solubility parameters showed an increase in drug solubility with different Gelucire® grades, with r^2 values varying between 0.98 and 0.99. The phase solubility diagram followed an A_L-type system as the computed slopes are less than unity (Higuchi and Connors 1965). The A_L type curve, indicates a positive linear effect on the solubility of the drug with increased concentration of Gelucire®. Hydrophilic carriers are known to interact with drug molecules mainly by electrostatic forces and occasionally by other types of forces like hydrogen bonds (Ra′cz 1989).

Further, Table 1 shows that all the values of ΔG°tr were negative at all the levels of carriers, unequivocally demonstrating spontaneity of drug solubilisation process. The ΔG°tr values were negative at the treated concentrations of the carriers, which reflect the spontaneous nature of the tacrolimus solubilization. Also, the values decreased with increasing concentrations of Gelucire®, thereby demonstrating that reaction became more favourable as the concentration of Gelucire® was increased.

In vitro dissolution study

The results of in vitro drug release studies at pH 4.5 for 2 h are depicted in Fig. 2. The pure drug showed a release of 15 % at the end of 2 h, while SD showed 50–65 % drug release in 2 h. The percent drug dissolution increased with an increase in the ratio. Physical mixtures (PM) also showed an improved dissolution rate compared with pure tacrolimus powder.

It is clear that the pure tacrolimus has the lowest dissolution rate and all the studied solid dispersion formulations had a higher dissolution rate where the fastest dissolution rate was obtained for the sample when the ratio of drug:carrier was 1:7 (w/w) for both Gelucire® grades, hence 1:7 ratio was selected for all further characterization. The dissolution rate increased as increased in carrier concentration. This enhanced dissolution rate can be explained by conversion of crystalline drug to amorphous form, increased in wetting property of drug, decreased interfacial tension between drug and dissolution medium and self-emulsification property of Gelucire® which keeps drug in solubilised state after emulsification (Damian et al. 2002). Apart from the mechanisms of the individual carriers, the presence of lactose might have also contributed to the better dissolution characteristics of tacrolimus in solid dispersions. The probable mechanism might be the increase in surface area of the free-flowing system (Deepti and Madan 2007). Table 2 summarized the dissolution

Table 1 Phase solubility and ΔG°tr of tacrolimus at different concentrations of Gelucire 44/14® and Gelucire 50/13®

Concentration of carriers %w/v	Gelucire 44/14®		Gelucire 50/13®	
	Concentration of tacrolimus (mg mL^{-1})	ΔG°tr (J K^{-1} mol^{-1})	Concentration of tacrolimus (mg mL^{-1})	ΔG°tr (J K^{-1} mol^{-1})
0	0.002		0.002	
1	0.0048	−2,168	0.0102	−4,036
2	0.01	−3,986	0.0153	−5,041
3	0.0128	−4,597	0.0203	−5,705
4	0.0172	−5,331	0.0305	−6,750
5	0.02	−5,703	0.0352	−7,105
r^2	0.993		0.989	
Type of curve	A_L		A_L	

