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RESEARCH PAPER

Nano Composite Emulsion for Sustained Drug Release and Improved Bioavailability

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ABSTRACT

Purpose To propose a novel composite nanoemulsion formulation that contains no surfactant, but offers great stability and improved oral absorption capabilities.

Methods The nanoemulsions were prepared by dispersing the oil phase into aqueous solutions containing different amounts of the PMMA/silica composite nanoparticles. The stability was tested under extreme conditions. The structure features of the nanoemulsion droplets were investigated using Electron microscope. The *in vitro* drug release and *in vivo* drug absorption profiles after oral administration were investigated using Cyclosporin A as a model drug.

Results The composite nanoemulsion demonstrated great stability under various disruptive conditions. Electron microscopy studies indicated the existence of internal and surface domains in the nano-droplet structure. *In vitro* drug release and *in vivo* uptake characterizations also confirmed the unique interfacial properties of such nanoemulsion structures.

Conclusions The novel nanoemulsion formulation may have modulated drug release profiles and alternative oral absorption mechanisms, which could offer significant advantages compared to traditional emulsion formulations.

KEY WORDS cyclosporin A · nano composite emulsion · oral bioavailability · physical stability · poorly soluble drugs

ABBREVIATIONS

CMC	Critical micellar concentration
CNC	Cellulose Nanocrystals
ddH_2O	Double distilled H_2O
EM	Electronic Microscopy
IR	Infrared Spectroscopy
MALT	Mucosal associate lymph tissue
NCE	New chemical entity
PDI	Polydispersity Index
P-gP	P-glycoprotein
PMMA	Polymethyl Methacrylate
PTA	Phosphotungstic Acid
SEDDS	Self-emulsifying drug delivery system
SGF	Simulated gastric fluids
SIF	simulated intestinal fluids
SMEDDS	Self-microemulsifying drug delivery system

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INTRODUCTION

Compounds with poor aqueous solubility account for a significant portion of NCEs discovered with therapeutic potentials (1). But they are usually considered to have poorer developability because their oral bioavailabilities are likely to be limited, by slow dissolution plus high intra-subject variability and poor dose proportionality (2). Great efforts have been put into new formulation technologies to address these issues. Many employed nano dispersion systems such as nano particulates or nanoemulsions (3). Nano systems would have finer and more consistent physical properties with greater surface areas resulting in faster and less variable dissolution upon oral administration (4,5). One possible drawback, however, is that most nano formulations require the use of significant amount of surfactants, in order to maintain the nano-dispersity (6). Some surfactant may cause irritation and be harmful in large doses or with repeated use (7). Another limitation could be that it has been difficult to develop modified release formulations based on nanoparticles (8).

A good example would be the cyclosporin self-emulsifying drug delivery system (SEDDS) that is widely used for immune suppression in the clinics (Sandimmune and Sandimmune Neoral) (9). Cyclosporin A is a lipophilic drug that's almost insoluble in water (10). Its oral bioavailability was highly

variable ranging from 10 to 60%, and depended heavily on bile salt flow and composition, presence of food, and gastrointestinal motility etc. (11,12). The Sandimmune Neoral was designed to form nano-sized emulsion droplets upon mixing with aqueous medium, resulting in faster drug absorption and more consistent pharmacokinetics (13). But the formulation contained a large amount of cremophor as emulsifiers/surfactants which could cause irritations and allergic reaction in patients especially after repeated use (14–16). Several other nano-based systems had been developed such as pH sensitive and cubic nano particles in order to avoid the use of cremophor detergents (12,17). Most of these approaches showed somewhat improved bioavailability, but the absorption usually resulted in a spike of plasma concentration, i.e. high C_{max}, short T_{max} and $T_{1/2}$. However, in fact, cyclosporin A has a relatively narrow therapeutic window (18,19). Considerable nephrotoxicity might be resulted at drug concentrations only about twice of the minimum effective concentration (20,21). So it would be more desirable to develop sustained release formulation to curb the C_{max} while prolong the effective drug concentration window.

In view of these difficulties, we proposed in this study a novel nanostructure containing polymer/silica composite nanoparticles and a cyclosporin A nanoemulsion formulation based on it. It's a surfactant free nanoemulsion with stable loading of cyclosporin A in the oil phase. We showed such a formulation had distinctively different drug release and absorption mechanisms to modify the pharmacokinetic profile after oral administration.

MATERIALS AND METHODS

Materials

The PMMA/silica composite nanomaterial 92206 was purchased from NOW materials (Wuxi, China). It contains about 5% wt. of silica and 95% wt. of PMMA, according to the producer's data. Refined corn oil was obtained from Jiangxi Golden Crabapple Medicinal Oil Co. Ltd. Cyclosporine A was purchased from Kayon biological technology Co. Ltd. (Shanghai, China). Cremophor EL was purchased from BASF (Germany). Lipiodol Ultra Fluide was made by Guerbet (US) and obtained as a gift from Shanghai Tumor Hospital. Acetonitrile and methanol were purchased from Merck AG.

