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Original Research Paper

# Extended tacrolimus release via the combination of lipid-based solid dispersion and HPMC hydrogel matrix tablets

Hui Xu<sup>a</sup>, Li Liu<sup>a</sup>, Xuehui Li<sup>a</sup>, Junyuan Ma<sup>b</sup>, Rui Liu<sup>b</sup>, Shaoning Wang<sup>b,\*</sup><sup>a</sup> School of Pharmacy, Shenyang Pharmaceutical University, Benxi 117004, China<sup>b</sup> School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, Benxi 117004, China

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## ABSTRACT

The objective of this study is to evaluate the feasibility of obtaining extended release of tacrolimus by a novel combination of lipid-based solid dispersion and matrix-type extended release tablet techniques. Tacrolimus solid dispersion was prepared using glycerylbehenate (Compritol® ATO888) and Pluronic F127 as the carrier materials with hot-melt method, which was then blended with hydrogel matrix materials, such as HPMC and lactose, the powders were directly compressed into tablets. *In vitro* drug release tests were carried out to evaluate the performance of the solid dispersions and the tablets. The dissolution rate of tacrolimus was significantly improved by the lipid-based solid dispersion, and the incorporation of HPC into the solid dispersion obviously improved its stability after storage. Extended release tablets loaded with tacrolimus solid dispersion showed prolonged drug release patterns over 24 h, the release patterns of the tablets can be tailored by the compositions of the matrix materials, including the types and content of HPMCs. A modified processing method that directly mixed the melted solid dispersion with HPMC powders improved the uniformity of the solid dispersion inside the tablet matrix and release profile. The release data of the extended release tablet fitted well to the Korsmeyer–Peppas model with *n* value of 0.85, which suggested diffusion- and erosion-controlled release mechanism. The combination of lipid-based solid dispersion and HPMC hydrogel matrix may find wide applications in the extended release dosage forms of high potent, water-insoluble drugs.

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## 1. Introduction

Tacrolimus (FK506), a typical immune-depressant, was isolated from *Streptomyces tsukubaensis* early in 1984 by Fujisawa

Pharmaceutical Co. Ltd. [1,2]. In clinical, tacrolimus has been widely used as the second generation of anti-rejection drug in kidney and liver transplantation since 1989, which displayed potent immunosuppressive activity, high organ survival rate and low incidence of acute rejection. Tacrolimus fast

\* Corresponding author: School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, No. 26 Huatuo Road, High & New Technology Development Zone, Benxi 117004, China. Tel.: +86 24 43520203

E-mail address: [wsn-xh@126.com](mailto:wsn-xh@126.com) (S. Wang).

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release capsule with the brand name Prograf® was the first approved tacrolimus oral solid dosage form developed by Astellas Pharma Inc. Although it is highly effective in clinical, as a BCS Class II drug with a very narrow therapeutic window, tacrolimus exhibits large intra- and inter-individual variability of bioavailability varied from 4% to 89% [3–5]. Thus the blood concentration of tacrolimus must be individually monitored to ensure its efficacy and safety.

In order to obtain suitable blood tacrolimus level and improve its oral bioavailability and patient compliance, tacrolimus sustained release dosage forms have been developed in recent year. Two of the successfully marketed products were tacrolimus extended release capsules (Advagraf® in Europe) by Astellas Pharma Inc, and tacrolimus prolonged release tablets (Envarsus® in Europe) by Veloxis Pharmaceuticals, both of them were developed as a once daily pharmaceutical versions of tacrolimus, with improved bioavailability, consistent pharmacokinetic performance and reduced peak to trough variability when compared with currently approved fast release tacrolimus products [6–9]. Advagraf® was fabricated based on a solid dispersion formulation using ethylcellulose and hydroxypropylmethyl cellulose by solvent evaporation method, which was firstly approved both in Europe with the brand name of Advagraf® and in Japan with the brand name of Graceptor® in 2007. Advagraf® is effective in reducing blood tacrolimus concentration fluctuation and improving patient complains. But the organic solvent involved in its fabrication process is inherently related to its higher cost, talent safety risk, and great endeavor to guarantee the content uniformity and reproducibility in quality. Envarsus® (also known as Envarsus® XR in America) utilized a proprietary drug formulation technology called MeltDose® to achieve modified release profiles [10,11], and specialized technology and processing equipment is required due to its sophisticated processing art. Various pharmaceutical techniques, including biodegradable implants, solid dispersions, nanoparticles, polymeric micelles, nanostructured lipid carriers, etc, were intensively studied to extend the release of tacrolimus [12–16]. In our previous study, lipid based tacrolimus solid dispersion was loaded into mesoporous silica for extending drug release [17].

It have been reported that various lipids is capable of enhancing oral absorption for poorly water-soluble drugs as inspired by the observations of the increased oral bioavailability of drugs when co-administered with food [18]. Of course, lipid-based drug delivery system (LBDDS) is a promising formulation strategy owing to its ability to overcome the problems that limit the oral absorption of poorly water-soluble drugs [19,20]. Glycerylbehenate (Compritol® ATO888, ATO888), a mixture of glyceryl mono-, di- and tri-behenate with a melting temperature of 74 °C, has good compatibility with various active drugs [21,22]. As a medium melting point lipid, the physicochemical properties of ATO888 means it can be easily formulated with other excipients and drugs using a cold or hot processing protocol. Many hydrophobic drugs can readily dissolve in melted ATO888 at elevated temperature and form a solid solution after cooling down to room temperature, such hot-melt (liquid state) dissolving process is preferential to ensure the content uniformity of high potent/low dose drugs, for example, the ordinary oral dose regimen of tacrolimus is only 1 mg. Other advantages of ATO888 based solid dispersion (SD) lies in

that its abilities to dissolve other substances and the melting points of the solid carrier can be easily adjusted by combining with other lipid or hydrophilic materials. These properties also render lipid materials versatile options to achieve desired drug release kinetics, dosage form performance and manufacturing methods [23,24]. Tablets fabricated using lipid materials may bear other advantages, including self-lubricate, self-adhesive, solvent-free, improved stability, no special equipment required, low cost, and versatile formulating.

In this study, a combination of lipid based solid dispersion and hydrogel matrix type sustained release technique were employed to prepare tacrolimus extended release tablets. Tacrolimus was firstly dissolved in hot-melted lipid based carrier to prepare solid dispersion (solution) by fusion method to obtain a mediate with improved drug solubility and dissolution, and acceptable stability. The tacrolimus loaded solid dispersion was then compressed into tablets with hydrogel matrix material (hydroxypropylmethyl cellulose, HPMC) and other pharmaceutical excipients. This study is aimed to provide a novel, convenient, and easily scalable method to obtain tacrolimus extended release tablets.