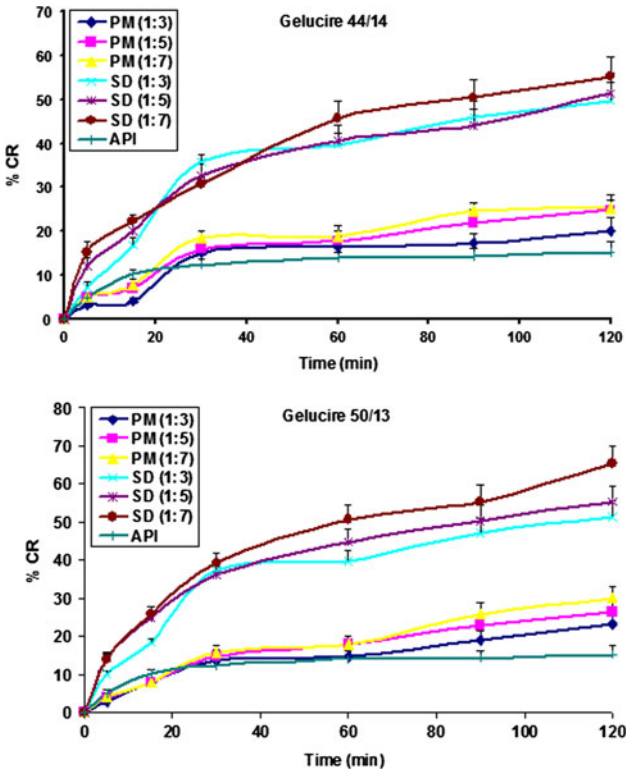

Fig. 2 Dissolution profile of Tacrolimus, physical mixtures and solid dispersions. 1:3, 1:5 and 1:7 indicate drug to carrier ratios; *API*, tacrolimus powder; *SD*, solid dispersion; *PM*, physical mixture; *% CR*, cumulative % drug released; *min*, minute

Table 2 Dissolution parameters of tacrolimus in various formulations

Gelucire 44/14®				Gelucire 50/13®			
Code	Q5	Q30	Q60	Code	Q5	Q30	Q60
Drug	5	12.37	14	Drug	5	12.37	14
SD 1:7	15.27	30.67	45.63	SD 1:5	14	39.27	50.47
SD 1:5	12	32.56	40.56	SD 1:4	14.24	35.98	44.83
SD 1:3	7.4	35.89	39.78	SD 1:3	10.2	37.45	39.78
PM 1:7	5	18.36	19	PM 1:5	4.2	15.87	18
PM 1:5	5	15.89	17.78	PM 1:4	4	14.78	17.9
PM 1:3	3.3	15	16.37	PM 1:3	3	13.8	14.8

Q5, Q30 and Q60 represents % drug released at 5, 30 and 60 min respectively

SD solid dispersion, *PM* physical mixtures

parameters of physical mixtures and solid dispersions for Gelucire 44/14® and Gelucire 50/13®.

DSC interpretation

Figure 3 shows the DSC thermograms of tacrolimus, lactose monohydrate, physical mixture and solid dispersion of Gelucire 44/14® and Gelucire 50/13®. The thermogram of tacrolimus showed an endothermic peak at around 129 °C, corresponding to its melting point. The thermogram of lactose monohydrate showed two characteristic peaks at 148 and 218 °C. The thermograms of the physical mixture and the solid dispersion showed no endothermic peak corresponding to tacrolimus. It might because of increased solubility of tacrolimus as a function of temperature in molten carrier (Ahuja et al. 2007). All remaining thermograms showed only two endothermic peaks which correspond to melting of lactose monohydrate. Similar DSC spectra of the physical mixture and the solid dispersion indicates the absence of any drug–carrier chemical interaction.

XRD interpretation

The XRD pattern of pure tacrolimus, solid dispersions and their physical mixtures are shown in Fig. 4 respectively. The XRD scan of pure tacrolimus showed intense peaks of crystallinity between 5 and 15 theta; whereas the XRD pattern of prepared solid dispersions and physical mixtures exhibited a reduction in both number and intensity of peaks between 5 and 15 theta, compared to the plain tacrolimus indicating the decrease in crystallinity or partial amorphization of the drug in its kneaded form (Babu et al. 2002).

Fourier transform infrared spectroscopy interpretation

The IR spectra of Tacrolimus, and solid dispersions of Gelcuire 44/14® and Gelucire 50/13® are presented in Fig. 5. Tacrolimus powder shows O–H stretching vibration

