Enhancement of oral bioavailability of cyclosporine A: comparison of various nanoscale drug-delivery systems

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Abstract: A variety of nanoscale delivery systems have been shown to enhance the oral absorption of poorly water-soluble and poorly permeable drugs. However, the performance of these systems has seldom been evaluated simultaneously. The aim of this study was to compare the bioavailability enhancement effect of lipid-based nanocarriers with poly(lactic-co-glycolic acid) (PLGA) nanoparticles (NPs) to highlight the importance of the lipid composition, with cyclosporine A (CyA) as a model drug. CyA-loaded PLGA NPs, nanostructured lipid carriers (NLCs), and self-microemulsifying drug-delivery systems (SMEDDS) were prepared. The particle size of PLGA NPs (182.2 ± 12.8 nm) was larger than that of NLCs (89.7 ± 9.0 nm) and SMEDDS (26.9 ± 1.9 nm). All vehicles are charged negatively. The entrapment efficiency of PLGA NPs and NLCs was 87.6 ± 1.6% and 80.3 ± 0.6%, respectively. In vitro release tests indicated that the cumulative release of CyA was lower than 4% from all vehicles, including Sandimmun Neoral®, according to the dialysis method. Both NLCs and SMEDDS showed high relative oral bioavailability, 111.8% and 73.6%, respectively, after oral gavage administration to beagle dogs, which was not statistically different from commercial Sandimmun Neoral®. However, PLGA NPs failed to achieve efficient absorption, with relative bioavailability of about 22.7%. It is concluded that lipid-based nanoscale drug-delivery systems are superior to polymeric NPs in enhancing oral bioavailability of poorly water-soluble and poorly permeable drugs.

Keywords: cyclosporine A, PLGA nanoparticle, nanostructured lipid carrier, self-microemulsifying drug-delivery systems, bioavailability

Introduction

It is well known that the oral route is the first choice clinically for drug administration due to better patient compliance. However, most new chemical entities (approximately 60% of drugs) coming directly from chemical synthesis are poorly water-soluble, and a large fraction of them are even poorly permeable across the biomembrane in the gastrointestinal tract (GIT). Drug substances with low solubility and poor permeability exhibit extremely low bioavailability after oral administration, which may result in limited therapeutic potential and thus insufficient curative effects. According to the definition of Biopharmaceutics Classification System (BCS), these drugs are categorized as BCS IV. Consequently, BCS IV drugs yield the most challenging absorption problems, such as low drug dissolution, efflux by transporters in the gut wall, and first-pass effect by metabolic enzymes.

Fortunately, smart drug carrier systems are emerging to handle each difficult problem. Colloidal carriers, whether directly nanosized or incorporated into polymeric or lipidic nanoparticles (NPs) (eg, nanocrystals, poly(lactic-co-glycolic acid) (PLGA) NPs, and microemulsions), are proved to facilitate adhesive interaction within the
mucosa and remain in the intestinal tract until the release of the loaded drug or their absorption in an intact particulate form. They can help to deliver drugs with poor aqueous solubility, low permeability, and extensive first-pass metabolism, because of the special mechanisms of uptake through the GIT. For example, NPs bind to the apical membrane of the M cells, followed by rapid internalization and shuttling to lymphocytes, wherein size and surface charge play a crucial role for their uptake. Apart from these common advantages, different colloidal carriers have distinguishing features of their own. Some polymeric NPs, such as PLGA NPs, improve oral absorption of drugs through increasing dispersion of drugs and epithelia endocytosis. Nevertheless, it is generally thought that digestion products of lipid-based nanocarriers, such as lipid NPs and nanoemulsion, can solubilize lipophilic drugs and that the presence of endogenous bile salts may alter the intrinsic permeability of the intestinal membrane, leading to increased absorption via paracellular or transcellular routes.

Both lipid-based nanocarriers and polymeric NPs were suggested as distinguished delivery systems in improving oral absorption of BCS IV drugs, according to many reports. Some reports have suggested that lipid-based nanocarriers are superior to polymeric NPs in improving oral bioavailability of BCS IV drugs. These comparisons are based on data from different research groups, however, and are therefore affected by choice of animal models, experimental design, and other experimental conditions. Thus, in order to clarify the differences between lipid-based nanocarriers and polymeric NPs and to provide valuable information for the formulation design of BCS IV drugs, bioavailability comparisons within the same experimental condition is necessary.

