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Evaluation of Organogel Nanoparticles as Drug Delivery System for Lipophilic Compounds

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Abstract. The purpose of the study was to evaluate organogel nanoparticles as a drug delivery system by investigating their stability, according to the formulation strategy, and their release profile. The gelled nanoparticles were prepared by hot emulsification (above the gelation temperature) of an organogel in water, and cooling at room temperature. In the first step, we used DLS and DSC to select the most suitable formulations by optimizing the proportion of ingredients (HSA, PVA, castor oil) to obtain particles of the smallest size and greatest stability. Then, two lipophilic drug models, indomethacin and ketoconazole were entrapped in the nanoparticles made of castor oil gelled by 12 hydroxystearic acid. Thermal studies (DSC) confirmed that there was no significant alteration of gelling due to the entrapped drugs, even at 3% *w/w*. Very stable dispersions were obtained (>3 months), with gelled oil nanoparticles presenting a mean diameter between 250 and 300 nm. High encapsulation efficiency (>98%) was measured for indomethacin and ketoconazole. The release profile determined by *in vitro* dialysis showed an immediate release of the drug from the organogel nanoparticles, due to rapid diffusion. The study demonstrates the interest of these gelled oil nanoparticles for the encapsulation and the delivery of lipophilic active compounds.

KEYWORDS: Drug delivery; Indomethacin; Ketoconazole; Organogel nanoparticles; 12 hydroxystearic acid.

INTRODUCTION

Interest in the use of colloidal lipid dispersions as drug carriers for poorly water soluble drugs is rising. Systems including a lipid matrix are particularly under study as they allow a higher drug loading of lipophilic drugs [1, 2]. These lipid core drug carriers can be composed of liquid lipids, e.g., nanoemulsions, solid lipids, e.g., solid lipid nanoparticles (SLN), or even a mixture of both, e.g., nanostructured lipid carriers (NLC) [3]. Many examples in the literature illustrate the potential of these lipid nanoparticles for drug delivery, in particular for oral and topical routes [4 6]. However, their development can be limited by drug encapsulation issues. Higher drug contents can be obtained in nanoemulsions by increasing the percentage of the oil phase, but such disper sions require the use of large amounts of surfactants [7]. SLN can be formulated at high lipid concentrations (up to 30% oil phase) with reasonable surfactant concentrations as high stability is provided by the use of a solid matrix [8]. However, the drug compounds to be encapsulated are generally poorly soluble in the lipid matrix and can be expelled because of polymorphic transitions following lipid crystallization [9]. The development of NLC has successfully decreased drug leakage during storage by the inclusion of liquid lipids in the solid matrix but this complicates the formulation process [2].

Organogels are an interesting family of gelled oil based materials with great potential in the pharmaceutical field and particularly for drug delivery [10 12]. Consequently, many studies have been reported in the literature, but the majority of them describe the use of organogels as matrix implants or more recently coated microparticles for drug delivery [13 16].

Dispersions of organogel in aqueous solution of stabiliz ing agent have led to a new type of semi solid colloidal dispersion, halfway between nanoemulsions and SLN. Prep aration of the so called o*rganogel nanoparticles* is solvent free, with a simple hot dispersion and homogenization procedure using an ultrasound probe or Ultraturrax® tech nique [17 19]. In previous studies, we developed organogel dispersions based on 12 hydroxystearic acid (HSA), a well known low molecular weight organic gelator (LMOG) com monly used in cosmetic formulations [17, 18]. HSA has shown an efficient gelling capacity over a broad variety of oils,

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including vegetable oils. We demonstrated an enhanced stability from organogel nanoparticles compared to emulsions (0% HSA) as well as their capacity to encapsulate a lipophilic compound [20, 21]. Furthermore, high drug loading can be obtained with stable dispersions of up to 23% vol. of oil phase, which make organogel nanoparticles a promising vehicle for lipophilic compounds [17]. To date, only a very few studies have been conducted on the use of organogel based dispersion as vehicle of lipophilic compounds, and there is still no clear evidence of the release behavior of such systems [20 24].

The aim of this study was to evaluate HSA organogel nanoparticles as a drug delivery system by conducting stability studies and assessing their release profile by *in vitro* release experiments.

In the first step, the influence of the proportions of stabilizing agent (polyvinyl alcohol) and organogel dispersed on the size and stability was investigated, in order to select the optimal formulation in view of the encapsulation studies. We prepared organogel nanoparticles based on castor oil and loaded with one of two lipophilic drug models indomethacin (INDO) or ketoconazole (KCZ). These two compounds are commonly used as models for *in vitro* dissolution studies as they show distinct ionization behavior and pH dependent solubility. They also present thermal stability compatible with the preparation process of the gelled particles (Table I). In addition, INDO and KCZ have already been studied in other lipid nanoparticulate systems and have shown promising results for several pharmaceutical applications, such as skin or oral delivery [25 27].