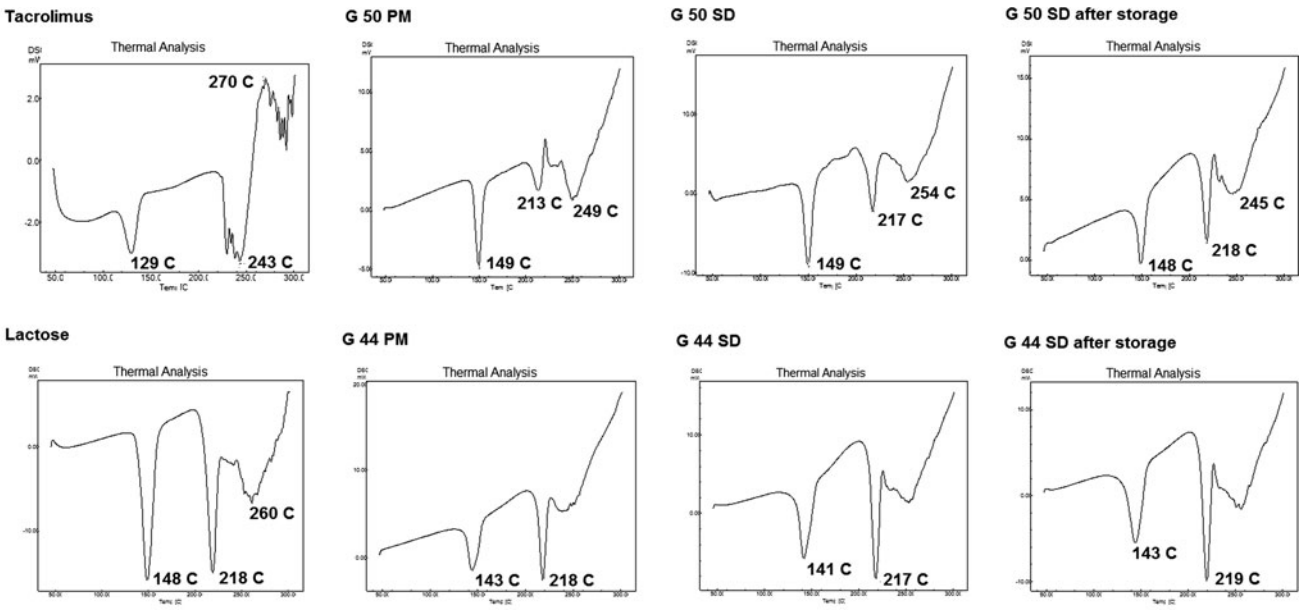

Fig. 3 DSC spectra of pure drug, lactose monohydrate, physical mixtures and solid dispersions. *G50 PM* physical mixture of drug, Gelucire 50/13® and lactose monohydrate; *G50 SD* solid dispersion of drug prepared with Gelucire 50/13® and lactose monohydrate; *G44 PM* physical mixture of drug, Gelucire 44/14® and lactose monohydrate; *G44 SD* solid dispersion of drug prepared with Gelucire 44/14® and lactose monohydrate. After storage indicates storage at 40 °C (75 % RH) for 45 days