This study utilized cyclosporine A (CyA), which is a cyclic polypeptide containing eleven amino acids and used as immunosuppressive, as a model drug. CyA is classified as a BCS IV drug due to its physicochemical properties, including high lipophilicity, polar surface area, and molecular weight. The factors impeding the absorption of CyA include the narrow absorption window in the upper gut, P-glycoprotein efflux from enterocytes, and extensive pre-systemic metabolism in the wall and liver. To date, how to improve CyA’s in vivo performance has been a widespread concern, and various oral drug carriers have emerged, such as solid dispersion, nanosuspension, liposomes, lipid NPs, self-microemulsifying drug-delivery system (SMEDDS), and PLGA NPs. Although each of these was reported to significantly increase CyA oral bioavailability, only the SMEDDS of CyA (Sandimmun Neoral®) was successfully marketed, revealing the superiority of lipid-based nanocarriers.

For this study selected CyA as the BCS IV drug model and beagle dogs as the animal model to compare the relative bioavailability of PLGA NPs (polymeric NPs) with two kinds of lipid-based nanocarriers (SMEDDS and nanostructured lipid carriers [NLCs]), with Sandimmun Neoral® used as a reference.

Materials and methods
Materials
CyA was obtained from the Pharmaceutical Factory of Sichuan Institute of Antibiotic Industries (Chengdu, People’s Republic of China). PLGA (Lakeshore Biomaterials™ 5050 DLG 2A, inherent viscosity: 0.20 dL/g) was kindly gifted from Evonik Degussa Co., Ltd (Shanghai, People’s Republic of China). Polyvinyl alcohol (average molecular weight =13–23 kDa) was purchased from Sigma-Aldrich (St Louis, MO, USA). Precirol ATO 5 and Captex 100 were kindly provided by Gattefossé Co. (Saint Priest, Cedex, France) and Abitec Co. (OH, USA), respectively. Polysorbate 80 (Tweeen-80) was supplied by Shenyu Pharmaceutical and Chemical Co., Ltd (Shanghai, People’s Republic of China). Oleoyl macrogolglycerides (Labrafil M® 1944 CS) and diethylene glycol monoethyl ether (Transcutol P®) were kindly gifted from Gattefossé Corporation (Brittany, France). Ethoxylated castor oil (Cremophor® EL) was obtained from BASF Corporation (Ludwigshafen, Germany).

High-performance liquid chromatography (HPLC)-grade methanol and acetone were purchased from Tedia (Carson City, CA, USA). Deionized water was prepared using a Milli-Q purification system (Millipore, Billerica, MA, USA). All other chemicals were of analytical grade and used as received.

Preparation of PLGA nanoparticles
PLGA NPs were prepared by a modified emulsion solvent-evaporation method. Briefly, 30 mg of CyA and 150 mg of PLGA were dissolved in 3 mL of ethyl acetate. The mixed solution was added dropwise to 3 mL of 1.5% polyvinyl alcohol solution under constant stirring to obtain the primary emulsion. The primary emulsion was then homogenized for 1 minute with the help of an ultrasonic machine (JY92-IIDN, NINGBO Scientz Biotechnology Co., Ltd, People’s Republic of China). Afterwards, NPs were formed through adding 25 mL of water under 1,000 rpm stirring. The obtained suspension was kept overnight with moderate stirring to evaporate ethyl acetate.
Preparation of nanostructured lipid carriers

NLC suspensions were prepared by the melting–emulsification technique, according to our previously described procedures with minor modifications. In brief, 1.0 g solid lipids (Precirol ATO 5) and 2.0 g liquid lipids (Captor100) were melted at 65°C, in which 80 mg CyA was dissolved. The CyA-containing melt was then dispersed in 50 mL water containing 1.4% (w/v) Tween 80 under high-speed stirring using an Ultra-Turrax blender (QiInBeier, Jiangsu, People’s Republic of China) at the same temperature. The obtained coarse emulsion was further homogenized by microfluidizer (Nano DeBEE, USA) applying four circles under 20,000 psi. The CyA-loaded NLCs were obtained when the homogenized emulsion was cooled to room temperature.

Preparation of CyA-loaded self-microemulsifying drug-delivery system

The formulation of CyA SMEDDS was prepared according to previously reported method by our group. In brief, CyA (160 mg) was dissolved in the mixture of 300 mg Labrafil M 1944 CS, 466.7 mg Cremophor EL, and 233.3 mg Transcutol P. The final mixture was vortex-mixed, and then observed visually to identify the formation of SMEDDS.