MATERIALS AND METHODS

Materials

Indomethacin (INDO, 99% p), Ketoconazole (KCZ, 99% p), castor oil and 80% hydrolysed polyvinyl alcohol (PVA, 98% p, Mn = 8000 10,000 g/mol) were purchased from Sigma Aldrich (USA). 12 Hydroxystearic acid (HSA, 85% p) was obtained from Alfa Aesar Gmbh (Germany). Ultrapure water was used to prepare the dispersions. All other reagents were of analytical grade.

Preparation Of Gelled Oil Nanoparticles

Gelled oil nanoparticles were prepared according to the protocol described by *Kirilov et al.* [17], with some modifica tions. Preparation was based on the hot dispersion of an organogel, forming emulsion droplets that led to organogel nanoparticles after cooling. Castor oil was used to prepare the organogels according to preliminary solubility assays showing the best results for INDO and KCZ. Organogels were prepared by adding HSA a low molecular weight organic gelator to castor oil. The mixtures were placed in an oven and heated at 90°C until complete dissolution of the HSA, then cooled at room temperature to form a compact, translucent gel. Organogels loaded with INDO or KCZ were prepared by initially dissolving 3% (*w/w*) of the drug in castor oil. Unloaded organogels (*blanks*) were also prepared.

A solution of PVA was used as a non ionic stabilizing agent for the dispersion of the organogel. The mixture was heated to 90°C in an oven for 1 h until the organogel melted, leading to an oily layer at the surface of the solution. The hot mixture was immediately emulsified by sonication (Vibracell, Bioblock Scientific with a titanium probe, 20 kHz, 600 W) for 10 min. Cooling at room temperature then led to a colloidal dispersion of organogel nanoparticles.

Particle Size, Polydispersity Index, And Zeta Potential Analysis

The particle size and dispersity (Đ) of the dispersions were assessed by dynamic light scattering (DLS) on a Malvern Instruments (Ireland) Nano ZS with a He Ne Laser (633 nm) at a scattering angle of 173° and at 25 ± 1°C. The mean hydrodynamic diameter was calculated using the software provided by Malvern Instruments, applying the Contin model to obtain data. Zeta potential measurements were made on the same apparatus by means of an electrophoretic light scattering technique at 25 ± 1°C. Both measurements were made on diluted samples (5 mg of dispersion in 3 mL of distilled water) of INDO, KCZ, and Blank dispersions.

Differential Scanning Calorimetry Of Organogels

The influence of drug loading on the gelation properties of organogels was assessed by differential scanning calorim etry (Mettler Toledo, Viroflay, France) experiments. Castor oil organogels were prepared (Blank, INDO, KCZ), then 5 20 mg samples were placed in hermetically sealed aluminum pans. DSC runs were carried out with two heating cooling cycles between 10 and 90°C at a constant rate of 3°C per minute, and with an empty aluminum pan used as reference. The sol gel transition temperatures (T_{gel}) and gel sol transi tion temperatures (T_{melt}) were determined on thermograms with the STARe software provided by Mettler Toledo, and using *onset* temperatures. ($n = 4$).

Quantification Of Drug Content In Organogel Nanoparticles

The INDO and KCZ contents of organogel nanoparticles were determined in two steps. The *total drug content* was determined by dissolving an accurately weighed aliquot of organogel nanoparticles dispersion (100 mg) in 10 mL of methanol, followed by UPLC analysis. Then, the non incorporated fraction of the drug, or *aqueous drug content*, was determined after separation of the aqueous phase by ultracentrifugation/ultrafiltration (Microcon Ultracel YM 100, Millipore, Ireland). The clear ultrafiltrate obtained was diluted with methanol (1/10) before UPLC analysis. Encap sulation efficiency (EE) was finally calculated as follows:

$$EE\,(\%) = \frac{\text{Total drug content }(\mu g)\ \text{free drug content}(\mu g)}{\text{Total drug content }(\mu g)}$$
$$\times 100$$

$$(1)$$

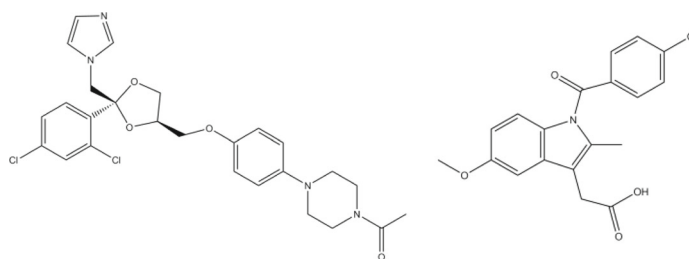### Formulation Selection and Stability Measurements

The formulation of organogel dispersions intended for the encapsulation study was selected in two steps. First, a