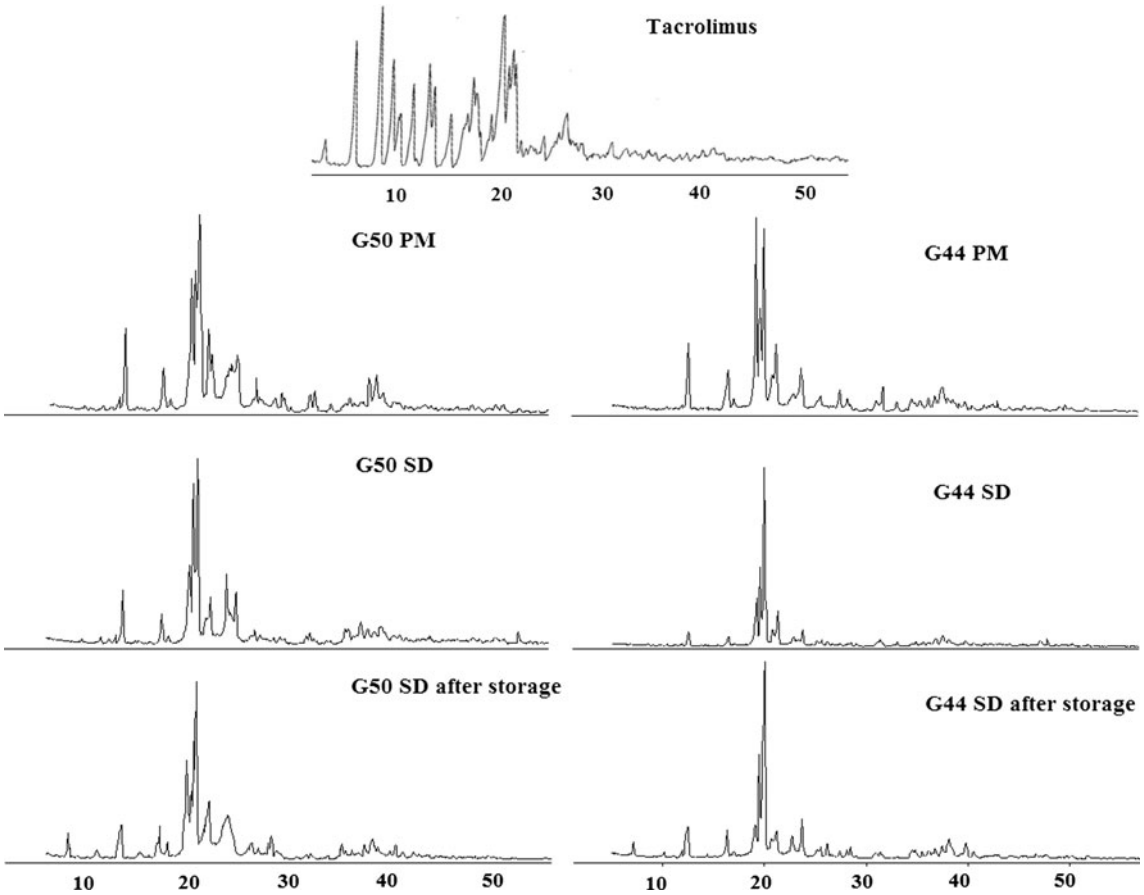

Fig. 4 XRD spectra of pure drug, physical mixtures and solid dispersions *G50 PM* physical mixture of drug, Gelucire 50/13® and lactose monohydrate; *G50 SD* solid dispersion of drug prepared with Gelucire 50/13® and lactose monohydrate; *G44 PM* physical mixture of drug, Gelucire 44/14® and lactose monohydrate; *G44 SD* solid dispersion of drug prepared with Gelucire 44/14® and lactose monohydrate. After storage indicates storage at 40 °C (75 % RH) for 45 days

at 3,450 cm^{-1}, C=O (ester and ketone) stretching vibrations at 1,733 and 1,690 cm^{-1}, C=O (keto-amide) and C=C stretching vibration at 1,638 cm^{-1}, C–O (ester) stretching vibration at 1,184 cm^{-1}, C–O–C (ether) stretching vibrations at 1,091 cm^{-1} (Hane et al. 1992). The absorption band at 3,450 cm^{-1} disappeared. The absorption band of 1733, 1690 and 1638 cm^{-1} were weakened. These results suggest that the C=O functional groups and O–H of tacrolimus are interacted with the functional group of Gelcuire® at the molecular level in solid dispersion. The result is in line with those of other researcher's (Kazunari et al. 2003).

Mathematical analysis

Table 3 enlists the regression parameters obtained after fitting various release kinetic models to the in vitro dissolution data. Based on the correlation coefficient (r^2), the goodness of fit for various models investigated for binary systems ranked in the order of Korsemeyer–Peppas > Higuchi > Zero-order > First-order. The results of kinetic study showed that the best fit was achieved with Korsemeyer–Peppas model for the prepared dispersions, which indicated that drug release mechanism from formulations was the one of diffusion (Table 3). This behaviour could be attributed to polymer relaxation (Ahuja et al. 2007).

Stability studies

Drug content (%) was evaluated after 0, 15 and 45 days and no major changed have been found during storage period. Moreover almost similar dissolution profile were observed (Fig. 6) for both Gelucire 44/14® and Gelucire 50/13®, after 45 days storage period at 40 °C (75 % RH). This similarity in dissolution can be explained by minor changed in XRD pattern over storage time as seen in Fig. 4. No specific changed have been seen in DSC spectra after storage period (Fig. 3).