Characterization of the PMMA/Silica Composite Nanomaterial

The PMMA/silica composite nanoparticles purchased were further purified to remove any small molecular weight polymer fragments or impurities by pelleting under ultracentrifugation (35,000 rpm, 22°C, 30 min), washing and re-suspending in ddH_2O for 3 times. They could be air-dried or lyophilized into white powder samples. The powder samples were analyzed to obtain the IR spectroscopy and thermo-gravimetric curve. The IR spectra were recorded using a Equinox 55 (Bruker, Germany). The Thermogravimetric analysis was carried out using a thermogravimetric analyzer TGA 7 (PerkinElmer, USA) by heating the sample (2 mg) under a stream of nitrogen gas (60 ml/min) at 10°C/min from room temperature to 750°C. Contact angle measurements were made using power compressed tablets observed by OCA 20 (Dataphysics, Germany).

Preparation of Nanoemulsions

The PMMA/silica nanocomposites were suspended in 10 ml of deionized water at the weight concentrations of 0.3%, 1%, 3%, 5%, 7%, and 10%. Then the oil phase was added at different volume ratios (1:4, 1:9, v/v), mixed and dispersed using an ultrasonic probe device (Scientz-IID, Ningbo, China) for 10 min. All preparations were done at least three times and assessed visually for reproducibility. For comparison, we also made a surfactant (Cremophor EL) stabilized emulsion formulation using the same oil to water ratio of 1:9 and similar dispersion procedures. The amount of Cremophor EL contained in the emulsion was about 3% weight concentration.

Size Distribution and Zeta Potential Measurements

The nanocomposite and nanoemulsion droplet size were measured using a Malvern Zetasizer Nano ZS90. For each measurement, at least three emulsion samples were prepared using the sample procedure, measurements were taken, and the results were averaged to obtain the mean and standard deviation.

Nanoemulsion Stability Tests

The centrifugation stress test was done by placing the nanoemulsion under 3,000 g centrifugation for 5 cycles of 5 min each at room temperature; The low pH test was carried out by mixing the 1 ml of nanoemulsion with 9 ml of 0.1 M hydrochloric acid; The freeze-thawing test used 3 freeze-thaw cycles followed by freezing at −20°C overnight and thawing in room temperature.

All the samples after various stability tests were first visually inspected for phase separation. Only those samples that maintained homogenous dispersion were further examined using size and zeta potential measurements.

In Vitro Drug Release from Nano Emulsions

The drug release characteristics from the nanoemulsions were examined *in vitro* in simulated gastric fluids (SGF) and simulated intestinal fluids (SIF) using the paddle method (75 rpm). In order to ensure the solubility of the released drug in the receiving medium, N, N-dimethyldodecylamine-N-oxide was added to the SGF and SIF as recommended by the China Pharmacopeia (2010). The SGF contained 4.0 g sodium chloride, 14 ml of concentrated hydrochloric acid and 26.6 ml of 30% N, N-dimethyldodecylamine-N-oxide diluted in 2,000 ml water. The SIF contained 6.8 g KH2P, 0.944 g NaOH, and 13.3 ml of 30% N,N-dimethyldodecylamine-N-oxide diluted in 1,000 ml water and the pH was adjusted to 6.8. The receiving medium were sampled, diluted in isopropanol, and assayed by HPLC (Agilent 1200 HPLC system with an Agilent 300SB-C8 column) for CsA quantification. The mobile phase (water-acetonitrile-methyl tert-butyl ether: 40-55-5) was run at 1.0 ml/min at 60°C, and the UV–VIS detector was set at 215 nm. The experiments were repeated 3 times using 3 independently prepared samples and the averaged data were reported.

Transmission Electronic Microscopy (TEM)

The detailed morphology of the nanoemulsions and nanocomposite was examined in detail using high definition transmission electron microscope (JEM-2010HT, Hitachi, JAPAN) coupled with a GATAN 794 CCD detector. For the negatively stained samples, the emulsion was diluted about 100–500 times with water containing 2% PTA. For the positive stained samples, the emulsion was made using corn oil mixed with 5% of Lipiodol and diluted in water. The TEM sample grids were made by dropping a small aliquot of the samples onto 400-mesh copper grids coated with carbon thin film.

In Vivo Drug Absorption After Oral Administration

The *in vivo* study protocol was approved by the animal welfare and medical ethics committee of Shanghai Jiao Tong University School of Pharmacy. Male Sprague–Dawley rats (240–260 g) were purchased from Sino-British Sipper/BK Lab animal Ltd. They were allowed to acclimatize in the institutional animal housing facility for at least 7 days with free access to standard chow and water. To avoid food interference on drug absorption, rats were fasted for 12 h prior to the study. The nanocomposite emulsion or the Cremophor EL stabilized emulsion at the fixed dose of 15 mg/kg were given by gastric intubation. Blood samples (100 μl each) were drawn before the experiment and at 15 min, 30 min, 1 h, 1.5 h, 2 h, 3 h, 5 h, 7 h, 10 h, 12 h, and 24 h after the drug administration.

The collected blood samples were analyzed using a Waters Acquity UPLC system coupled with a triple quadrupole mass spectrometer (QTRAP 5500, Applied Biosystems) with TurboIonSpray source (ESI). Briefly, the whole blood samples were immediately added in 0.1 M ZnSO4 solution, mixed in cold acetonitrile, and stored at −20°C before analysis. Supernatants were collected after centrifugation at 15.6× 1,000 g at 4°C for 10 min, and directly injected into the LC-MS system for analysis. A UPLC® BEH C18 column (50.0 mm×2.1 mm, 1.7 μm) was used for separation set at 70°C using Methanol- 0.1% ammonium acetate (80: 20) as the elution phase. The flow rate was set at 0.5 ml/min. The Cyclosporine A peak was quantified at the positive ion m/z 1209.9 position.