Table I. Physicochemical characteristics of ketoconazole and indomethacin

	Ketoconazole	**Indomethacin**
Ionization behaviour	Dibasic	Weak acid
Solubility in water (pH 6.8)[a]	5 µg/mL	565 µg/mL
pKa[b,c]	6.5 and 2.9	4.5
LogP[b,c]	3.8−4	3.4−4.3
Thermal stability[d,e]	>105°C	>200°C

[a] Determined by saturation method. An excess amount of drug was stirred for 24 h at 37°C, followed by syringe filtration (0.45 µm) and UPLC analysis
[b,c] [28, 29]
[d,e] [30, 31]

study was conducted on *blank* castor oil organogels in order to determine the right HSA percentage to obtain gelled oil particles of sufficient strength and stability. Series of castor oil organogels ($n = 3$) were prepared at the following HSA concentrations: 4, 5, 7, 10, 12, 15, 20, and 25% (*w/w*), and subjected to DSC analysis. Transition temperatures (T_{gel} and T_{melt}) were calculated on DSC thermograms using *onset* temperatures and were then represented on a phase diagram. Once the HSA organogel concentration was fixed, two series of *blank* organogel dispersions were prepared with various PVA amounts: 0.5, 1, 2, 5% (*w/w*) and different proportions of phase of organogel dispersed: 5, 10, 20, 30% (*w/w*). The stability of the dispersions, kept in sealed glass bottles at 4°C, was assessed over a period of 28 days with combined DLS measurement and macroscopic observations scheduled at different times: initial time, 1, 7, and 28 days. Formulations were judged stable if no changes in particle size and no visual destabilization creaming, phase separation, or presence of compact aggregates were observed. Proportions of PVA and gelled oil phase (OG) that gave dispersions of small size and excellent stability were selected.

The stability of the organogel nanoparticles loaded with INDO or KCZ was assessed by determining drug encapsulation and particle size over a period of 3 months. This was performed on three different batches of each formulation, which were kept in sealed glass bottles at 4°C.

Morphological Study

The morphology of castor oil organogel nanoparticles was determined by transmission electron microscopy (TEM) (JEOL JEM 1200EX, 70 kV). Diluted samples (5 mg of dispersion in 5 mL of ultrapure water) were deposited on copper grids and negatively stained with a sodium phospho tungstate solution (1%, pH 7).

Drug Release Experiments

The drug release profile of the dispersions was charac terized by equilibrium dialysis in triplicate. Dialysis bags (MWCO membrane, 6000 8000 Da, Spectrum Labs) were filled with 15 mL of fresh organogel dispersions, then suspended in 600 mL of release medium under 300 rpm magnetic rotation at 37°C. At scheduled intervals, 1 mL of release medium was collected for UPLC analysis, a constant volume of release medium being maintained by addition of fresh buffer. Drug concentration at each interval was converted to release percentage by considering the initial concentration of drug in the formulation, also determined by UPLC.

Dialysis with KCZ organogel nanoparticles was carried out with release media of various pH, with extreme values corresponding to gastric (NaCl 0.05 M, HCl pH 1.2) and

intestinal conditions (Phosphate buffer 0.1 M, pH 6.8). Intermediate buffers of pH 4, pH 5, and pH 6 were also prepared with different volume ratios of acetic acid/sodium acetate 0.1 M solutions. Formulations in the dialysis bag were previously diluted with the corresponding buffer medium to a drug concentration of 0.1 mg/mL.

Dialysis with INDO organogel nanoparticles was carried out with pH 6.8 buffer. The dialysis experiment was performed on control groups in the same conditions with either INDO dissolved in buffer medium at 0.1 mg/mL or INDO dispersed as a suspension in the buffer medium at 1.0 mg/mL. For this part, drug concentration at each interval was converted into release rate, corresponding to the amount of drug released per unit of time.

In complement to the dialysis study, a simple release study was performed by diluting INDO organogel nanopar ticles in pH 6.8 buffer at a volume ratio of 1:5 or 1:50, and stored either at 4 or 37°C for 48 h. The proportion of INDO released was determined by assay of the aqueous phase separated by centrifugation filtration. The release was also studied on non diluted samples in similar experimental conditions.

Ultra Performance Liquid Chromatography Analysis

Samples from dialysis and encapsulation experiments were analyzed by UPLC using a *WATERS Acquity H Class system* combined with a UV detector. Separation was performed through an Acquity UPLC BEM C18 (1.7 µm; 2.1×50 mm) column maintained at 40°C. Quantification of KCZ used a mobile phase of acetonitrile:ammonium acetate 10 mM (60:40), with a flow rate of 1 mL/min and UV detection at 220 nm, while INDO was quantified with a mobile phase of acetonitrile:formic acid 0.1% (60:40), with a flow rate of 1 mL/min and UV detection at 265 nm. Calibration curves were established with external solutions (from 10^{-7} to 10^{-4} M) of INDO and KCZ in acetonitrile.