Measurement of particle size and zeta potential

The Zetasizer Nano® (Malvern Instruments, Malvern, UK) equipped with a 4 mW He–Ne laser (633 nm) was employed to measure particle size and zeta potential at 25°C. The NLCs and PLGA NPs were diluted 15-fold with deionized water before measurement. The particle sizes of SMEDDDS and Sandimmun Neoral® were determined after microemulsifying in deionized water. The zeta potential was also determined by Zetasizer Nano® at 25°C, and samples were placed into folded capillary cells integrated with gold electrodes. Three replicated samples were measured and each sample was conducted in triple measurements.

Transmission electron microscopy

The morphology of PLGA NPs, NLCs, SMEDDDS, and Sandimmun Neoral® was observed by transmission electron microscopy (TEM). The microemulsion droplets were obtained by microemulsifying SMEDDDS and Sandimmun Neoral® in deionized water. Then the PLGA NPs, NLCs suspension, and microemulsion droplets were placed on copper grids and negatively stained with 2% (w/v) phosphotungstic acid for 5 minutes at room temperature. Finally, the grids bearing PLGA NPs, NLCs, and microemulsion droplets were observed with a JEM-1230 TEM (JEOL, Tokyo, Japan).

Determination of entrapment efficiency of PLGA NPs and NLCs

PLGA NPs were centrifuged at 30,000×g for 30 minutes to separate NPs with free drugs. The precipitant was dissolved in acetonitrile, which was analyzed by HPLC to determine the amount of CyA incorporated into NPs. The entrapment efficiency (EE) of PLGA NPs was calculated by the following equation.

\[
EE(\%) = \frac{\text{Amount of CyA incorporated into NPs}}{\text{Total amount of CyA}} \times 100\% \tag{1}
\]

The EE of NLCs was determined by ultrafiltration method and utilized centrifugal filter tubes with a molecular weight cutoff of 100 kDa. The concentration of total CyA in NLCs suspension and ultrafiltrate (free CyA) was analyzed by HPLC. The EE was calculated using the following equation.

\[
EE(\%) = \frac{\text{Total amount of CyA} - \text{Amount of free CyA}}{\text{Total amount of CyA}} \times 100\% \tag{2}
\]

Release test

The release test of NLCs, PLGA NPs, SMEDDDS, and commercial Sandimmun Neoral® capsules were evaluated by a dynamic dialysis method in a ZRS-8G dissolution tester (Tianjin, People’s Republic of China). NLCs, PLGA NPs, and SMEDDDS dispersions containing 6 mg CyA were sealed in dialysis bags (molecular weight cutoff 14,000; Millipore, Boston, MA, USA), while Sandimmun Neoral® capsules were dispersed in 12.5 mL deionized water, 3 mL of which was sealed in dialysis bags. In order to maintain the sink condition, phosphate-buffered saline (PBS, pH 6.8) with 0.2% (w/v) sodium lauryl sulfate was used as a release medium. The dialysis bags were immersed in 100 mL release medium and stirred at a speed of 100 rpm. The 1 mL of medium was withdrawn at time intervals of 0.25 hour, 0.50 hour, 1.0 hour, 2.0 hours, 3.0 hours, 6.0 hours, and 12.0 hours, and then determined by HPLC.

Oral bioavailability study

Six beagle dogs (adult male, 15.0±0.5 kg) used in the experiments received care in compliance with the Principles of Laboratory Animal Care and the Guide for the Care and
Use of Laboratory Animals. Prior to experiment, the dogs were fasted overnight and allowed free access to water. The four carriers (NLCs, PLGA NPs, SMEDDS, and Sandimmun Neoral®) were respectively administered to the dogs by oral gavage at an equivalent dose of 10 mg/kg CyA and the washout period was set as 1 week. After administration, about 3 mL blood was collected through the hind leg vein into heparinized tubes at 0.25 hour, 0.5 hour, 1.0 hour, 1.5 hours, 2.0 hours, 2.5 hours, 3.0 hours, 4.0 hours, 6.0 hours, 8.0 hours, 12.0 hours, 24.0 hours, 36.0 hours, and 48.0 hours. Blood samples were stored at −20°C until analysis. CyA in whole blood was extracted by liquid–liquid extraction procedures established in our previous study, and concentration of CyA was determined by HPLC.

DAS professional software version 2.0 (Anhui, People’s Republic of China) was employed to calculate pharmacokinetic parameters. The pharmacokinetic parameters, such as peak plasma concentration (Cmax), the time to maximum plasma concentration (Tmax), and the area under the concentration-time curve (AUC) between 0 hour and 48 hours (AUC0–48) were obtained by noncompartmental analysis based on statistical moment theory.