## 2. Materials and methods

### 2.1. Materials

Tacrolimus was obtained from Hisun Pharmaceutical Co. Ltd (Jiangsu, China); Glycerylbehenate (Compritol 888 ATO, ATO888) and stearyl polyoxyl-32 glycerides (Gelucire 50/13, G50/13) were kindly donated by Gattefossé (France); HPMC K100LV, K4M, K15M and K100M (80–120, 2663–4970, 13 275–24 780 and 75 000–140 000 mPa s, 2% solution in H<sub>2</sub>O at 20 °C) (METHOCEL™) was donated by Shanghai Colorcon Coating Tech. Ltd. (China); Pluronic® F127 Prill and low substituted hydroxypropylcellulose (HPC-L) was received as gifts from BASF Corporation (Germany) and Nisso (Japan), respectively; Stearic acid (SA) was purchased from Shanghai Sinopharm Chemical Reagent Co. (China). All other chemicals used were of chemical or analytical grades and used as received.

### 2.2. Preparation of tacrolimus solid dispersion

Tacrolimus solid dispersion was prepared by melting method as described below. Briefly, excipients, with or without HPC, were accurately weighed into a glass vial according to the formulations listed in Table 1, the excipients were heated in a water bath at 80 °C with stirring to form a melted liquid, tacrolimus was then added into the melted liquid, the mixture

**Table 1 – Formulations of tacrolimus solid dispersions with various carriers.**

No.	Ingredients, mg					
	Tacrolimus	ATO888	G50/13	PF127	SA	HPC
1	10	150				2
2	10	75	75			
3	10	60		90		2
4	10	125			25	2

**Table 2 – Formulations of tacrolimus extended release tablets.**

No.	Ingredients, mg						
	SD1 *	SD2 **	HPMC K100LV	HPMC K4M	HPMC K15M	HPMC K100M	Lactose
1	16			20			64
2		16		20			64
3		16			20		64
4		16				20	64
5		16		10			74
6		16		30			54
7		16		40			44
8		16	10	20			54

\* SD1, solid dispersion composed of 1 part of tacrolimus in 15 parts of carrier (ATO888:HPC=150:2); \*\* SD2, solid dispersion composed of 1 part of tacrolimus in 15 parts of carrier (ATO888:PF127:HPC=60:90:2).

was kept at 80 °C with stirring until the drug was completely dissolved, the melted solution was cooled to room temperature and kept at 4 °C for 6 h, and then grinded to fine powders less than 60 mesh. The solid dispersion powders were aged at 40 °C for another 24 h.

### 2.3. Differential scanning calorimetry (DSC)

Thermo-properties of the solid dispersions were monitored with a TA-60WS DSC equipment (Shimadzu Corp., Japan). Sample of about 5 mg were accurately weighed into an aluminum pan and hermetically sealed, the DSC curve was determined at a heating rate of 10 °C/min from 25 to 100 °C under a N<sub>2</sub> gas purge of 40 ml/min, and an empty pan was used as reference. The DSC patterns of the physical mixture and the raw tacrolimus were also measured with the same method.

### 2.4. Preparation of tacrolimus extended release tablets

The tacrolimus extended release tablets were fabricated by direct compression method, the representative formulations were listed in Table 2. Briefly, the tacrolimus solid dispersions, HPMC, and lactose were mixed to uniform, and then directly compressed using a die of 6 mm in diameter, the weight of the tablet was about 100 mg. In another modified preparation process, the melted solid dispersion was directly mixed with HPMC powders, cooled and then mixed with lactose, and compressed to tablets.

### 2.5. In vitro drug release

In vitro drug dissolution/release test was performed with the paddle method using a ZRS-8G Dissolution Tester (Tianfa-Tianfa Technology Co., Ltd., Tianjin, China) installed with small beakers. 100 ml of distilled water (adjusted to pH 4.5 with phosphoric acid) containing 0.005% hydroxypropyl cellulose was used as the dissolution/release medium, the medium was kept at 37 °C and the paddle rotation speed was set at 50 r/min. The solid dispersion (equivalent to 1 mg of tacrolimus) or tablet was placed in the dissolution medium, at predetermined intervals, 3.0 ml of the medium was withdrawn from the beaker and replaced with equal volume of fresh medium. The sample was filtered through a membrane filter (0.45 µm

pore size, Millipore, USA), and then quantified using a HPLC system (Hitachi, Japan), the wavelength of the UV-vis detector was set at 210 nm. The chromatographic separation of tacrolimus was performed using Dikma ODS C<sub>18</sub> chromatography column (200 mm × 4.6 mm, 5 µm). The mixture of acetonitrile-water (75:25, v/v) at 50 °C was used as the mobile phase, which was pumped at a flow rate of 1.0 ml/min. Validation of assay method showed good linearity in the concentration range of 0.5 µg/ml to 12.0 µg/ml ( $A = 14\,669C + 13.799$ ,  $R^2 = 0.999$ ) and precision ( $RSD < 2\%$ ).

### 2.6. Swelling and erosion of tablet matrices

The swelling ratio (water content) and matrices erosion of the tablet during the release test were monitored gravimetrically under the same conditions for the in vitro drug release tests according to the methods in literatures [25–27]. The initial weight of the tablet ( $M_0$ ) was accurately weighed before placing it into the beaker containing 100 ml of release medium. At predetermined time intervals, tablets were withdrawn, wiped with fiber-free filter paper, and reweighed as the wet mass ( $M_w$ ). The wet tablets were freeze-dried (FD-1 freeze dryer, LABFREEZ Instruments Co. Ltd., China) and weighed again as the dry mass ( $M_d$ ). The water content (%) and matrix erosion (%) were separately calculated with the equations below. The appearance of the tablets at each time point was photographed with a camera.

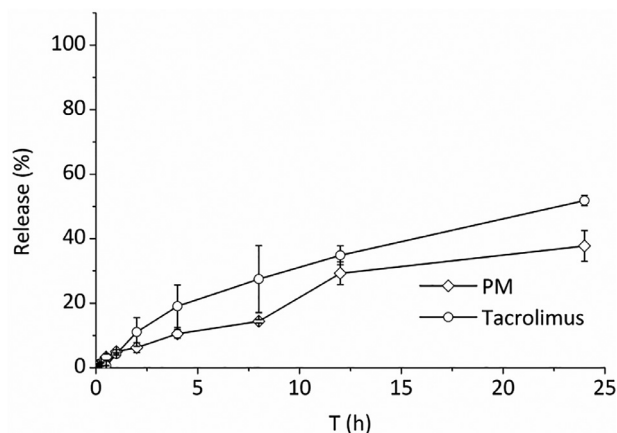
$$\text{Water content(\%)} = \frac{M_w - M_d}{M_w} \times 100\%$$

$$\text{Matrices erosion(\%)} = \frac{M_0 - M_d}{M_0} \times 100\%$$

## 3. Results and discussion

### 3.1. Lipid based tacrolimus solid dispersion

In the design of orally administered, extended release solid preparations of water-insoluble drugs, an important consideration is to obtain an intermediate with improved solubility/dissolution of the active drugs. Solid dis-



