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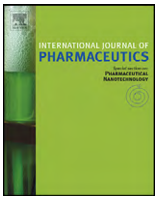

Pharmaceutical Nanotechnology

Quick and efficient extraction of uranium from a contaminated solution by a calixarene nanoemulsion

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ABSTRACT

This work aims to evaluate the efficiency of a calixarene emulsion for uranium extraction from a contaminated solution prior to apply such a delivery system to uranium skin decontamination. For this purpose, various experimental parameters that can influence the efficiency of the calixarene emulsion on uranium extraction were determined. The results show that the calixarene nanoemulsion effect can be observed after a very short time of contact with uranium-contaminated solution (5 min) and that it is still efficient in case of small volumes of contaminated solution. The pH of the contaminated solution was found to be the most important parameter affecting the calixarene nanoemulsion efficiency with a dramatic reduction of the uranium extraction rate in case of acidification of the contaminated medium. This lack of efficiency can be overcome by buffering the nanoemulsion continuous phase. The obtained results reveal that the calixarene nanoemulsion could represent a promising system for the emergency treatment of uranium cutaneous contamination.

1. Introduction

Despite protection means have been implemented in the nuclear industry, contamination of workers by actinides such as uranium is still occurring through inhalation, ingestion or penetration across wounds or intact skin. The wound or cutaneous pathways represent very critical modes of contamination in terms of frequency and health consequences (Blanchin et al., 2004). Particularly, contamination with uranium can induce renal chemical toxicity and bone tumor formation (Bailey et al., 2002; Bleise et al., 2003; Miller et al., 2005; Zhu et al., 2009). However, no effective and specific pharmaceutical dosage form is so far known to decontaminate skin in emergency cases (ASN, 2008). Indeed, the current medical treatment only consists in local decontamination by rinsing the wound with soaped water or a calcium salt of diethylene triamine pentaacetic acid (Ca-DTPA) solution which exhibits a poor efficiency towards uranium (Durbin, 2008; Durbin et al., 1998). Moreover, in order to avoid deep penetration of uranium and transport across the skin to the systemic compartment, decontamination should be highly efficient and quick. Besides, our previous works demonstrated that the macrocyclic molecule named 1,3,5-OCH_3-2,4,6-OCH_2COOH-*p*-*tert*butylcalix[6]arene proved to be an efficient and selective ligand for uranium extraction from biological or environmental samples (Boulet et al., 2006; Bouvier-Capely et al., 2009). For all these reasons we have previously developed a topical formulation consisting of oil in water nanoemulsion incorporating this calixarene, in order to treat uranium-contaminated intact or wounded skin (Spagnul et al., 2010). The physico-chemical properties of this nanoemulsion have been characterized demonstrating that calixarene molecules were mainly located at the surface of the dispersed oily droplets of the nanoemulsion, making them highly available for uranium chelation. The present work aims then to determine the optimal conditions of use of the calixarene nanoemulsion to obtain enhanced decontamination efficiency. In particular, we have studied the kinetics of uranium extraction by this topical form and the influence of various parameters such as pH and uranium concentration of the contaminated solution on the efficiency of the calixarene nanoemulsion.

2. Materials and methods

2.1. Materials

Calixarene molecule (Fig. 1) was synthesized as described in the patent by Duval et al. (2006). Other components used for formulation were paraffin oil ($d = 0.86$), (VWR, Fontenay sous Bois, France), non ionic surfactants sorbitan monooleate (Span® 80) and polyoxyethylene glycol sorbitan monooleate (Tween® 80), purchased

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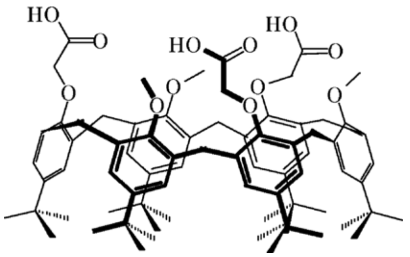

Fig. 1. Structure of 1,3,5-OCH_3-2,4,6-OCH_2COOH-*p-tert*butylcalix[6]arene.

from Sigma–Aldrich (Saint-Quentin-Fallavier, France). Water used in all experiments was obtained from a Milli-Q® Synergy 185 water purification system (Millipore, Saint-Quentin-en-Yvelines, France). Acetonitrile, trifluoroacetic acid and tetrahydrofuran of HPLC grade used in HPLC studies were purchased from Sigma–Aldrich (Saint-Quentin-Fallavier, France). Uranium-contaminated solutions were prepared by diluting a depleted uranium standard solution (1000 mg l^{-1} in 2% HNO_3, SPEX Certiprep, Horiba Jobin Yvon, Longjumeaux, France).