The Plasma concentration-time curve of cyclosporine A was obtained and analyzed using the non-compartmental pharmacokinetic models in kinetica® (version 4.4). The C_{max} and T_{max} were determined and AUC from time zero to the last measured time point (AUC0-t) was calculated according to the linear trapezoidal rule.

Statistical Methods

All the data was presented as mean ± SD, and compared using two way t-test for pairs. Statistical differences were noted at probability levels of $*p<0.05$, and $**p<0.01$.

RESULTS

Characterization of Silica-Polymer Nanocomposites

The PMMA/silica nanocomposite material was supplied by the Wuxi Now materials Inc. They were obtained from *in situ* polymerization in the presence of silica. We had further purified the samples by repeated washing and pelleting using ultracentrifugation, in order to remove any smaller molecular weight surface active materials. The obtained nanocomposite materials were characterized using various physicochemical methods and demonstrated distinctive features as shown in Fig. 1. Both the TEM (Fig. 1a) and size and zeta-potential measurements (Fig. 1b) indicated the nanocomposites were mainly spherical particles with mean diameters less than 200 nm and surface potentials around −45 mV. The FTIR spectrum (Fig. 1c) showed strong peaks at 1,461 cm-1, 1,737 cm-1, and 2,963 cm-1, indicative of the methyl, carboxyl, carbon-hydro bond in methoxyl group in methacrylic acid ester. But based on the TGA analysis (Fig. 1d), the nanoparticles were made of mainly organic polymers and only 5% of silica. The material's surface was wettable by both water and oil (Fig. 1e, f), suggesting the amphiphilic property of the particles. Indeed, the composite nanoparticles were easily dispersible in water as well as in oil as shown in Fig. 2.