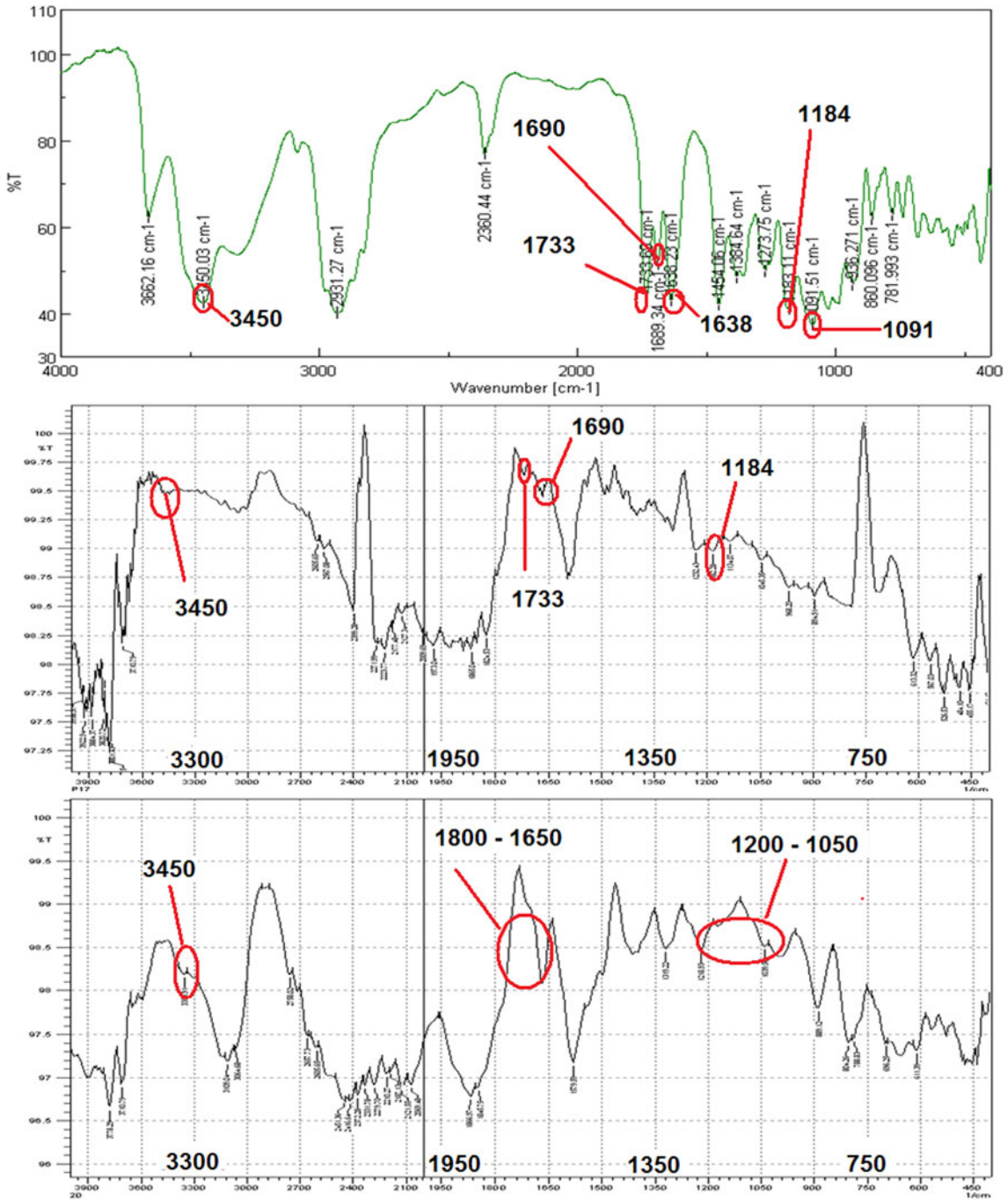

Fig. 5 IR spectra of pure drug and solid dispersion of Gelucire 44/14® and Gelucire 50/13® *G44 SD* solid dispersion of drug prepared with Gelucire 44/14® and lactose monohydrate; *G50 SD* solid dispersion of drug prepared with Gelucire 50/13® and lactose monohydrate