RESULTS AND DISCUSSION

Optimal Formulation Selection

Firstly, it was necessary to determine the most suitable composition of the basic ingredients of the formulation. The main ingredients were the organogelator (HSA), the castor oil, and the water containing the stabilizing agent (PVA). The amount of HSA was the first parameter conditioning the gelation temperature and the hardness of the organogel. A DSC study investigated the influence of HSA concentration on sol gel transition temperatures ($\underline{T}_{gel}$) and gel sol transi tion temperatures (T_{melt}) of the organogel (Fig. 1). Hysteresis was seen between T_{gel} and T_{melt}. The hysteresis diminished continuously as more HSA was added and was thus consid ered to be linked to the strength of the organogel. However, stability problems had been observed previously with an excess of organogelator [21]. Then, the formulation with 15% *w/w* of HSA was selected as it showed appropriate mechan ical strength with T_{gel} and T_{melt} above 37°C (physiological temperature).

We then investigated the influence of the amount of organogel dispersed and the PVA percentage on the mean
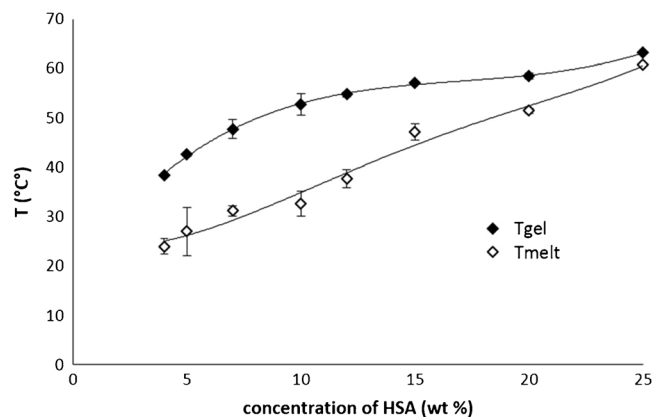

Fig. 1. Sol gel and gel sol transition temperatures of HSA organogels

diameter of the particles (Fig. 2a). As expected, the particle size variation of the dispersions was strongly correlated to the amount of stabilizing agent used [32]. Indeed, at high organogel content, the concentration of PVA was not sufficient to stabilize smaller droplets and a reduction in particle size was observed when more PVA was added in the dispersant phase. Interestingly, as shown in Fig. 2b, it was possible to correlate directly the size of the dispersions to PVA/OG ratio regardless of organogel content. For instance, three different dispersions formulated at the same PVA/OG phase ratio of 0.1 showed similar size dispersion of 400 nm. Dispersions tended to reach a limit in terms of particle size when high amounts of stabilizing agent (PVA) were used. This is probably inherent to the dispersion method by sonication which does not provide enough energy to produce smaller particles [33]. A ratio of 0.2 appeared to be an optimal ratio to provide good stability and limit the addition of surfactant. Stabilities of the dispersions assessed by visual/ macroscopic observations combined with DLS measurements are summed up in Table II. Dispersion stability was directly correlated to the proportions of PVA employed. Stable formulations (no creaming or aggregates before 1 month) were achieved with PVA/OG phase ratios equal to at least 0.1. On the other hand, formulations with ratios below 0.05 could not lead to stable dispersions. Considering all these results, we selected a formulation with 10% OG dispersion in 2% PVA. This formulation should provide small sized organogel nanoparticles of excellent stability and limit the use of stabilizing agent.

Influence Of Drug Loading On Gel Formation

DSC experiments were carried out in order to provide information about the thermal properties of the organogel and the influence of the two loaded drugs (3% *w/w*). This study was done with organogels and not dispersions as previous inves tigation by rheology had shown similar sol gel transitions between organogels and organogel dispersions [17].