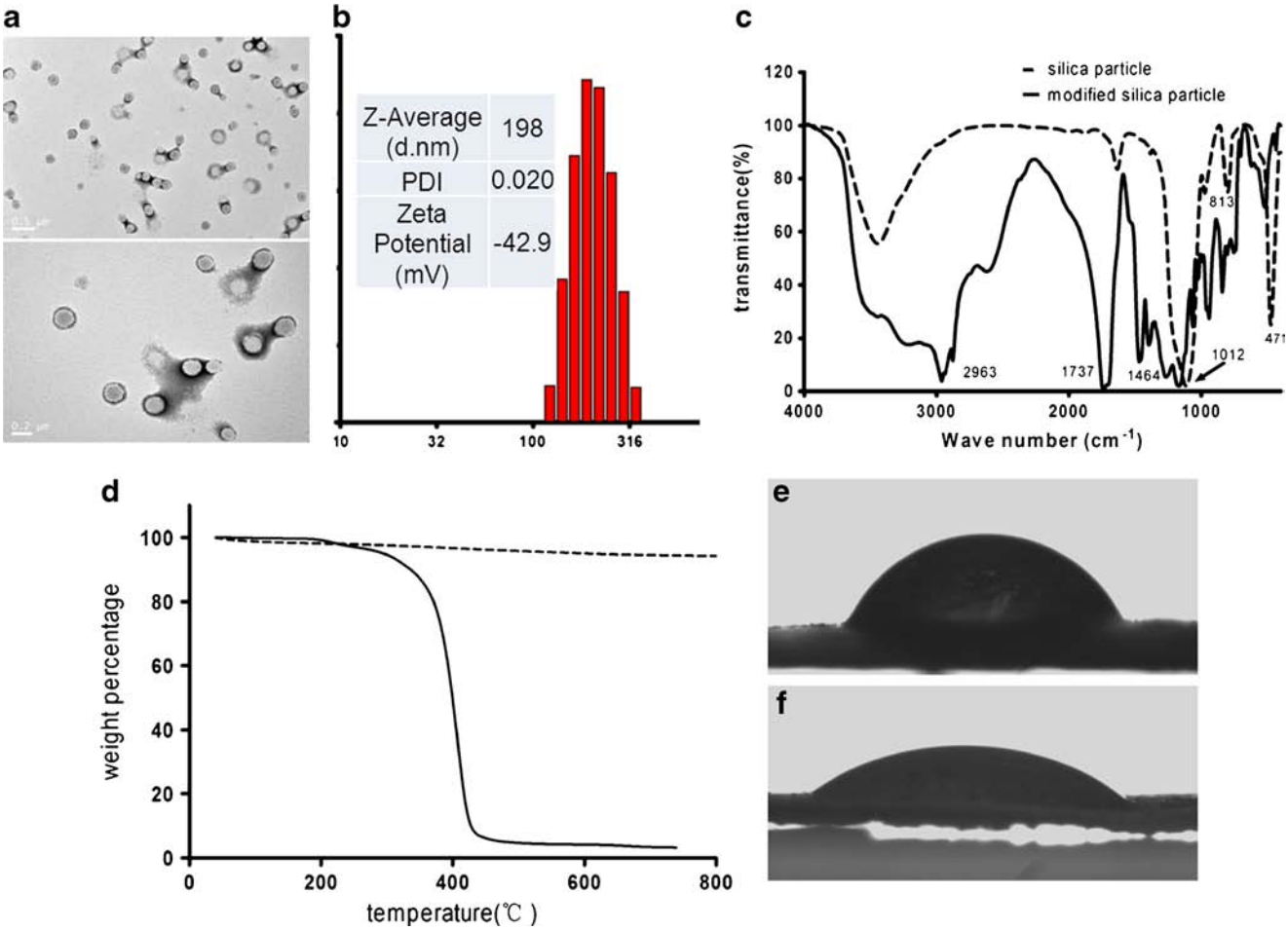

Fig. 1 General characteristics of the PMMA/silica nanoparticles. (**a**) TEM images of negatively stained samples. (**b**) size distribution and Zeta potential. (**c**) FTIR spectrum. (**d**) Thermogravimetric Analysis. (**e**) Contact angle of water droplet on the nanoparticle pellet. (**f**) Contact angle of oil droplet on nanoparticle pellet.

Preparation and Characterization of the Composite Nanoemulsions

The composite nanoparticles were dispersible in both aqueous solution and in oil. As shown in Fig. 2a, after added in corn oil, the composite particles would adsorb the oil to show a semi-solid texture. Addition of excess water and disruption by physical forces could break up the semi-solid oil into nano-sized oil droplets. On the other side, the composite nanoparticles can also be easily dispersed in water, and such suspension can be used to disperse and stabilize oil droplets as well. These resulted oil in water dispersion were called composite nanoemulsion in this study.

The mean droplet diameters and PDI of the nanoemulsions containing different oil phase volume and different composite particle concentration were summarized in Fig. 2b. Most nanoemulsion droplets had average sizes of around 250 nm. The more composite nanoparticles added, the smaller the droplet sizes. The less volume of oil phase to be dispersed, the smaller the droplets. Fig. 2b plotted the droplet mean sizes and PDI of o/w = 1/4 and 1/9 emulsions containing different amount of composite particles. They both indicated the emulsions were better dispersed and more homogeneous with the presence of more composite particles.

Stability of the Composite Nanoemulsions

The 1:4 and 1:9 o/w emulsions containing different amount of composite nanoparticles were subjected to stability tests using ultracentrifugation force, low pH medium, or repeated freeze-thaw treatments. The nanoemulsions were visually inspected first after treatment. Only those that didn't show any phase separation or distinguishable changes were further examined for the microscopic size changes (Table I). The composite nanoemulsions had showed remarkable stability when compared to traditional emulsion formulations. Only about 5% of the composite nanoparticles were sufficient to stabilize the nanoemulsion droplets against various disruptive forces.

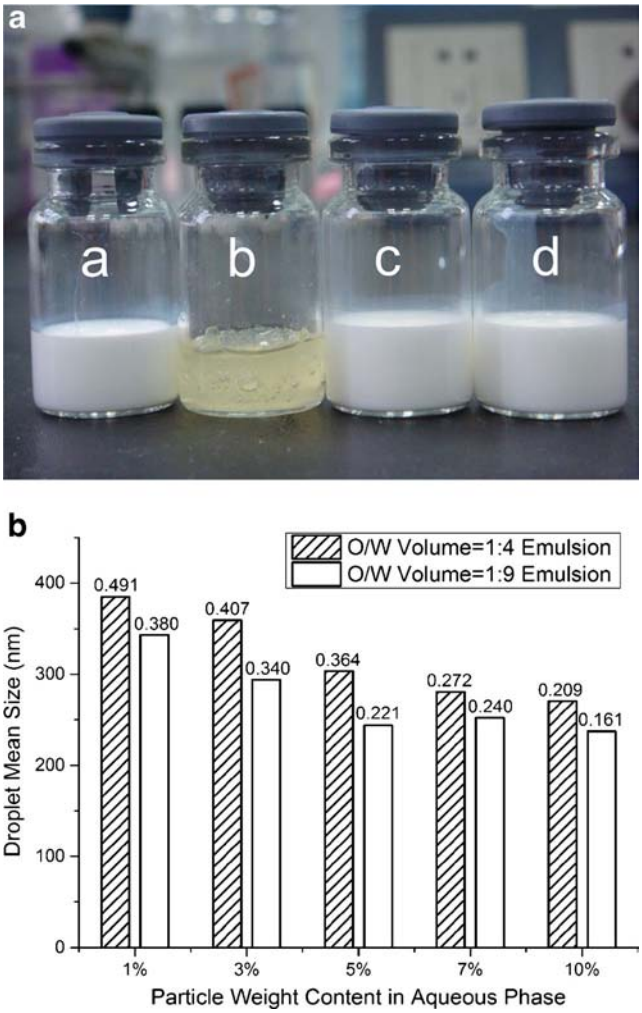

Fig. 2 (**a**) The visual appearance of the nanoparticle suspensions and nanoemulsion. *a*) PMMA/silica nanocomposites in water. *b*) PMMA/silica nanocomposites in oil. *c*) oil in water nanoemulsion (o/w = 1/9). *d*) oil in water nanoemulsion (o/w = 1/4). (**b**) The mean droplet sizes of o/w = 1/4 and 1/9 emulsions containing different composite particle weight concentration (1%, 3%, 5%, 7%, 10%). The PDI of these were labeled on the column top.