Conclusion

The present study demonstrated a successful and simple method to prepare tacrolimus free flowing solid dispersion to enhance its dissolution rate. The amount of the carrier used and presence of water soluble adsorbent, played an important role in the enhancement of dissolution rate. The solid state studies showed the decreased in crystallinity of tacrolimus. Mathematical treatment to dissolution data showed that possible drug release mechanism was diffusion (fickian/non-fickian). Prepared dispersions were stable for at least 45 days. Thus a new and stable free flowing solid

Table 3 Statistical parameters of various formulations obtained after fitting the drug release data to various release kinetic models

Sample code	Higuchi		Zero-order		Korsemeyer–Peppas		First-order	
	Slop	r^2	Slop	r^2	Slop	r^2	Slop	r^2
Drug	1.031	0.921	0.070	0.833	0.327	0.940	0.003	0.755
Gelucire 44/14®								
SD 1:7	4.781	0.992	0.346	0.964	0.422	0.995	0.004	0.920
SD 1:5	4.389	0.984	0.313	0.945	0.456	0.990	0.004	0.877
SD 1:3	4.808	0.957	0.330	0.901	0.601	0.968	0.005	0.812
PM 1:7	2.423	0.957	0.171	0.912	0.538	0.968	0.005	0.849
PM 1:5	2.318	0.976	0.166	0.945	0.528	0.974	0.005	0.881
PM 1:3	1.97	0.925	0.138	0.873	0.624	0.930	0.006	0.817
Gelucire 50/13®								
SD 1:7	5.664	0.989	0.405	0.954	0.475	0.992	0.004	0.877
SD 1:5	4.628	0.986	0.329	0.943	0.425	0.992	0.004	0.872
SD 1:3	4.650	0.959	0.327	0.908	0.514	0.972	0.005	0.835
PM 1:7	2.94	0.988	0.215	0.974	0.619	0.989	0.006	0.899
PM 1:5	2.53	0.992	0.184	0.967	0.593	0.991	0.006	0.88
PM 1:3	2.12	0.979	0.153	0.951	0.604	0.974	0.006	0.841

1:3, 1:5 and 1:7 indicate drug to carrier ratios

SD, solid dispersion; *PM*, physical mixtures

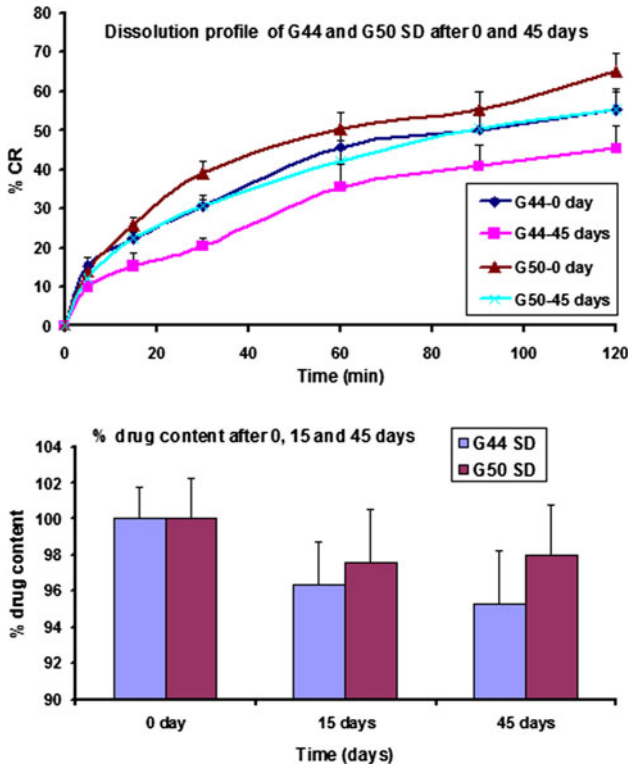

Fig. 6 Dissolution profile and % drug content after specified time interval. *G44 SD* solid dispersion of drug prepared with Gelucire 44/14® and lactose monohydrate; *G50 SD* solid dispersion of drug prepared with Gelucire 50/13® and lactose monohydrate; *% CR* cumulative percentage drug released

dispersion with enhance dissolution rate of tacrolimus have been developed.

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