The influence of drug on gel formation was assessed, as plotted on Fig. 3, which shows DSC heating and cooling thermograms of unloaded, INDO loaded, and KCZ loaded organogels. During cooling, *onset* temperatures correspond ing to sol gel transitions (T_{gel}) were 55.8 (±1.8), 52.1 (±1.2)
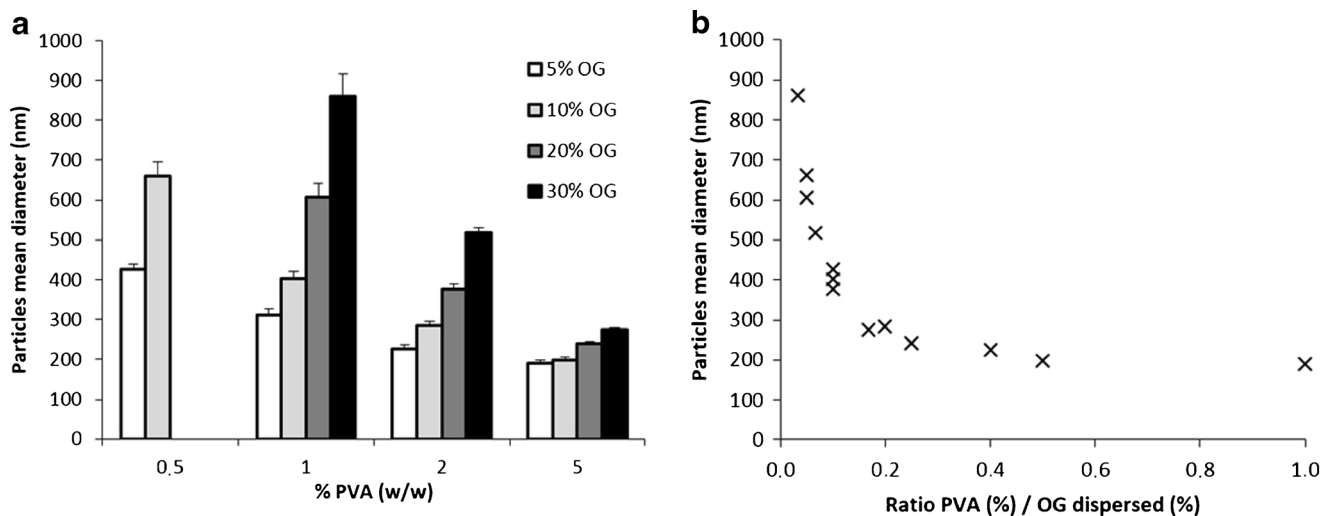
Fig. 2. a Mean diameter of the particles obtained by DLS from 5, 10, 20, and 30% organogel dispersions according to the PVA percentage. **b** Mean diameter of the particles according to the PVA (%)/OG dispersed (%) ratio

and 54.4°C (±0.6) for unloaded, INDO and KCZ organogels, respectively. Thus, drug loading did not interfere with the gelation process to any great extent.

A small interference was also observed during heating, with gel sol transition temperatures (T_{melt}) of 45.0 (±3.8), 39.8 (±2.0), and 41.4°C (±1.3) for unloaded, INDO and KCZ organogels, respectively.

When heating and cooling transitions were compared, significant hysteresis was observed between T_{gel} and T_{melt} for each organogel. In a previous study, similar DSC experiments with soybean oil organogels loaded (0.06% *w/w*) with a highly lipophilic compound, chloroaluminium phthalocyanine (ClAlPc), had shown that the gelation process was affected by drug loading [21]. Nevertheless, in the present study, limited gelling alteration was observed with KCZ or INDO, despite higher drug loading (3% *w/w*). This could be explained either by the entrapment of less hydrophobic compounds or by the use of a large amount of gelator in our formulations.

Stability Of Gelled Oil Nanoparticles

The characteristics of gelled oil nanoparticles over a storage period of 3 months at 4°C are shown in Table III. The mean diameter of the gelled oil nanoparticles did not seem to

Table II. Stability by visual assessment (no creaming or aggregates) at °C of organogel nanoparticles according to organogel dispersed phase (%) and PVA (%)

		PVA			
		0.5%	1%	2%	5%
Organogel phase	5%	≥28 days	≥28 days	≥28 days	≥28 days
	10%	<28 days	≥28 days	≥28 days	≥28 days
	20%	Unstable	<28 days	≥28 days	≥28 days
	30%	Unstable	<7 days	<28 days	≥28 days

be influenced by drug loading, with values stable between 250 and 300 nm, and drug loading did not affect the size distribution according to Đ measurements. In addition, the stability of the organogel nanoparticles diluted in pH 1.2 and pH 6.8 buffers was assessed by DLS, and no changes in particle size were observed for at least 48 h. Zeta potential measurements showed similar negative surface charge for all formulations, due to the ionization of the carboxylic functions of the HSA present at the surface of the particles.

EE were determined to highlight possible drug leakage occurring during storage. Both INDO and KCZ organogel nanoparticles showed good drug entrapment results (Table III). EE was stable for a period of 1 month, with no significant drug leakage during this storage period. The small proportion of free drug in the water phase of the dispersion was probably due to initial leakage occurring during the hot dispersion phase of the organogel.

However, extending the stability test to a longer period (>3 months) revealed a slight decrease in EE for INDO organogel nanoparticles, pointing to possible drug leakage over longer periods. EE remained unchanged for KCZ organogel nanoparticles. This may be explained by the better
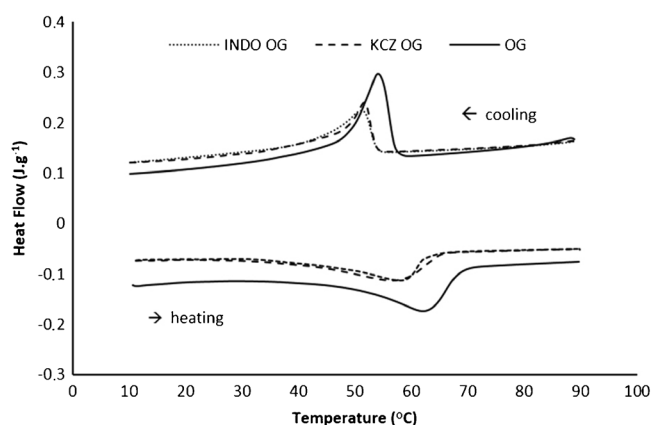