**HPLC determination of CyA**

Both in vitro and in vivo samples were determined using an HPLC system (LC-10 ATvp, Shimadzu, Japan) comprising a binary pump, a tunable ultraviolet detector, and a column heater. The analytical column was a C18 column (Venusil XBP, 5 µm, 4.6×150 mm; Agela, Tianjin, People’s Republic of China) guarded with a refillable precolumn (C18, 2.0×20 mm; Alltech, Lexington, KY, USA). The ultraviolet detector was set at a wavelength of 287 nm. The column temperature was set to 70°C. For in vitro determination of CyA, the mobile phase consists of acetonitrile/water/tert-butyl methyl ether/phosphoric acid (60/35/5/0.1, v/v/v/v) at a flow rate of 1.0 mL/minute. However, the mobile phase was a mixture of acetonitrile/water/tert-butyl methyl ether/phosphoric acid (525/425/50/1, v/v/v/v) at a flow rate of 1.5 mL/minute for in vivo determination.

**Statistical analysis**

All data were expressed as mean ± standard deviation. One-way analysis of variance followed by Tukey’s test was performed to assess the statistical significance of difference. Results with P<0.05 were considered statistically significant.

**Results**

**Preparation and characterization of PLGA NPs, NLCs, and SMEDDS**

CyA-loaded PLGA NPs, NLCs, and SMEDDS were prepared successfully. The particle size, polydispersion index (PDI), and zeta potential of each vehicle are summarized in Table 1.

The order of particle size of obtained nanovehicles was PLGA NPs > NLCs > SMEDDS. PLGA NPs are rigid NPs, and thus it is difficult to decrease particle size to <100 nm by high-pressure homogenization. However, NLCs are NPs that are between “soft” and “hard”, as they are composed of liquid and solid lipids. The formulation components are different between self-made SMEDDS and Sandimmun Neoral®. Sandimmun Neoral® is composed of alcohol, corn oil (mono-di-triglycerides), Cremophor RH40 (polyoxyxyl 40 hydrogenated castor oil), and DL-α-tocopherol. The formulation components of self-made SMEDDS include Labrafil M 1944 CS (oleoyl macroglycercides), Cremophor EL (polyoxyxyl 35 castor oil), and Trancutol P (diethylene glycol monoethyl ether), which removes the ethanol in formulation. Nevertheless, the particle size of self-made SMEDDS was not significantly different from that of Sandimmun Neoral® after dispersing in deionized water. The PDI of all vehicles was lower than 0.24, which indicated relatively narrow particle-size distribution. Owing to the fatty acid in lipids of NLCs, NLCs had a higher negative charge than other vehicles. High zeta potential is necessary to keep the in vitro stability of nanosuspensions. The other vehicles had negative charge of lower than −5 mV, but the particles size and PDI of all vehicles had no significant increase within 24 hours (Figure 1). The EEs of PLGA NPs and NLCs were

<table>
<thead>
<tr>
<th>Vehicle</th>
<th>Size (nm)</th>
<th>PDI</th>
<th>Zeta potential (mV)</th>
<th>EE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLGA NPs</td>
<td>182±12.8</td>
<td>0.15±0.04</td>
<td>−5.0±3.4</td>
<td>87.6±1.6</td>
</tr>
<tr>
<td>NLCs</td>
<td>89.7±9.0</td>
<td>0.24±0.02</td>
<td>−16.2±3.6</td>
<td>80.3±0.6</td>
</tr>
<tr>
<td>SMEDDS</td>
<td>26.9±1.9</td>
<td>0.12±0.05</td>
<td>−3.1±1.1</td>
<td>−</td>
</tr>
<tr>
<td>Sandimmun® Neoral®</td>
<td>30.0±0.1</td>
<td>0.14±0.02</td>
<td>−4.2±1.1</td>
<td>−</td>
</tr>
</tbody>
</table>

**Abbreviations:** CyA, cyclosporine A; EE, entrapment efficiency; NP, nanoparticle; NLC, nanostructured lipid carrier; PDI, polydispersion index; PLGA, poly(lactic-co-glycolic acid); SMEDDS, self-microemulsifying drug-delivery systems.
87.6%±1.6% and 80.3%±0.6%, respectively, suggesting efficient encapsulation of CyA.