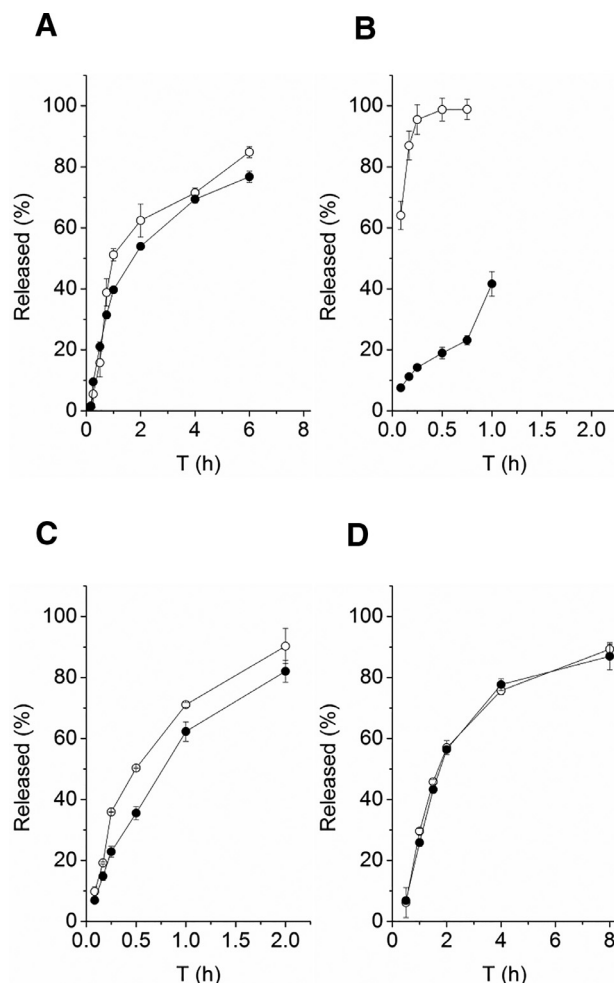
**Fig. 1 – In vitro tacrolimus release profiles of raw tacrolimus and the physical mixture composed of tacrolimus:ATO88:G50/13=10:75:75 (w/w/w) (n=3).**

person is one of the well adopted techniques to fulfill this purpose [28,29].

As shown in Fig. 1, the dissolution rate of raw tacrolimus was extremely low, which was only about 50% at 24 h. Simply blending tacrolimus with other excipients (a physical mixture of tacrolimus:ATO88=10:150) showed no improvement in drug dissolution. As a lipophilic drug, tacrolimus is insoluble in water ( $\log P$  3.3, predicted solubility 4.02  $\mu\text{g}/\text{ml}$ , Drug-bank), but soluble in many organic solvents such as ethanol, acetone, acetyl acetate, etc. Tacrolimus can also be readily dissolved in certain melted lipid or water-soluble polyesters, such as ATO888, polyethylene glycol (PEG) and Pluronic polymers, etc., which inspires the exploring of various low melting point solid or semisolid substances as the carrier materials of tacrolimus solid dispersion.

In this study, ATO888 based solid dispersions were simply prepared by dissolving tacrolimus in the melted liquid composed of ATO888 and excipient(s) followed by cooling down. Compared to the raw tacrolimus or the physical mixture, the drug dissolution rates of SDs using ATO888 or mixed lipid as the matrix materials greatly improved, while the mixed lipids showed different influence on drug dissolution (as shown in Fig. 1). The solid dispersions composed of mixed lipids composed of ATO888-G50/13 and ATO888-PF127 showed relatively higher dissolution rates, which almost completely released the loaded tacrolimus at 1 h and 2 h, respectively. The solid dispersions composed of ATO888 alone and mixed lipids of ATO888-SA displayed slower drug dissolution.

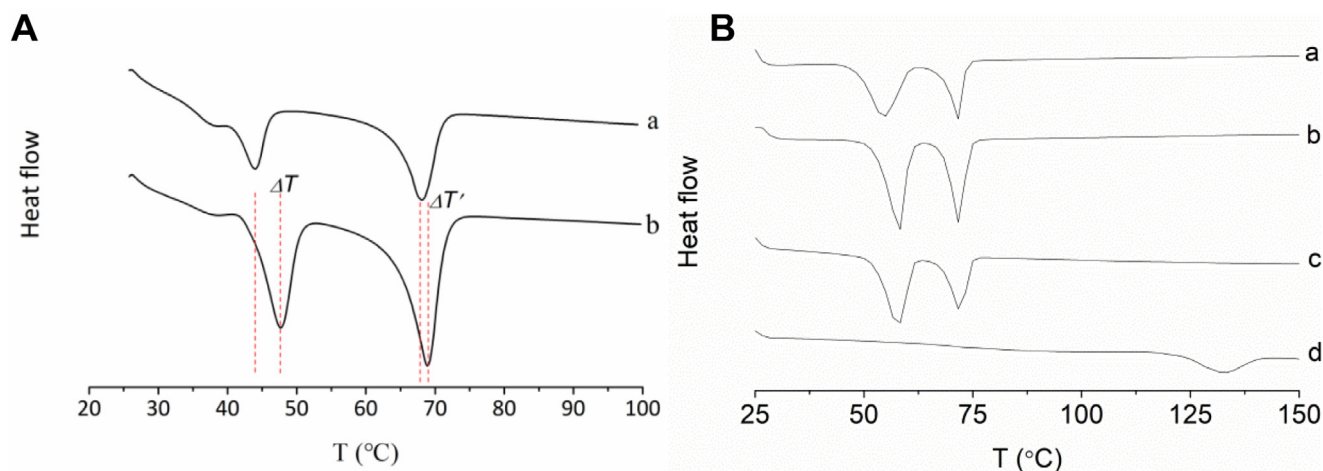
Both G50/13 (melting point=50 °C, HLB=13) and PF127 (melting point=52–57 °C, HLB=18–23) are low melting point, nonionic surfactants, which are very soluble in aqueous media. Improved dissolution rates of tacrolimus are expected when G50/13 or PF127 is combined with ATO888 as the carrier of the solid dispersion [30]. On the contrary, SA, as a kind of hydrophobic material with a melting point of 63–64 °C, has no obvious contribution to increase drug dissolution when it is incorporated in the solid dispersion.