Fig. 3. DSC thermograms examples of unloaded and drug loaded (3% *w/w*) HSA (15% *w/w*) organogels

Table III. Stability assessment of gelled oil nanoparticles, 4°C (*n* 3), pH 7

		Mean diameter (nm)	Đ	ξ Potential (mV)	Encapsulation efficiency (%)
1 day	Blank	259 (±12)	0.32 (±0.05)	−34.7 (±5.8)	
	INDO	269 (±23)	0.31 (±0.12)	−36.7 (±6.7)	99.0 (±0.1)
	KCZ	282 (±28)	0.30 (±0.03)	−31.2 (±6.3)	98.4 (±0.1)
1 month	Blank	263 (±11)	0.23 (±0.02)	−37.8 (±6.7)	
	INDO	271 (±20)	0.28 (±0.07)	−32.4 (±5.8)	98.0 (±0.1)
	KCZ	267 (±15)	0.25 (±0.03)	−31.1 (±5.5)	97.4 (±0.1)
3 months	Blank	250 (±19)	0.23 (±0.03)	−37.2 (±6.6)	
	INDO	244 (±13)	0.26 (±0.05)	−30.0 (±5.6)	91.9 (±0.2)
	KCZ	266 (±16)	0.25 (±0.03)	−25.9 (±4.7)	97.4 (±0.1)

aqueous solubility of indomethacin leading to higher partitioning in the water phase. Thus, drug partitioning may be prevented by adjusting the pH of the dispersions. For instance, formulations of indomethacin in submicron emulsion or SLN were adjusted to pH 4 in order to favour the localization of the drug in the oil phase, thus leading to better entrapment efficiency [34, 35].

Morphological Study

The morphology and size of castor oil organogel nanoparticles were observed by TEM (Fig. 4). The images show spherical particles with diameters in accordance with the DLS measurements. We also observed that there is no differences (size and morphology), before and after drug encapsulation.

Drug Release Profiles Of Organogel Nanoparticles

Figure 5a shows the release profiles of KCZ organogel nanoparticles in release media of various pH. It was observed that KCZ release increased when the pH of the release medium was lowered, in accordance with the solubility profile of KCZ at different pH. KCZ solubility increased dramatically under acidic conditions because of the basicity of the molecule and its protonation. Consequently, the release of KCZ from organogel nanoparticles depends strongly on its solubility in the release medium.

Figure 5b compares the release profile of KCZ organogel nanoparticles with INDO organogel nanoparticles and reveals differences. Although INDO and KCZ have similar lipophilicity (LogP values in Table I), they exhibit strongly contrasting ionization behavior, leading to different solubility profiles. For instance, the solubility of INDO at pH 6.8 is a hundred times that of KCZ. As a result of these observations, we can conclude that organogel nanoparticle release is mostly dependent on drug partitioning with the external medium.

Further dialysis experiments were done exclusively under "sink conditions," otherwise the release would have been dependent on the test conditions and would not describe the properties of the delivery system [36]. Free drug was used as the "control" in order to investigate the release from organogel nanoparticles. The experiments were done with INDO, at two different concentrations that framed the solubility limit of the compound in pH 6.8 buffer, used as the release medium.

At 0.1 mg/mL, release from organogel nanoparticles was compared to that from a solution, as plotted in Fig. 6a. Identical release rates were observed, signifying the immediate release of drug from organogel nanoparticles. In contrast to these observations, previous work on massive organogels loaded with ibuprofen showed sustained release, implying both diffusion and erosion mechanisms [14]. Incidentally, in this previous study, organogels with a larger amount of HSA presented lower erosion rates and low diffusion, leading to slower release rates. With organogel nanoparticles, the large
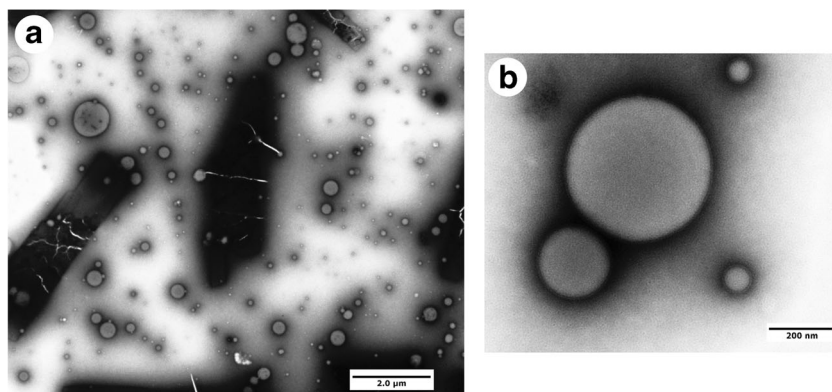