TEM Examination of the Composite Nanoemulsion Droplets

The microscopic features of the nanoemulsion were expected to be different from those of emulsion stabilized by traditional surfactants. TEM was used to investigate the special features. Negative staining using PTA was employed to improve the contrast. As shown in Fig. 3, the droplets were nano-sized and spherical in general. But higher magnification images revealed that the oil phase was not homogenous, and the droplet surfaces were not smooth either. There were always some small domains inside or on the surface of the oil droplets (Fig. 3). The pictures shown were taken at different time on samples that may be prepared with slightly different staining and transfer procedures, the background and imaging angles may vary as well.

Nevertheless we could display and compare the pictures side by side in Fig. 3 and propose that the PMMA/silica nanoparticles may have provided the general framework of the droplets and divided the droplets space into smaller domains. Oil molecules would adsorbed in between the more hydrophobic polymer chains, while the more hydrophilic polymer chains also self-assemble into aqueous domains and partition near the oil/water interface. Since there were only very small amount of silica (5% wt.) present in the composite nanoparticles, we didn't find any structure under TEM that was distinctively indicating SiO_2.

In order to depict the possible internal structures of the composite nanoemulsion, we tried to use different staining methods to prepare the TEM samples to improve the imaging contrast. One method was to mix 5% of iodinated oil into the refined corn oil when making the nanoemulsions. Because of the higher electron density of iodine, the oil phase would be darker than the aqueous background (positive staining). Both the positive staining EM pictures and negative staining EM pictures were displayed in Fig. 4. From all the images, we could clearly see fine structures at the oil/water interface

Table I Stability of the Composite Nanoemulsion

Oil–water volume ratio(φ)	Aqueous phase solid content	Original size(PDI)	Low pH	Centrifugation	Frozen-thaw cycles
20%	1%	385.2(0.491)	-	-	-
	3%	359.6(0.407)	-	-	-
	5%	303.5(0.364)	561.3(0.675)	-	-
	7%	280.6(0.272)	442.7(0.359)	275.1(0.273)	290.0(0.305)
	10%	270.4(0.209)	307.4(0.326)	258.3(0.211)	252.1(0.199)
10%	1%	343.3(0.380)	-	-	-
	3%	293.8(0.340)	-	-	-
	5%	243.9(0.221)	327.3(0.322)	-	-
	7%	252.1(0.240)	263.1(0.258)	258.0(0.287)	249.7(0.278)
	10%	237.3(0.161)	230.8(0.204)	228.8(0.171)	220.3(0.139)