**Fig. 2 – Tacrolimus release from lipid based solid dispersions before (open circle) and after storage at room temperature for 5 d (solid circle) (n=3). (A) ATO888, (B) ATO888-G50/13, (C) ATO888-PF127, and (D) ATO888-SA.**

Besides the improved dissolution rate, physical stability is another prerequisite for the applicable of the tacrolimus loaded solid dispersion. The dissolution of tacrolimus solid dispersions after storing under challenged conditions (40 °C-RH75% for 5 d) showed obvious decrease except that of the solid dispersion using ATO888-SA mixed lipids (Fig. 2). The stability of the solid dispersion after storing seemed related to the melting points of the excipients incorporated to modify drug dissolution rate. Incorporation of G50/13 in ATO888 led to fast dissolution and poor stability, followed by PF127.

The commonly used lipid excipients are glyceride mixtures and they naturally exhibit more than one possible crystalline packing arrangement. The type of acyl chain arrangement in the final dosage form mostly depends on the processing technique or heat history, which is probably the explanation for the change on drug release over time [31]. Triacylglyceride was found bearing three crystal habits,  $\alpha$ -form is the least stable form with the highest Gibbs free energy, followed by  $\beta$  form, and  $\gamma$  form has the highest thermo-dynamical stability [32–34]. The less stable forms existed in the lipid based solid dispersions will gradually transform to more stable forms with



**Fig. 3 – (A) Differential scanning calorimetry profiles of tacrolimus solid dispersions composed of tacrolimus:ATO888:G50/13=10:75:75 at 0 d (a), and after storing at 40°C, RH75% for 10 d (b), respectively; (B) Differential scanning calorimetry profiles of solid dispersion composed of tacrolimus:ATO888:PF127:HPC=10:60:90:2 (a), the corresponding physical mixture (b), the excipients (c), and the raw tacrolimus (d).**

time, and subsequently resulted to slower drug dissolution. Due to the smaller molecular size and lower melting point of G50/13, it will more sensitive to elevated temperature, and will easily allow the rearrangement of the lipid crystal lattice from unstable to stable polymorphs. The DSC patterns of the solid dispersions composed of ATO888 and G50/13 at 0 d and after 5 d storage at challenging condition clearly verified the shift of melting point to higher temperature (Fig. 3A), which corresponded to the transformation from unstable to stable lipid polymorphs.

Although the solid dispersion composed of ATO888 or ATO888-SA showed optimum stability, the low dissolution rate prevented its further possible application as the intermediate to fabricate tacrolimus extended release tablets. The solid dispersions were then doped with various hydrophilic polymers, including HPC, polyvinyl pyrrolidone (PVP), Kollidon VA64, and HPMC, in order to improve the stability. Normally, hydrophilic gelling agents are often selected as the stabilizer owing to their capacity to restrict the molecular motion and prevent rearrangement of the lipid crystal lattice [27,35–37]. Interestingly, of these polymers tested, HPC performed to be effective in improving the stability of the solid dispersion composed of ATO888 and ATO888-PF127, but less effective to that of ATO888-G50/13 as shown in Fig. 4. This result can also be attributed to the strong molecular motion caused by low melting point G50/13. On the thermo-dynamic basis, completely aging will be required to be performed on the prepared solid dispersion to decline the tendency of polymorphism transformation, and prevent any changes on dissolution rate.

It should be noted that the solid dispersions composed of ATO, ATO-SA, and ATO-HPC showed delayed release over about 20 min at the beginning of the release test. The solid state at body temperature and hydrophobic nature of ATO render the solid dispersions poor wettability to aqueous media, thus retarded drug release.

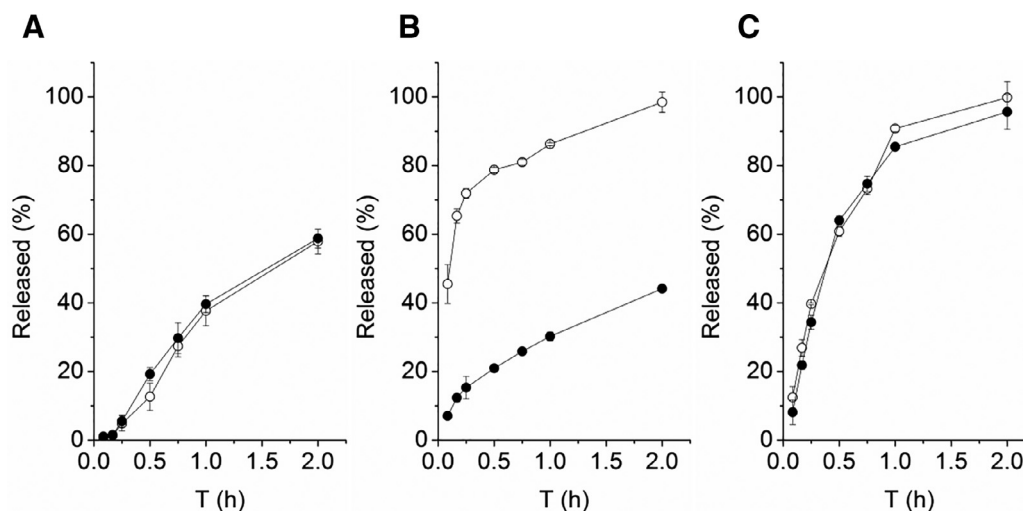
Due to the low dosage regimen (<5 mg per tablet or per capsule) and low solubility of tacrolimus, large portion of excipients were incorporated in the solid dispersion in order to

obtain satisfied dissolution. For the preparation of the solid dispersion, tacrolimus was firstly dissolved in the melted excipients mixture at elevated temperature, tacrolimus may tend to presented as solid solution or amorphous state even after it was cooled down to room temperature. Fig. 3B showed the DSC curves of the tacrolimus solid dispersion, physical mixture, excipients mixture, and raw tacrolimus. Two endothermic peaks were observed in the DSC curves of the solid dispersion and physical mixture, which corresponded to the melting point of ATO888 (about 70 °C) and G50/13 (about 50 °C), respectively, while the DSC curves both indicated no characteristic peak of tacrolimus. Based on the present results, it can only be concluded that tacrolimus should existed as molecular or amorphous state in the solid dispersion, and further characterization to its physical properties is needed.

### 3.2. *In vitro* release of extend release tacrolimus tablets

In the formulation of extend release tablets, HPMC of high viscosity grade was used as the hydrogel matrix material, and water-soluble lactose was added to modify the release rate, HPMC and lactose comprised the main part of the tablets (see Table 2). As the main lipid material, ATO888, is self-lubricate, no lubricant was added. In this study, conventional technique for hydrogel matrix extended release tablets was adopted to prepare tacrolimus extended release tablets, minor modification to the method was also made in order to fulfill complete drug release, as illustrated in Fig. 5. Tablets varying on the compositions of tacrolimus solid dispersion, types and content of HPMC, and combination of two different grades of HPMCs were prepared, and the *in vitro* release profiles of the tablets were shown in Fig. 6.