For uranium measurement by Inductively Coupled Plasma Mass Spectrometry (ICP-MS), a bismuth stock solution at 100 $\mu g\,l^{-1}$ (from 10 mg l^{-1} single element internal standard, SPEX Certiprep, Horiba Jobin Yvon, Longjumeaux, France) and a multielemental stock solution containing depleted uranium at 1 $\mu g\,l^{-1}$ (from 10 mg l^{-1} tuning solution SPEX Certiprep, Horiba Jobin Yvon, Longjumeaux, France) were prepared in 2% HNO_3 (from 67% HNO_3 solution, Normatom, VWR, Fontenay sous Bois, France). All reagents were used as received without further purification.

2.2. Preparation of nanoemulsions

Nanoemulsions were prepared by the emulsion inversion point method as described previously (Spagnul et al., 2010). Briefly, water was slowly added to a mixture of paraffin oil, non ionic surfactants and calixarene under slight stirring using a magnetic stirrer. The emulsification temperature was kept at 50 °C. Samples were then cooled at room temperature under slight stirring. The amounts of surfactants, oil and water were 5%, 20% and 75% (w/w), respectively. The mixture ratio of Tween® 80 and Span® 80 was adjusted to reach the hydrophilic–lipophilic balance (HLB) that ensures the optimum emulsification conditions. All the components used in the nanoemulsion were selected in order to meet the qualities required for a topical application which are a good cutaneous tolerance, a low percutaneous penetration (Spagnul et al., 2010).

2.3. In vitro evaluation of the calixarene nanoemulsion efficiency

The contaminated solution was added to the nanoemulsion and the mixture was either shaken (referred thereafter as “dynamic condition”) or kept without shaking (referred thereafter as “static condition”) during definite times. The extraction of uranium by the calixarene nanoemulsion was then determined by estimating the quantity of free uranium present in the aqueous phase recovered by ultrafiltration–ultracentrifugation of the mixture using Microcon® centrifugal filter devices (3000 Da, Millipore, Saint-Quentin-en-Yvelines, France). Aliquots of the mixture were introduced into the Microcon® devices and centrifuged at 3800 × *g* for 30 min at 20 °C. These Microcon® devices, that infer the passage of oil, surfactant and calixarene through their filters (Spagnul et al., 2010), allow recovering the water phase of the mixture in the filtrate. Free ^{238}U present in this filtrate was then quantified by ICP-MS using optimized protocols originally designed for human urine samples (Baglan et al., 1999; Bouvier-Capely et al., 2003; Bouvier-Capely et al., 2004). Filtrate aliquots were then properly diluted in 2% HNO_3 and ^{209}Bi was added as internal standard at 1 $\mu g\,l^{-1}$. As diluted solutions were prepared by weighing, the related uncertainties can be neglected compared to the statistical ones. The combination of the statistical errors was made using the conventional law of error propagation. A multielemental standard solution was used before each ICP-MS measurement series to optimize the ^{238}U signal and get the best instrumental conditions.

Previous results showed that the uranium chelation by the calixarene nanoemulsion was reversible after acidification of the medium and that the recovered uranium could be also quantified by ICP-MS after ultrafiltration (Spagnul et al., 2010). Since this procedure makes it possible to determine the mass balance, then the extracted uranium percentage can be deduced from the quantification of free uranium in the nanoemulsion aqueous phase.

The calixarene nanoemulsion efficiency was studied as a function of various experimental conditions such as the contact time between the nanoemulsion and the uranium-contaminated solution, the calixarene nanoemulsion to uranium volume ratio and the pH of the contaminated solution.