"-" represents phase separation

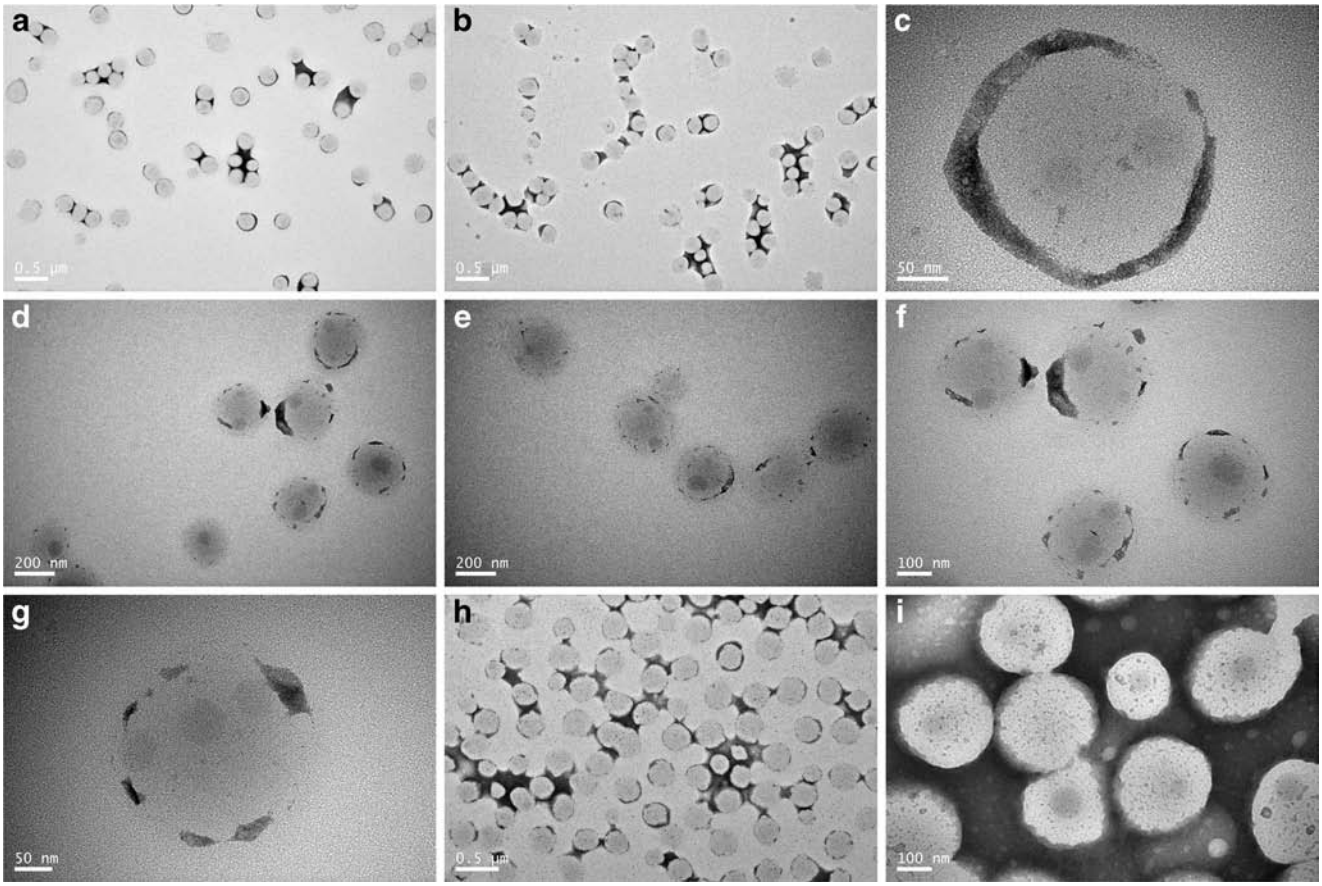

Fig. 3 Representative TEM images of composite nanoemulsions. The emulsion samples were diluted 100–400 times in water and negatively stained using PTA.

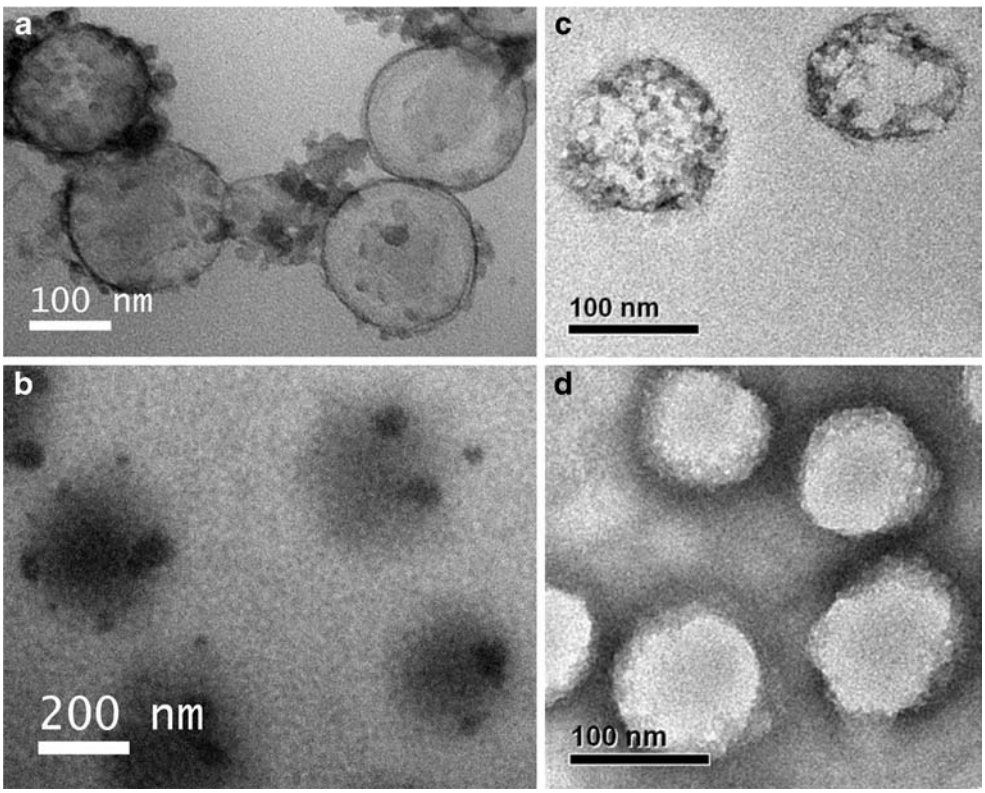

Fig. 4 TEM images of nanoemulsion droplets under different contrast staining conditions. (**a**, **b**) Emulsion droplets containing 5% lipiodol and no other staining; (**c**, **d**) Emulsion droplets negatively stained using PTA.

suggesting the polymer chains on the nanocomposite were essential for emulsion droplet stabilization.

Drug Release from Nanoemulsions in SGF and SIF

In vitro drug release assays were performed using SGF and SIF containing N, N-dimethyldodecylamine-N-oxide. The drug release profile in SGF was only monitored for an hour considering the limited gastric residence time. 3% Cremophor EL emulsions releases almost all drug content within 30 min as expected based on prior studies. Our composite nanoemulsion, however, only released less than 20% after an hour (Fig. 5a). Drug release in SIF was also evaluated for a longer period of time as shown in Fig. 5b. Again, the composite nanoemulsion was quite stable with only 30–40% of the drug released in 4 h.