Ideally, the lipid based solid dispersion provides a fast tacrolimus release pattern, while the hydrogel matrix sustains drug release via diffusion-controlled, matrix erosion-controlled or combined mechanisms. The *in vitro* release of the tablet was greatly dependent on the performance of the



**Fig. 4 – Tacrolimus release from lipid based solid dispersions spiked with HPC before (open circle) and after storage at room temperature for 5 d (solid circle) ( $n=3$ ). (A) ATO888-HPC, (B) ATO888-G50/13-HPC, and (C) ATO888-PF127-HPC.**

solid dispersion. As discussed above, the drug release of solid dispersion composed of ATO888-HPC (denoted as SD1 in Table 2) was slower than that of ATO888-PF127-HPC (denoted as SD2 in Table 2). According to Fig. 6A, the release of tablet derived from SD1 was obviously slower than that of SD2, which released less than 85% of the total loaded drug at 24 h. Faster dissolution of the solid dispersion is expected for reproducible release patterns of the final tablets.

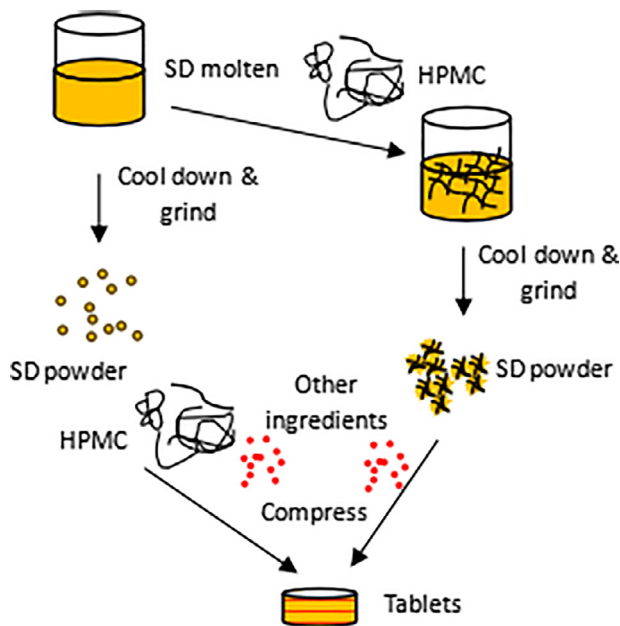
Depending on its molecular weight, hydration rate, etc, the grade and content of HPMC exert marked influence on the viscosity of the inert hydrogel layer and thus the drug release. As shown in Fig. 6B and C, the higher viscosity and the higher

content of HPMC used, the slower and the less completely the drug release were, which can be attributed to the slower hydration and erosion rate of HPMC with higher viscosity (high molecular weight).

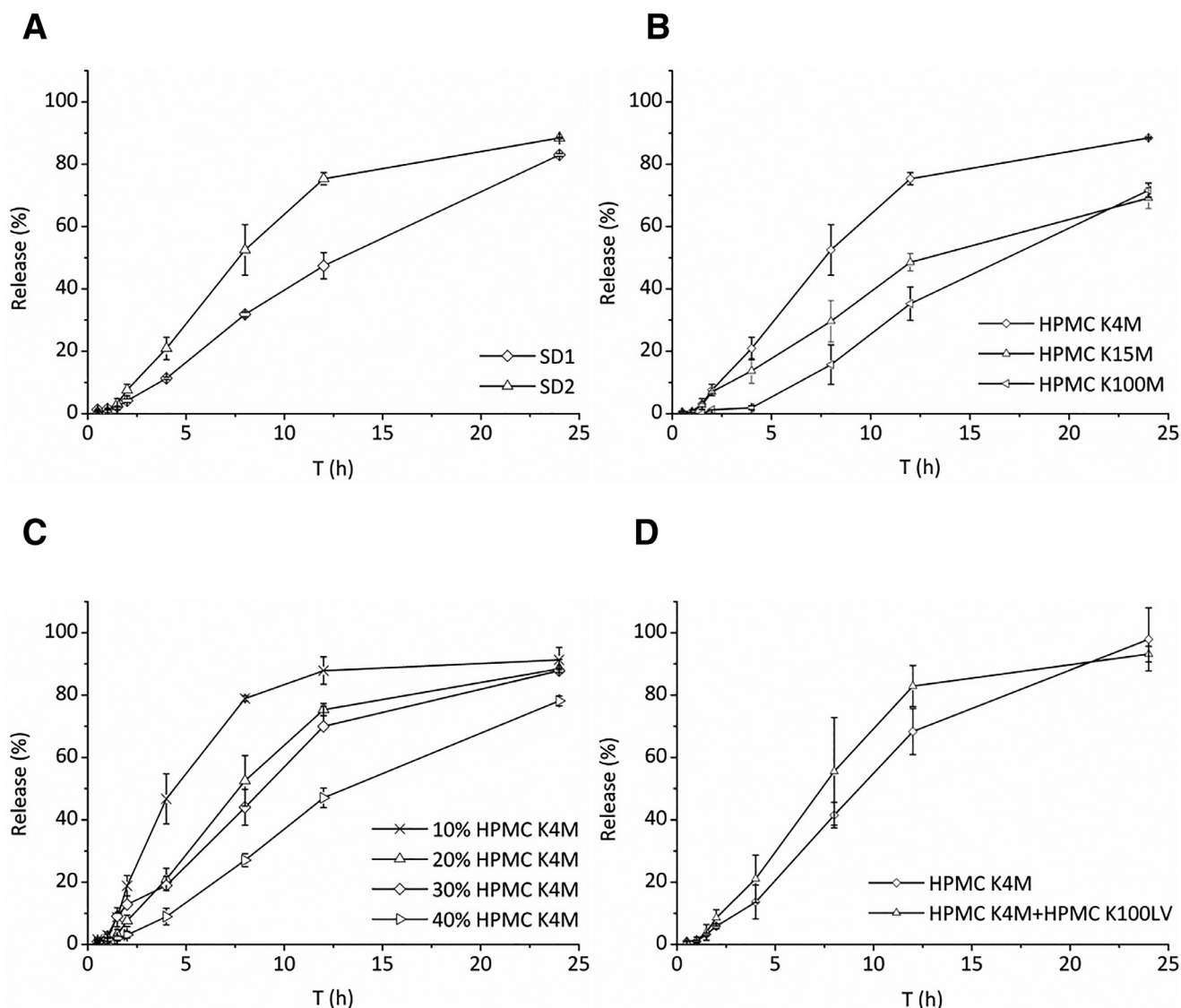
The combination of two different grades of HPMCs can further tailor the release patterns. A blend of HPMC K4M and HPMC K100LV as the matrix material showed higher early stage release rate when compared to the tablet of HPMC K4M, the release rates were about 60% and 80% at 12 h, respectively (Fig. 6D). HPMC K100LV has a smaller molecular weight and lower viscosity than HPMC K4M, which hydrate and erode faster than HPMC K4M when contact to the release medium, and release the loaded drug rapidly.