**Morphology**

TEM was employed to observe the morphology of PLGA NPs, NLCs, and microemulsions reconstituted from SMEDDS and Sandimmun Neoral® (Figure 2). Both the PLGA NPs (Figure 2A) and the NLCs (Figure 2B) were spherical in shape and similar in size, according to the results of dynamic light scattering. The particle size of PLGA NPs was more well-distributed than that of NLCs. Figure 2C and D demonstrate the morphology of microemulsions formed by self-made SMEDDS and Sandimmun Neoral®, respectively, and indicate that there are no significant differences between them.

**Release test**

Release profiles of the four vehicles were shown in Figure 3. CyA almost cannot release from the four vehicles. In this study, the sink condition was achieved by the addition of 0.2% sodium lauryl sulfate in PBS. In addition, CyA in solution could diffuse completely across the dialysis bag within 1 hour, suggesting a negligible hindering effect of the dialysis bag on release of CyA. CyA cannot release from NLCs or SMEDDS, as CyA has good affinity for lipids. It is generally thought that NLCs and SMEDDS release drug molecules by digestion with lipase when they enter into the GIT. However, PLGA NPs release drugs by erosion, which may take a few days or months. Therefore, cumulative release amount of drug from carriers in PBS was extremely low within 12 hours.

**Oral bioavailability**

To investigate the role of different vehicles in enhancing oral absorption of CyA, oral bioavailability of CyA-loaded PLGA NPs, NLCs, and SMEDDS in beagle dogs were compared. The mean whole-blood CyA concentrations versus time plots for the four vehicles are shown in Figure 4, and
the pharmacokinetic parameters obtained by the statistical moment method are shown in Table 2.

After oral administration, the \( T_{\text{max}} \) of CyA in Sandimmun Neoral® was 1.92±0.58 hours, which was similar to previous reports.\(^\text{33,38} \) Although the \( T_{\text{max}} \) of NLCs, SMEDDS, and PLGA NPs was lower than that of the reference, there was no significant difference in \( T_{\text{max}} \) after oral administration of the four vehicles, mainly due to the larger individual variation. In terms of \( C_{\text{max}} \), NLCs showed the maximum value among the four vehicles (2.32±1.05 \( \mu \)g/mL) but was not significantly different from Sandimmun Neoral® (1.76±0.77 \( \mu \)g/mL). In contrast, the \( C_{\text{max}} \) of PLGA NPs was lower than that of others and statistically different from Sandimmun Neoral® (\( P<0.05 \)). Similarly, NLCs obtained statistically higher AUC\(_{0-48}\) than PLGA NPs, but no statistical difference with Sandimmum Neoral® or SMEDDS.

**Figure 2** Morphology of CyA-loaded delivery systems observed by transmission electron microscopy.

**Notes:** (A) PLGA NPs, (B) NLCs, (C) microemulsions droplets formed by SMEDDS, and (D) Sandimmun Neoral®.

**Abbreviations:** CyA, cyclosporine A; NP, nanoparticle; NLC, nanostructured lipid carrier; PLGA, poly(lactic-co-glycolic acid); SMEDDS, self-microemulsifying drug-delivery systems.
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Nanoscale delivery systems for enhancing oral bioavailability of cyclosporine A

Discussion

The improvement in BCS IV drug bioavailability was dependent not only on increase of dissolution in GIT but also on enhancement of permeability across intestinal epithelia. PLGA NPs are polymeric NPs, which were not degraded in GIT within a short time and could not release drug rapidly. However, PLGA NPs can adhere to mucus to increase the retention time of drugs in GIT due to their very small particle size and inhibit the efflux of P-glycoprotein to enhance the transport of CyA across the intestinal epithelia. Furthermore, intact PLGA NPs may be endocytosed by intestinal epithelia or M cells and can protect the drug from degradation in GIT. Nevertheless, it is well known that adsorptive endocytosis is initiated by electrostatic forces, by which positively charged particulate vehicles can readily adhere to the negatively charged cell surface of intestinal mucosa. In our study, PLGA NPs were prepared without any chemical modification and displayed negative charge. Meanwhile, it is generally believed that endocytosis of intestinal epithelial is a slow and infrequent process compared with passive transport. Consequently, PLGA NPs showed no significant enhanced ability of oral absorption, indicating that uptake of NPs by endocytosis of intestinal epithelia cannot increase oral bioavailability of BCS IV drugs to a large extent. Although the endocytosis may be also affected by particle size, one study suggested the uptake of PLGA NPs by intestinal epithelia was not significantly different for particles sized 100–200 nm. However, our previous study concluded that a single mechanism of increased dissolution, such as solid dispersion or nanocrystals, cannot sufficiently promote the bioavailability of a BCS IV drug.