Plasma Drug Concentrations Resulted from Oral Administration of the Emulsions

The cyclosporine A blood concentration-time profiles following single dose oral administration of the different emulsion formulations were examined and plotted in Fig. 6. The two emulsions had drastically different profiles. The Cremophor EL emulsion showed the typical SEDDS absorption profile, with a quick concentration spike within 2 h of administration. The composite nanoemulsion, on the other hand, had an interesting sustained release and accumulation profile. The pharmacokinetic parameters were summarized in the insert table. The C_{max} of the composite nanoemulsion was higher than the conventional Cremorphor EL emulsion. More importantly, The T_{max} had reached 8.50 ± 1.73 h.

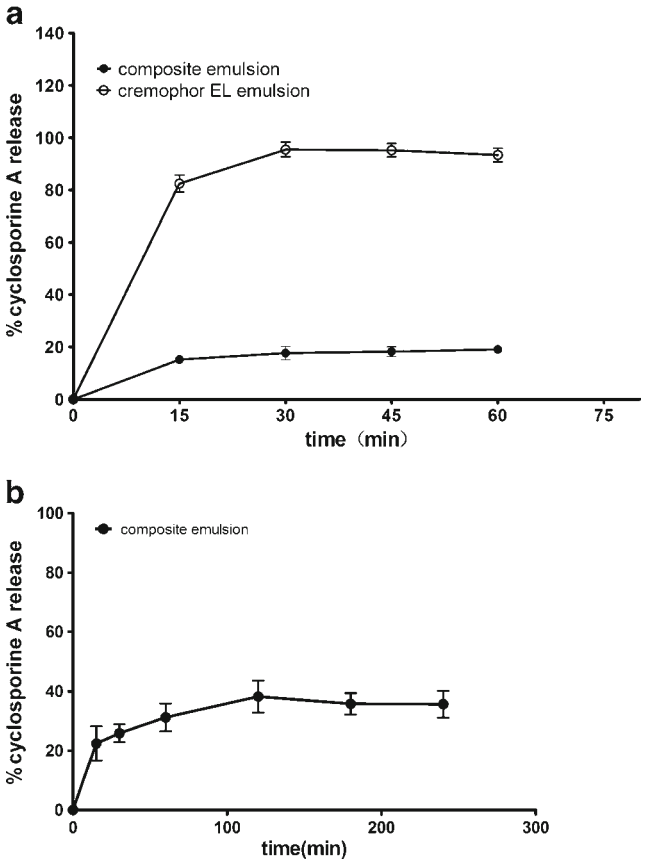

Fig. 5 (**a**) *In vitro* drug release profile from composite nanoemulsions in SGF. (**b**) *In vitro* drug release profile from composite nanoemulsions in SIF.

DISCUSSION

Emulsions are typically stabilized by surface active agents (surfactants) that partition at the oil/water interface (22). The finer size of the droplets, the bigger oil/water interface area, and the more surfactants are needed (23). For microemulsions and nano-emulsions that are preferred in pharmaceutical formulations, surfactants are essential for maintaining the formulation stability, dose proportionality, and bioavailability (24). Especially for most self-emulsifying formulations (SEDDS and SMEDDS), large amounts of surfactants may be required in order for the generation and maintenance of nano-sized oil droplets under mild GI agitation (25). In the Sandimmune Neoral SMEDDS formulation, surface active agents accounted for an almost 50% of the dose (26,27).

But on the other hand, surfactants especially small molecular weight surface active molecules can readily partition into other interfaces such as cell membranes and protein folding structures, resulting in protein denaturation and even cell lysis (28). Larger molecular weight surfactants that have slower inter-surface exchange rate and also lower CMC values were considered safer. But their dispersion and partition into oil/water interfaces require higher energy input so those emulsions had to be pre-made using industrial processes including high shear homogenisation and solvent evaporation (29).

Compared to emulsions stabilized by larger molecular weight surfactants, Pickering emulsions that contain solid particles without any surfactants had also been reported to be even more stable and inert when interacting with biological fluids (30). Inorganic particles such as silica, clay, calcium carbonate, titanium dioxide could all be used to generate Pickering emulsions with distinctive properties. Depend on the surface properties of the solid particles, w/o or o/w emulsions may be resulted. The solid particles were proposed to form a dense shell around oil droplets to be able to stabilize the oil/water interface and prevent coalescence (31). Therefore pickering emulsions could be exceptionally stable at high concentrations, with the presence of electrolytes, and even can be safely dried and re-dispersed (32,33).

There have been quite a few paper published recently describing Pickering emulsion drug formulations based on silica nanoparticles (34,35). They were mostly made for topical use and the emulsions were micro-sized. Both o/w or w/o