In the molten blending method, the tacrolimus solid dispersion was prepared as described above, and the difference to the post blending method lay in that the melted dispersion/solution of tacrolimus was directly mixed with HPMC powders before cooling it down. The melted blend was kept at 80 °C for about 1 h under continuous stirring to make sure a uniform mixing, and then annealed or quenched it to room temperature. The grinded powders were then kept at 40 °C for aging, mixed with lactose, and compressed to tablets.

The minor modification to the blending method really improved the release pattern. As shown in Fig. 7A, the release rate of the tablet prepared with the melt blending method (> 90% at 24 h) was much higher than the ordinary method (> 80% at 24 h), while there was no notably difference between the annealing and quenching processes. It was postulated that the melted blend can be easily mixed with HPMC and uniformly solidified on the surface of the HPMC powders once it cooled down. The solid dispersion covered on HPMC powders rendered it increased contact area to the release medium, and more uniform distribution of the solid dispersion inside the tablet matrix or even inside the hydrogel formed when the tablet was exposed to the release media.



**Fig. 5 – Illustration to the preparation of tacrolimus solid dispersions and extend release tablets.**

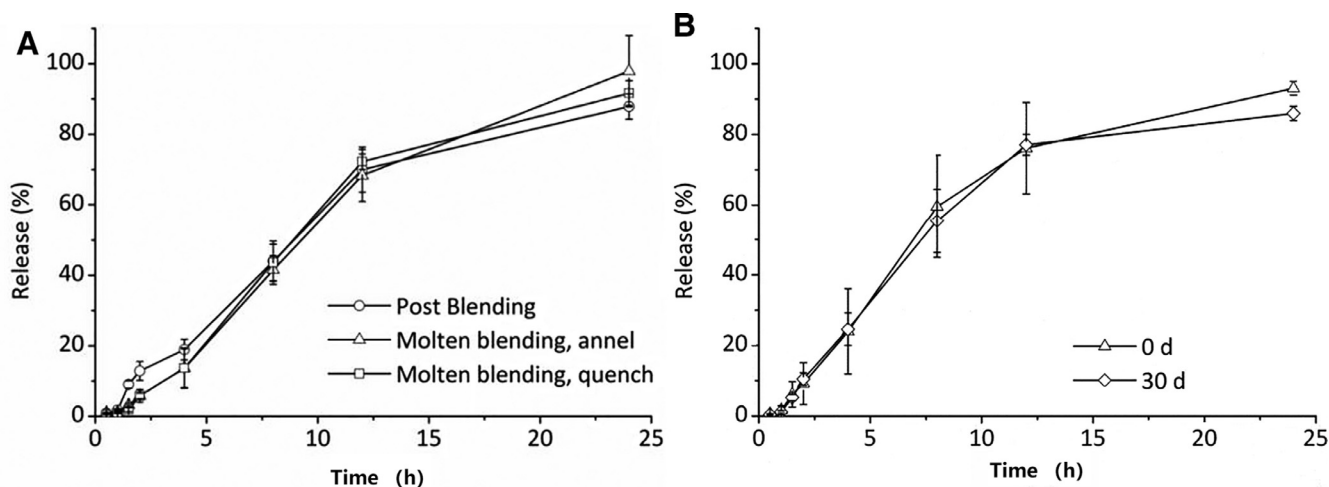


**Fig. 6 – The effect of formulation variables on *in vitro* tacrolimus release of sustained-release tablets ( $n=3$ ). (A) Solid dispersion composed of ATO888-HPC or ATO888-PF127-HPC; (B) Types of HPMC; (C) Contents of HPMC; (D) Combination of HPMCs.**

Lipid based solid dosage forms may frequently experience poor stability due to the relatively low melting point, crystal form transformation, or degradation of lipids, which subsequently result to changes on physical states and *in vitro* drug releases, etc., and thus *in vivo* performances. Elaborately designing to the formulation and processing technology is generally required to solve this problem. In this study, the combination of lipid-based solid dispersion and HPMC hydrogel matrix was introduced to obtain extended released tacrolimus tablets with acceptable stability. Fig. 7B showed the release profile of the typical tablets after storage. There was no obviously difference in the release profile before and after storing 30 d at room temperature, which indicated that the lipid based tablets had good stability.

Some studies had indicated that the *in vivo* drug adsorption from solid lipid based preparations of various dosage forms or

fabrication methods can be well quantitatively predicted by *in vitro* dissolution test [24,31]. Patere et al. [24] prepared a metoprolol succinate tablet of lipid matrix by melt granulation-compression method, which showed similar plasma drug concentrations–time profile to the commercially available metoprolol succinate tablet in healthy humans, and linear relationship between the *in vivo* drug absorption fractions and the *in vitro* drug dissolution fractions [24]. Mercuri et al. [38] predicted the *in silico* concentration profiles of tacrolimus released from the two marketed modified release formulations (Envarsus® tablets and Advagraf® capsules) after building a three compartments PK model with GastroPlus™. Although Envarsus® tablets and Advagraf® capsules were fabricated using totally different arts, *in vitro-in vivo* correlations (IVIVC) were obtained after deconvolution of *in vivo* data from a clinical trial. The easy to be established IVIVC is one of the



**Fig. 7** – The *in vitro* drug release profiles of tacrolimus extended release tablets ( $n=3$ ). (A) Tablets prepared with different processes, and (B) before and after storage at room temperature for 30 d.

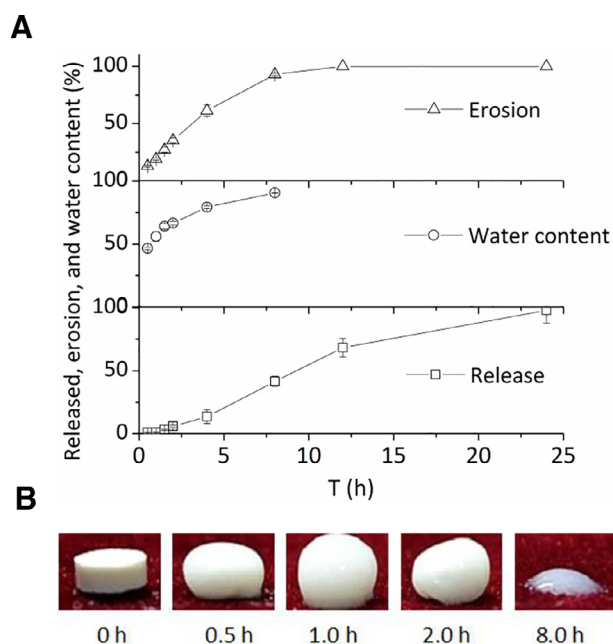
advantages in developing lipid based, especially in eliminating the expensive and ethically disputable *in vivo* studies at earlier development stages, and reduce *in vitro/in vivo* trial-and-error experiments [31].