2.3.1. Uranium extraction kinetic

To assess uranium extraction kinetics by the calixarene nanoemulsion, contact time between unloaded or 2 mg g^{-1} calixarene loaded nanoemulsions and the contaminated solution was varied from 5 min to 4 h. Experiments were conducted under static and dynamic conditions. After each contact time, both phases were separated whether by ultrafiltration (3800 × *g* for 30 min) (Spagnul et al., 2010). Other conditions were the following: the volume ratio of the nanoemulsion over the contaminated solution was equal to 1; the molar ratio of calixarene over uranium was equal to 10,000; the contaminated solution pH was of 5.0 ± 0.1.

2.3.2. Calixarene nanoemulsion to uranium volume ratio

The influence of the 2 mg g^{-1} calixarene nanoemulsion to uranium solution volume ratio was studied by varying this volume ratio between 1 and 10. The molar ratio of calixarene over uranium was kept constant to 10,000 by compensating the uranium concentration. This study was conducted under static and dynamic conditions during 1 h. The pH was similar to the values previously mentioned.

2.3.3. Contaminated solution pH

To estimate the uranium extraction by the 2 mg g^{-1} calixarene loaded nanoemulsion as a function of the contaminated medium acidity, the pH of the uranium solution was varied from 5 to 2 by acidifying with 67% nitric acid. This study was conducted under static and dynamic conditions during 1 h. The volume ratio of the nanoemulsion over the contaminated solution was fixed to 1 and the molar ratio of calixarene over uranium was equal to 10,000.

2.3.4. Influence of uranium concentration

Uranium concentrations ranging from 40 to 400,000 $\mu g\,l^{-1}$ were used to study the influence of the calixarene:uranium molar ratio after 1 h of static contact. The calixarene concentration in the nanoemulsion was fixed to 2 mg g^{-1}, the ratio between the volume of the nanoemulsion over the volume of the contaminated solution was fixed to 1 and the contaminated solution pH was of 5.0 ± 0.1.

2.3.5. Influence of calixarene concentration in the nanoemulsion

The optimal calixarene amount in the nanoemulsion in terms of uranium extraction efficiency was evaluated by testing different calixarene load (2, 4 and 8 mg g^{-1}) during 1 h of static contact. All other experimental conditions were the following: the volume ratio of the nanoemulsion over the contaminated solution was equal to 1; the molar ratio of calixarene over uranium was equal to 10,000; the contaminated solution pH was of 5.0 ± 0.1.

Table 1
List of parameters studied in this work.

Studied parameters	Constant parameters	Variation range
[Calix] mg g^{-1} in the nanoemulsion	2	2–8
pH of the U solution	5	2–5
Nano/U volume ratio	1	1–10
Calix/U molar ratio	10,000	1–10,000
Contact time	1 h	5 min–4 h
Contact conditions	Static/dynamic	

The various parameters that were investigated in this study are summed up in Table 1. The second column indicates the value of the parameters when kept constant in the study and the third column indicates the range in which each parameter was successively varied.

3. Results and discussion

3.1. *Preliminary results*

As the ultrafiltration was used in all experiments to separate the aqueous phase from the nanoemulsion/uranium solution mixture, a preliminary study was carried out to determine the uranium retention yield at each uranium solution pH by the Microcon® filters used for the ultrafiltration step (Spagnul et al., 2010). Thus, uranium retention by the filters decreased from 50% to 10% between pH 5 and 3 and was relatively constant between pH 3 and 2. The fact that uranium retention is influenced by the pH of the ultrafiltered solution may be explained by an interaction between the uranyl ions and the hydroxyl groups of the cellulose filters (Guo et al., 2007). For each experimental conditions, the uranium retention percentage by the filters was taken into account to determine the total amount of free uranium, i.e. not complexed by the calixarene.