With respect to lipid-based nanocarriers, not only did they achieve a higher $C_{\text{max}}$ value in an earlier absorption stage, but they also maintained a higher level of drug concentration over the whole absorption process, compared with PLGA NPs. Hence, we concluded that lipid-based nanocarriers achieved a better bioavailability-enhancing effect, which may be mainly due to a combined promotion mechanisms as follows.

Firstly, the ability to adhere to gut wall should be taken into account. Though negatively charged particulates and droplets should encounter electrostatic repulsion by the negatively charged mucus gel layer of enterocytes, which is unfavorable to the absorption of CyA, ultrafine dispersions within nanometer range were realized in all three lipid nanocarriers and this endows them with a tremendous specific surface area and thus the possession of adhesion to gut wall, which is helpful to oral absorption.

Secondly, lipid-based nanocarriers, such as NLCs or SMEDDS, would be degraded by lipase to transform into a series of secondary derivatives (eg, mixed micelles, cubic and hexagonal NPs, vesicular carriers) with the help of endogenous bile salts and phospholipids in GIT. Drugs are able to be solubilized in these secondary derivatives, which is very helpful to drug absorption. Meanwhile, reports have confirmed that the cellular uptake was size-dependent and the endocytosis was mediated via clathrin as particle diameter was smaller than 200 nm, which may be helpful to increase oral bioavailability.

### Table 2 Pharmacokinetic parameters after oral administration of CyA-loaded PLGA NPs, NLCs, SMEDDS, and commercial Sandimmun Neoral® capsule (n=6)

<table>
<thead>
<tr>
<th>Vehicles</th>
<th>$T_{\text{max}}$ (hours)</th>
<th>$C_{\text{max}}$ (µg/mL)</th>
<th>AUC$_{0-48}$ (µg*hours/mL)</th>
<th>RBA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLGA NPs</td>
<td>1.05±0.94</td>
<td>0.56±0.15*</td>
<td>2.21±0.96*</td>
<td>22.71±6.73</td>
</tr>
<tr>
<td>NLCs</td>
<td>1.40±0.65</td>
<td>2.32±1.05</td>
<td>11.43±3.27</td>
<td>111.83±40.0</td>
</tr>
<tr>
<td>SMEDDS</td>
<td>1.50±0.35</td>
<td>1.12±0.20</td>
<td>6.96±1.63</td>
<td>73.57±25.65</td>
</tr>
<tr>
<td>Sandimmun Neoral®</td>
<td>1.92±0.58</td>
<td>1.76±0.77</td>
<td>10.28±4.25</td>
<td>—</td>
</tr>
</tbody>
</table>

Note: *P<0.05 compared with Sandimmun Neoral® capsule.

Abbreviations: AUC, area under the concentration-time curve between 0 and 48 hours; CyA, cyclosporine A; NP, nanoparticle; NLC, nanostructured lipid carriers; PLGA, poly(lactic-co-glycolic acid); RBA, relative bioavailability calculated with Sandimmun Neoral as reference; SMEDDS, self-microemulsifying drug-delivery systems; $T_{\text{max}}$, time to maximum plasma concentration; $C_{\text{max}}$, peak plasma concentration.
Thirdly, intestinal lymphatic drug transport may be recruited by lipid-based vehicles and prolong the later absorption period of CyA (about 6–8 hours after administration in our study), since lymphatic transport is slow, sporadic, and able to avoid first-pass metabolism.99

It should be noted that lipid excipient like Cremophor® EL added in SMEDDS should be digested as well. Digestion of surfactants may cause loss of capacity to keep the drug compound in solution, especially when that excipient is included in relatively high proportion (46.67% of total excipients in our study).50.51

Conclusion
Through the development of a variety of drug nanocarriers (including PLGA NPs, NLCs, and SMEDDS), the oral bioavailability of CyA was well studied. Compared with commercial Sandimmune Neoral®, lipid-based nanocarriers (NLCs and SMEDDS) achieved similar oral bioavailability, but polymeric NPs (PLGA NPs) failed to improve the oral bioavailability of CyA to a great extent. It was suggested that lipid-based drug-delivery systems were more advantageous than others in improving oral absorption of BCS IV drugs, due to the multiple absorption enhancement mechanisms.

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Disclosure
The authors report no conflicts of interest in this work.

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