Fig. 4. TEM micrograph of castor oil organogel nanoparticles, general view (**a**) and a detail (**b**)
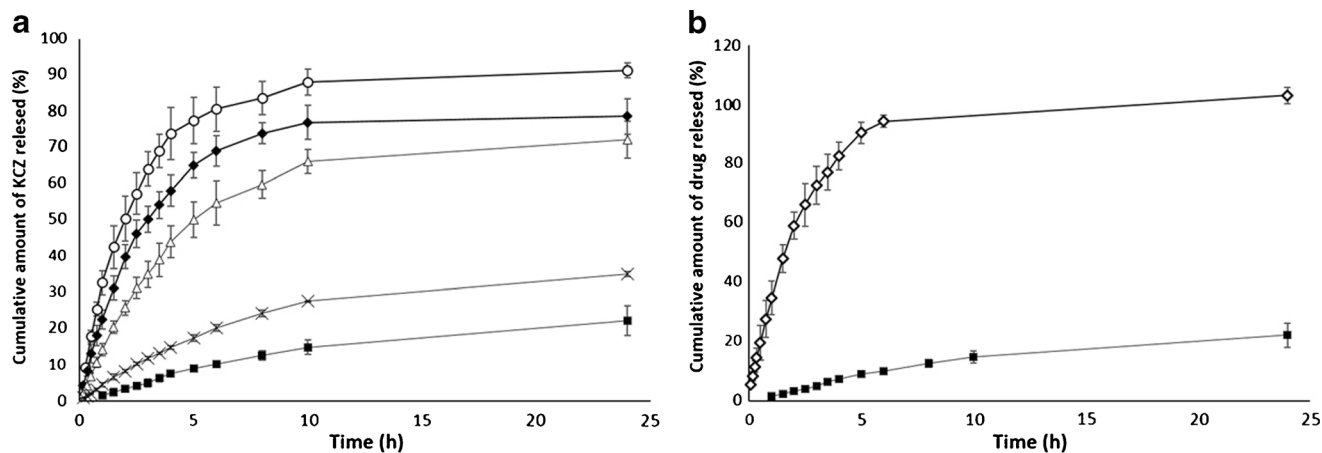
Fig. 5. **a** Release profiles of KCZ loaded organogel nanoparticles at 37°C according to release medium: pH 1.2 (*white circle*), pH 4 (*black diamond suit*), pH 5 (*increment*), pH 6 (*multiplication sign*), pH 6.8 (*black square*). **b** Release profiles in pH 6.8 release medium of organogel nanoparticles loaded with INDO (*lozenge*) or KCZ (*black square*)

surface area of the dispersion implied a huge increase in the diffusion, which enabled rapid release of the compound. In consequence, we observed that release from organogel nanoparticles depended only on the diffusion mechanism.

When the concentration was increased to 1.0 mg/mL, the free drug "control" went beyond the solubility limit of INDO and became a saturated solution. As shown in Fig. 6b, release rates were higher for organogel nanoparticles during the first 3 h of the dialysis experiment and then became similar to those of free drug for the rest of the study. This rapid release can be explained by the enhanced solubility of INDO in the oily vehicle, with the entrapped drug being solubilized and readily available from diffusion. Thus, gelled oil nanoparticles should exhibit a faster release profile than SLN, in which the encapsulated drug is generally in the solid state [9].

In addition to the dialysis experiments, release studies were done by diluting INDO organogel nanoparticles in pH 6.8 buffer. As shown in Fig. 7, non diluted samples gave drug release of 1.3 and 1.4% at 4 and 37°C, respectively, indicating that temperature was of no major importance for drug release during storage. Moreover, the amounts of *free drug* were in accordance with the encapsulation in Table III. A massive release of INDO was observed after dilution of the dispersions. Higher dilutions led to higher leakage, as about 50% of INDO

was leaked after a 1:5 dilution, but the percentage was near 100% after 1:50 dilution. This is a confirmation of the dialysis experiments, in which near 100% release was obtained after 24 h under similar dilution conditions. Thus, these results confirm that the release mechanism from organogel nanoparticles is mostly governed by diffusion, with a partitioning of the drug strongly correlated to its solubility and to the concentration gradient in the aqueous phase.

Taking the example of the oral route, better bioavailability would be expected as dissolution is often a rate limiting step for absorption [37, 38].