3.2. *Study of the uranium extraction kinetics by the calixarene nanoemulsion*

In a previous report (Spagnul et al., 2010), we designed a calixarene nanoemulsion for the extraction of uranium from an aqueous contaminated solution. Calixarene was shown to be present at the surface of the nanoemulsion dispersed oily droplets being thus able to interact with uranyl ions of a contaminated solution under dynamic or static conditions. As a quick extraction is necessary for an emergency treatment of uranium skin contamination, the extraction kinetics by the calixarene nanoemulsion was evaluated by varying the contact time between the calixarene nanoemulsion and the uranium-contaminated solution from 5 min to 4 h. The extraction kinetics represented in Fig. 2 show that after 5 min of contact, the calixarene nanoemulsion reaches an optimal extraction yield of 83.4 ± 0.6% and 90.6 ± 0.3% respectively under static contact (Fig. 2, curve 4) and under dynamic (shaking) contact (Fig. 2, curve 1). The addition of calixarene to the nanoemulsion allows uranium extraction increase from 49.3 ± 2.2% to 90.6 ± 0.3% after 4 h of dynamic contact with the uranium-contaminated solution (Fig. 2, curves 1 and 2) and from 25.3 ± 8.8% to 80.0 ± 4.0% under static condition (Fig. 2, curves 4 and 5). Therefore, it is clearly observed that the nanoemulsion without calixarene can extract uranium from the contaminated solution. This phenomenon may be explained by the presence within the nanoemulsion of non ionic surfactants micelles which could be able to trap uranyl ions (Kumar Das and Nandi Ganguly, 1996; Moulin et al., 1993). Indeed, it is also shown that a simple oily solution extracts only about 7% of the uranium from the contaminated solution (Fig. 2, curve 6) and that the addition of calixarene into this oily solution does not allow to enhance the extraction rate under static condition (Fig. 2, curve 7). As expected, when the oil/aqueous phases contact surface is increased by shaking (Fig. 2, curve 3), the uranium extraction rate is significantly improved (91.7 ± 2.5%). Hence, the advantage of the emulsified system ensuring a larger oil/water interfacial contact which enhances the uranium extraction yield and allows a quick elimination of the radionuclide is clearly demonstrated.

3.3. *Effect of various parameters on calixarene nanoemulsion efficiency*

3.3.1. *Calixarene nanoemulsion to uranium volume ratio*

In case of skin contamination, the volume of the uranium-contaminated solution is expected to be smaller than the volume of the calixarene nanoemulsion. To determine whether the calixarene nanoemulsion is still efficient on a smaller uranium solution volume, we have compared calixarene nanoemulsion efficiency for the same volume of nanoemulsion and contaminated solution and also for 10-fold smaller contaminated solution volume. The contact time was 1 h (in static and dynamic conditions) and the calixarene:uranium molar ratio was kept at 10,000. The reduction of the contaminated solution volume led to a slight decrease of the nanoemulsion efficiency with an extraction yield dropping from 87.0 ± 6.0% to 76.3 ± 4.5% under dynamic conditions and from 79.8 ± 5.1% to 62.3 ± 6.0% under static conditions (Fig. 3). This phenomenon may be explained by the fact that the mixture of calixarene nanoemulsion and uranium-contaminated solution is less well homogenized under static condition in case of small-contaminated solution volume. Hence, the calixarene nanoemulsion becomes slightly less efficient in case of small-contaminated volume, but its efficacy could still be high enough to prevent uranium diffusion through contaminated skin, in particular if the calixarene nanoemulsion application is repeated.

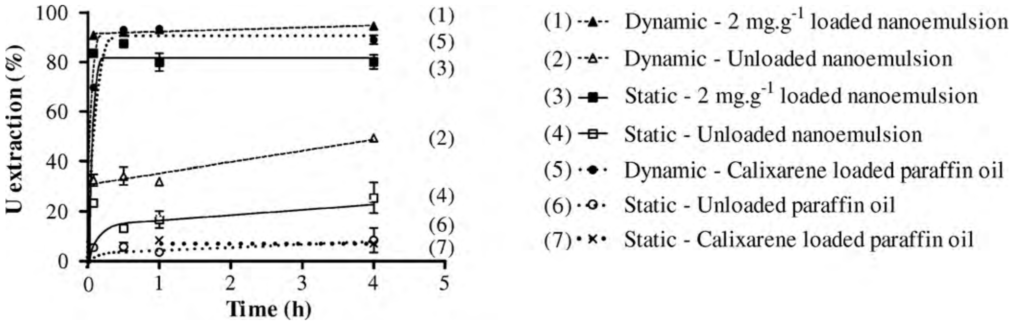

Fig. 2. Uranium extraction kinetics by paraffin oil and nanoemulsion against the presence of calixarene (percentage of uranium extracted from a contaminated solution as a function of time). Each plot corresponds to the contact time between the tested form and the uranium-contaminated solution; the duration of the nanoemulsion ultrafiltration (30 min) and the oil centrifugation (15 min) are included. Experimentations were conducted under static and dynamic conditions, with equal volumes of nanoemulsion and uranium-contaminated solution, 10,000-fold calixarene molar excess and a pH 5 contaminated solution.