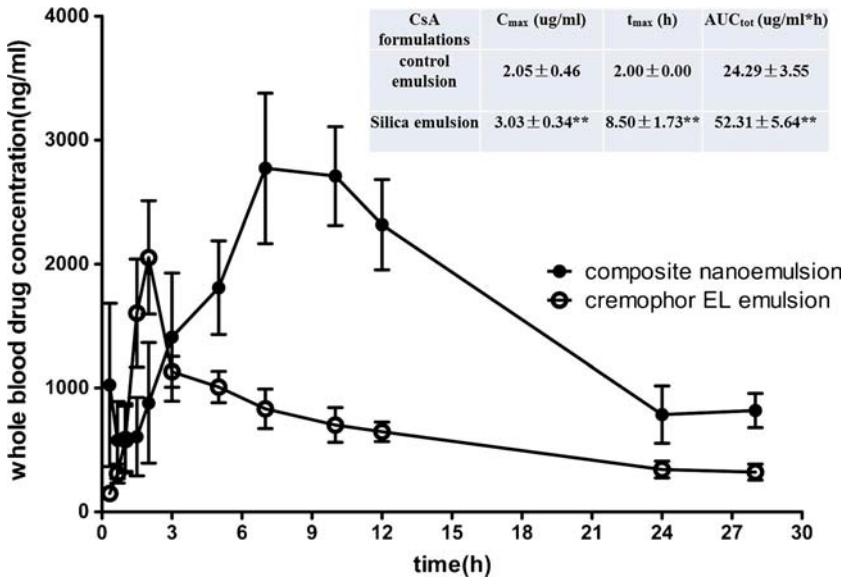

Fig. 6 The cyclosporin A blood concentration profiles after oral administration. The C_{max}, T_{max} and AUC results calculated based on these curves were also listed.

Pickering emulsions loaded with hydrophobic or hydrophilic drugs were reported with improved adhesion to the skin and deep penetration into the stratum corneum. There was less small molecule surfactant needed, which would imply less irritation and skin damage (34,35). In addition, another distinctive feature of these Pickering emulsions was that the drug release rate could be modulated. Simovic and Prestidge (2007) described a rigid shell structure model of the stabilizing silica layer and suggested the correlations of drug release rate with shell thickness and density (36). The shell made of solid nanoparticles was estimated to have ten times greater barrier effect than those made of typical polymeric stabilizers. Therefore it may be possible to engineer the nanoparticle layers to enable a range of release behaviors and offer great potential in the delivery of poorly soluble drugs.

In this study, we used a PMMA/silica composite nanoparticle which is a bit different from the more commonly used inorganic solid nanoparticles. The resulted emulsion is also different, both in terms of size and structure. Since the nanocomposite particles were already ~200 nm in diameter and the emulsion droplets were only slightly bigger, we propose that the oil phase was mostly "soaked in" rather than encapsulated. Based on the TEM images, there must be certain areas inside the droplets that were oil rich and the oil/water interfaces were not smooth and homogenous either. We would like to compare our structure to the one proposed by Capron and Cathala when they used Cellulose Nanocrystals (CNC) to prepared "Surfactant-Free High Internal Phase Emulsions" (37). Although the emulsion droplets they prepared were bigger than 10 μm and their purpose was to load as much oil as possible. There was neither microscopic structure nor stability data presented. But they estimated by calculation that it's not necessary for the nanoparticles to cover all the oil/water interface for the stabilization effect. We could do similar calculations using the size and surface area of the droplets and nanoparticles. There were not enough nanoparticles to cover half of the oil/water interface, definitely not possible to form a dense shell.

Despite the distinctively different structure, our composite nanoemulsion did show some great features similar to Pickering emulsions. It's exceptionally stable, at high concentrations (with strong mechanical force), at extreme pH conditions, and even with freeze and thaw cycles. In addition, drug release from the droplets in both SGF and SIF were greatly deterred, compared to that of the conventional cremophor emulsions. Almost all other nanoemulsion or nano particle formulations of cyclosporine up to date resulted fast drug release and absorption. Very few had attempted and achieved sustained release and prolonged systemic exposure. Yuan *et al.* described the advantages of linker stabilized micro-emulsions for extended release of lidocaine after topical use (38). But for oral administration, it would be even harder because of the harsh digestive fluids could be highly disruptive. Only our composite nanoemulsion is very special, because it could not only withhold the many mechanical and chemical disturbances, its drug release profile in the digestive tract was also unique. We think those stable nanoemulsion droplets may be taken up based on a different mechanism, resulting in the completely different PK profile as shown in Fig. 6.

There have been many studies proposing unique mechanisms of oral uptake of nanoparticles *in vivo*. Some drugs in nano particles may be taken up through the peyer's pathes into mucosa associated lymph tissue (MALT) and distributed via the lymph circulation. But most nanoparticles are not stable enough to keep the drug inside to take advantage of such a mechanism. Especially for conventional nanoemulsions, the surfactants maintain the oil–water interface could be quickly dissolved and replaced by biles and other digestive molecules.

The drugs were quickly released. The intestinal permeability enhancement effect sometimes observed using SEDDS may be attributed to damage to the intestinal epithelial barrier (39). The PK profile usually remained the same. Only in our study, we observed completely different PK profiles, suggesting the possibility of a new lymphatic uptake mechanism. This would also explain the gradual accumulation and prolonged systemic exposure observed. Cyclosporin A is a substrate of P-gP and could be quickly metabolized by CYP3A4 and CYP3A5 in the liver. The lymphatic uptake mechanism may help to bypass some of these degradation and elimination pathway, and therefore achieve greatly improved bioavailability.

To summarize, we think our novel nanoemulsion formulation may have combined advantages of detergent stabilized nanoemulsions and solid nanoparticle stabilized formulations. It can be easily made into nano size, but at the same time offer great stability and controlled drug release rate. We think this nanoemulsion may have significant advantages as oral formulations for poorly soluble drugs.

ACKNOWLEDGMENTS AND DISCLOSURES

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Wenqiang Sun and Xinrui Ma contributed equally to this work and should be considered co-first authors.

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