### 3.3. Drug release mechanism of the extended release tablet

Fig. 8 showed the drug release, matrix erosion and swollen (water content), as well as the changes in appearance of the prepared tacrolimus extended release tablet during the *in vitro* release test. The drug release mechanism of the extended release tablet is generally categorized to diffusion-controlled, erosion-controlled, and combination of both mechanisms. For the hydrogel matrix-type tablet, the water-soluble polymer (e.g. HPMC) on the tablet surface hydrate and swell to form a highly viscous and inert hydrogel layer quickly in the release media, the boundary of the inert hydrogel layer moves inward to the tablet core until the total tablet is hydrated. The drug release process is accompanied with concomitant matrix erosion of the most outer gel layer. The inert gel layer of low diffusivity and the matrix erosion composed of the main factors that tailor drug release pattern. It is evident that the tacrolimus release rate is related to the diffusion of drug across the inert gel layer and the erosion rate of the tablet matrix (Fig. 8). The hydrophobic lipid incorporated inside the tablet may also render the tablet poor wettability, retard matrix hydration and drug diffusion outward, thus minor or zero initial release was reasonable for such extended release tablets.

The solid state at body temperature and hydrophobic nature of ATO render the solid dispersions poor wettability to aqueous media, thus retarded drug release.

The drug release data was fitted with various mathematic models to elucidate the release mechanism, and the results were listed in Table 3. According to the correlation coefficients of the fitted curves, the release dynamics of tacrolimus tablet fitted very well to the Korsmeyer–Peppas equation ( $Q=6.63902t^{0.85}-2.83593$ ,  $R^2=0.9703$ ). The release



**Fig. 8** – Drug release, matrix erosion and swollen (water content) (A), as well as the changes in appearance (B) of the tacrolimus extended release tablet during the *in vitro* release test.

data of tacrolimus solid dispersion was fitted with the same equation,  $Q=97.75t^{0.766}$  ( $R^2=0.974$ ), the markedly higher constant before the time item indicated the dissolution of drug from the solid dispersion is not the rate-controlling step of drug release from the tablet. The exponent ( $n$ ) value derived from the power law equation enlightens in understanding the release mechanism from the dosage form. According to the Korsmeyer–Peppas equation, the  $n$  value of 0.85 indicated an anomalous transport mechanism of the tacrolimus release [26]. The anomalous transport is a combination of diffusion-



**Table 3 – The fitted equations of tacrolimus extended release tablet.**

Models	Fitted equation *	R <sup>2</sup>
Zero order	$Q = 4.3963t + 4.7393$	0.8419
First order	$Q = -0.1196t + 0.0704$	0.9188
Higuchi	$Q = 25.877t^{1/2} - 22.862$	0.9302
Korsmeyer-Peppas	$Q = 6.63902t^{0.85} - 2.83593$	0.9703
Hixson Crowell	$(1-Q)^{1/3} = -0.0269t + 1.0006$	0.8942
Weibull	$\ln[1/(1-Q)] = 0.6358\ln t + 0.0596$	0.768

\* In the fitted equations, Q is the accumulated drug released.

and erosion-controlled release mechanism, this result is consistent with our direct experimental observation.

#### 4. Conclusion

In this study, we utilized a combination of solid dispersion and matrix-type extended release techniques to prepare tacrolimus extended release tablets. Compritol® ATO888, a lipid material normally used as the sustained release solid matrix, and polymeric nonionic surfactant Pluronic F127 were used as the main matrix components to obtain tacrolimus solid dispersion with increased drug dissolution. Incorporation of HPC into the solid dispersion can obviously improve its stability after storage. The release patterns of the tacrolimus extended release tablets can be tailored by the compositions of the matrix materials, such as the types and content of HPMCs. Certain modification to the tableting process, i.e. directly mixed the melted solid dispersion with HPMC powders, improved the uniformity of the solid dispersion inside the tablet matrix and release profile. The release profile of the tablet had no obviously changes after 30 days' storage. The release data of the extended release tablet fitted well to the Korsmeyer-Peppas model with *n* value of 0.85, which suggested diffusion- and erosion-controlled release mechanism. The combination of lipid-based solid dispersion and HPMC hydrogel matrix may find wide applications in the extended release dosage forms of high potent, water-insoluble drugs.

#### Conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

#### REFERENCES

- [1] Yamashita K, Nakate T, Okimoto K, et al. Establishment of new preparation method for solid dispersion formulation of tacrolimus. *Int J Pharm* 2003;267:79–91.
- [2] Kino T, Hatanaka H, Hashimoto M, et al. FK 506, a novel immunosuppressant isolated from a streptomyces I. Fermentation, isolation and physico-chemical and biological characteristics. *J Antibiot* 1987;42:1249–55.
- [3] Tamura S, Tokunaga Y, Ibuki R, Amidon GL, Sezaki H, Yamashita S. The site-specific transport and metabolism of tacrolimus in rat small intestine. *J Pharmacol Exp Ther* 2003;306:310–16.
- [4] Venkataramanan R, Swaminathan A, Prasad T, et al. Clinical pharmacokinetics of tacrolimus. *Clin Pharmacokinet* 1995;29:404–30.
- [5] Sam WJ, Tham LS, Holmes MJ, et al. Population pharmacokinetics of tacrolimus in whole blood and plasma in asian liver transplant patients. *Clin Pharmacokinet* 2006;45(1):59–75.
- [6] Tremblay S, Alloway RR. Clinical evaluation of modified release and immediate release tacrolimus formulations. *AAPS J* 2017;19(5):1332–47.
- [7] Song GW, Lee SG, Hwang S, et al. A pilot study of the pharmacokinetics of the modified-release once-daily tacrolimus formulation administered to living-donor liver transplant recipients. *Exp Clin Transplant* 2016;14(4):412–18.
- [8] Grinyó JM, Petruzzelli S. Once-daily LCP-Tacro MeltDose tacrolimus for the prophylaxis of organ rejection in kidney and liver transplantations. *Expert Rev Clin Immunol* 2014;10(12):1567–79.
- [9] Muduma G, Saunders R, Odeyemi I, Pollock RF. Systematic review and meta-analysis of tacrolimus versus ciclosporin as primary immunosuppression after liver transplant. *PLoS One* 2016;11(11):e0160421.
- [10] Gaber A, Alloway R, Bodziak K, Kaplan B, Bunnapradist S. Conversion from twice-daily tacrolimus capsules to once-daily extended-release tacrolimus (LCPT): a phase 2 trial of stable renal transplant recipients. *Transplantation* 2013;96(2):191–7.
- [11] Budde K, Bunnapradist S, Grinyó JM, et al. Novel once-daily extended-release tacrolimus (LCPT) versus twice-daily tacrolimus in de novo kidney transplants: one-year results of Phase III, double-blind, randomized trial. *Am J Transplant* 2014;14(12):2796–806.
- [12] Rahman Z, Siddiqui A, Bykadi S, Khan MA. Near-infrared and fourier transform infrared chemometric methods for the quantification of crystalline tacrolimus from sustained-release amorphous solid dispersion. *J Pharm Sci* 2014;103(8):2376–85.
- [13] Tsunashima D, Yamashita K, Ogawara KI, Sako K, Hakomori T, Higaki K. Development of extended-release solid dispersion granules of tacrolimus: evaluation of release mechanism and human oral bioavailability. *J Pharm Pharmacol* 2017;69(12):1697–706.
- [14] Kalam MA, Alshamsan A. Poly (d, l-lactide-co-glycolide) nanoparticles for sustained release of tacrolimus in rabbit eyes. *Biomed Pharmacother* 2017;94:402–11.
- [15] Khan S, Shaharyar M, Fazil M, Baboota S, Ali J. Tacrolimus-loaded nanostructured lipid carriers for oral delivery - Optimization of production and characterization. *Eur J Pharm Biopharm* 2016;108:277–88.
- [16] Tajdaran K, Shoichet MS, Gordon T, Borschel GH. A novel polymeric drug delivery system for localized and sustained release of tacrolimus (FK506). *Biotechnol Bioeng* 2015;112(9):1948–53.
- [17] Liu L, Li J, Zhao M, Xu H, Li L, Wang S. Loading of tacrolimus containing lipid based drug delivery systems into mesoporous silica for extended release. *Asian J Pharm Sci* 2016;11:751–9.
- [18] Dening TJ, Rao S, Thomas N, Prestidge CA. Novel nanostructured solid materials for modulating oral drug delivery from solid-state lipid-based drug delivery systems. *AAPS J* 2016;18(1):23–40.

- [19] Chakraborty S, Shukla D, Mishra B, Singh S. Lipid-an emerging platform for oral delivery of drugs with poor bioavailability. *Eur J Pharm Biopharm* 2009;73(1):1–15.
- [20] Pouton CW. Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systems. *Eur J Pharm Sci* 2000;11(S2):S93–8.
- [21] Jannin V, Rosiaux Y, Doucet J. Exploring the possible relationship between the drug release of Compritol®-containing tablets and its polymorph forms using micro X-ray diffraction. *J Control Release* 2015;197:158–64.
- [22] Aburahma MH, Badr-Eldin SM. Compritol 888 ATO: a multifunctional lipid excipient in drug delivery systems and nanopharmaceuticals. *Expert Opin Drug Deliv* 2014;11(12):1865–83.
- [23] Zhang YE, Tchao R, Schwartz JB. Effect of processing methods and heat treatment on the formation of wax matrix tablets for sustained drug release. *Pharm Dev Technol* 2001;6(2):131–44.
- [24] Patere SN, Desai NS, Jain AS, et al. Compritol® 888 ATO a lipid excipient for sustained release of highly water soluble active: formulation, scale-up and IVIVC study. *Curr Drug Deliv* 2013;10(5):548–56.
- [25] Anirudhan TS, Parvathy J, Nair AS. Carbohydr Polym, a novel composite matrix based on polymeric micelle and hydrogel as a drug carrier for the controlled release of dual drugs. *Carbohydr Polym* 2016;136:1118–27.
- [26] Siepmann F, Eckart K, Maschke A, Kolter K, Siepmann J. Modeling drug release from PVAc/PVP matrix tablets. *J Control Release* 2010;141(2):216–22.
- [27] Barakat NS, Elbagory IM, Almurshedi AS. Controlled-release carbamazepine matrix granules and tablets comprising lipophilic and hydrophilic components. *Drug Deliv* 2009;16(1):57–65.
- [28] Cho JH, Kim YI, Kim DW, et al. Development of novel fast-dissolving tacrolimus solid dispersion-loaded prolonged release tablet. *Eur J Pharm Sci* 2014;54:1–7.
- [29] Tsunashima D, Yamashita K, Ogawara K, Sako K, Higaki K. Preparation of extended release solid dispersion formulations of tacrolimus using ethylcellulose and hydroxypropylmethylcellulose by solvent evaporation method. *J Pharm Pharmacol* 2016;68(3):316–23.
- [30] Ilić I, Dreu R, Burjak M, Homar M, Kerc J, Srcic S. Microparticle size control and glimepiride microencapsulation using spray congealing technology. *Int J Pharm* 2009;381(2):176–183.
- [31] Rosiaux Y, Jannin V, Hughes S, Marchaud D. Solid lipid excipients - matrix agents for sustained drug delivery. *J Control Release* 2014;188:18–30.
- [32] Hagemann JW. Thermal behaviour and polymorphism of acyl glycerides. In: Garti N, Sato K, editors. *Crystallization and polymorphism of fats and fatty acids*. New York: Marcel Dekker Inc; 1988. p. 9–95.
- [33] Hernquist L. Crystal structures of fats and fatty acids. In: Garti N, Sato K, editors. *Crystallization and polymorphism of fats and fatty acids*. New York: Marcel Dekker Inc; 1988. p. 97–137.
- [34] Sato K. Crystallization behaviour of fats and lipids: a review. *Chem Eng Sci* 2001;56:2255–65.
- [35] Hariharan M, Wowchuk C, Nkansah P, Gupta VK. Effect of formulation composition on the properties of controlled release tablets prepared by roller compaction. *Drug Dev Ind Pharm* 2004;30(6):565–72.
- [36] Gu X, Fediuk DJ, Simons FE, Simons KJ. Evaluation and comparison of five matrix excipients for the controlled release of acrivastine and pseudoephedrine. *Drug Dev Ind Pharm* 2004;30(10):1009–17.
- [37] Lo JB, Appel LE, Herbig SM, McCray SB, Thombre AG. Formulation design and pharmaceutical development of a novel controlled release form of azithromycin for single-dose therapy. *Drug Dev Ind Pharm* 2009;35(12):1522–1529.
- [38] Mercuri A, Wu S, Stranzinger S, Mohr S, Salar-Behzadi S, Bresciana M, Fröhlich E. *In vitro* and *in silico* characterization of tacrolimus released under biorelevant conditions. *Int J Pharm* 2016;555(1–2):271–80.