CONCLUSION

Organogel nanoparticles form an interesting family of colloidal nanoparticles based on gelled oil. Past experiments had already illustrated their potential use for drug encapsulation, with enhanced stability compared to emulsions and high drug loading potency. In this study, we prepared castor oil organogel nanoparticles loaded with KCZ or INDO, two lipophilic compounds with distinct ionization behaviors. Drug loading showed no impact on the particle size and stability of the dispersions and did not much hinder the gelling process according to DLS and DSC experiments. Encapsulation effi
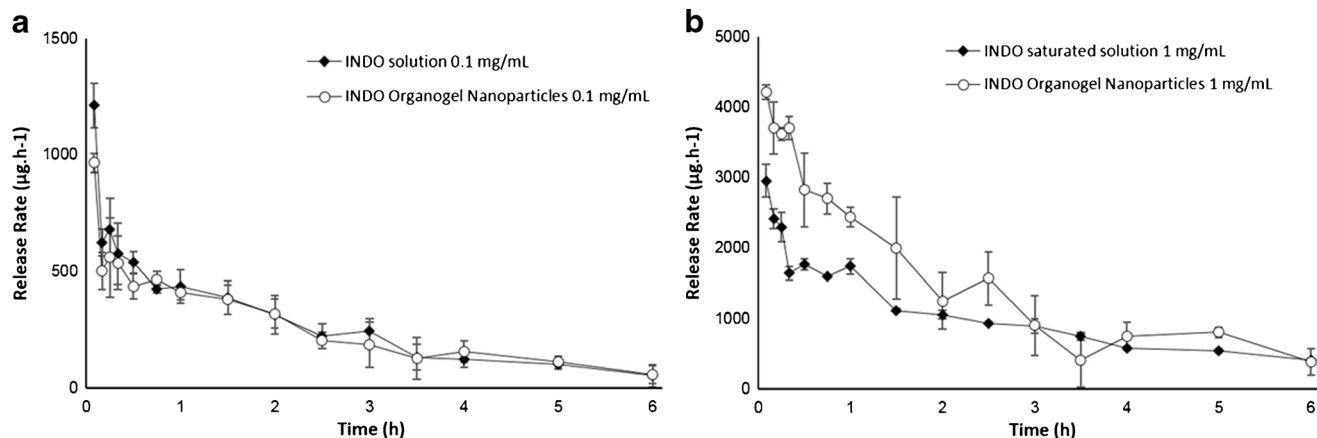

Fig. 6. Release rate of INDO loaded organogel nanoparticles at 37°C (*white circle*) vs pure drug (*black diamond suit*) in pH 6.8 release medium buffer, at initial drug concentrations of 0.1 mg/mL (**a**) and 1 mg/mL (**b**)
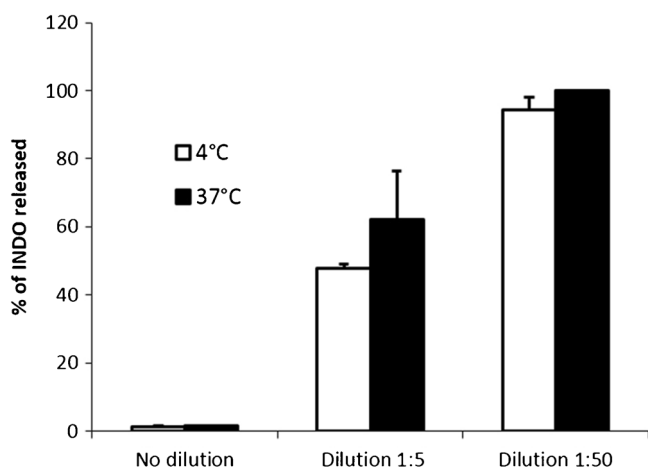
Fig. 7. Proportion of INDO released after 48 h at 4 and 37°C for increasing dilution of organogel dispersions in pH 6.8 buffer

ciency was very satisfactory for both compounds, with stability results suggesting very limited drug leakage occurring during storage. The small amount of initial drug leakage had probably happened during the dispersion step. In addition, EE results at 3 months suggest possible drug partitioning that would be correlated with the solubility of the drug in the aqueous phase. Release profiles determined by *in vitro* dialysis suggested an immediate release of the drug from the organogel nanoparticles. It seems that the solubilization of the drug enabled its rapid diffusion out of the vehicle. Thus, the gel network of HSA fibres would not hinder the drug release. Also, the increased solubility of the drug in the oil phase may lead to a better bioavailability, as more drug is readily available for diffusion. This first evaluation of organogel nanoparticles as vehicles for drug delivery has confirmed their potential in the pharmaceutical domain. Even though no sustained release was enabled, the immobilization of the oil in a gelled matrix was probably responsible for the improved stability of the dispersions and the limited escape of the drug during storage. These systems may constitute a profitable alternative to nanoemulsions or SLN for the delivery of lipophilic compounds with regards to biocompatibility, stability or scale up. Moreover, the adhesiveness of the lipid based nanoparticle, which has been proved to facilitate the drug tissue permeation, brings out the specific interest of organogel nanoparticles in the field of oral delivery.

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