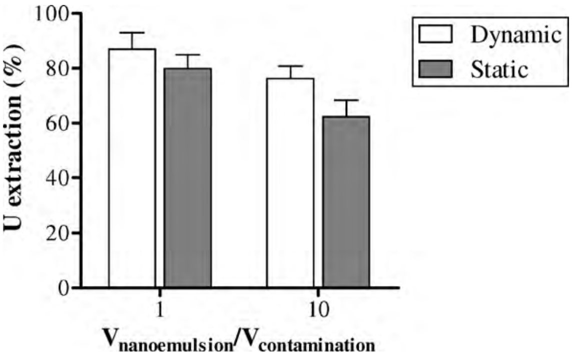

Fig. 3. Percentage of uranium extracted from a contaminated solution by 2 mg g^{-1} calixarene loaded nanoemulsion as a function of the volume ratio of calixarene nanoemulsion over uranium-contaminated solution (under 1 h dynamic and static conditions with 10,000-fold calixarene molar excess at pH 5).

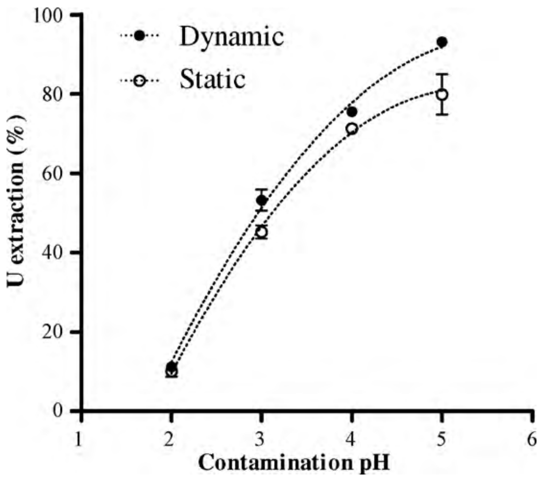

Fig. 4. Percentage of uranium extracted from a contaminated solution by 2 mg g^{-1} calixarene loaded nanoemulsion as a function of the uranium-contaminated solution pH. Experimentations were conducted during 1 h under dynamic and static contact with equal volumes of nanoemulsion and contaminated solution and 10,000-fold calixarene molar excess.

Table 2
Uranium concentrations of contamination solutions (μg l^{-1}) and corresponding $Q_{calixarene}/Q_{uranium}$ ratios used for studying the influence of the calixarene:uranium molar ratio on the uranium extraction efficiency of the 2 mg g^{-1} calixarene loaded nanoemulsion.

$Q_{calixarene}/Q_{uranium}$ molar ratio	Uranium concentration (μg l^{-1})
10,000	40
2000	200
40	10,000
32	12,500
16	25,000
8	50,000
4	100,000
1	400,000

3.3.2. *Contaminated solution pH*

Since most of the contaminated injuries occurring to nuclear workers happen with acidic solutions, it was necessary to study the influence of the uranium-contaminated solution pH on the calixarene nanoemulsion efficiency. Boulet et al. (2006) in their previous liquid–liquid extraction experiments showed a decrease of the uranium extraction by calixarene from 100% at pH 5 to 0% at pH 2.5 due to the protonation of the carboxylic functions of the calix[6]arene molecules. In the present work, the influence of the contaminated solution pH on uranium extraction by the calixarene nanoemulsion was investigated by reducing this pH from 5 to 2. The protonation of these hydroxyl groups seems to be significant enough for pH values lower than 3 to limit uranium retention. The influence of the contaminated solution pH on the uranium extraction by the calixarene nanoemulsion was then studied. The percentage of extracted uranium by the calixarene nanoemulsion decreased from 93.2 ± 0.4% to 11.4 ± 0.7% under dynamic condition and from 79.8 ± 5.1% to 10.0 ± 1.3% under static condition when the contamination pH was reduced from 5 to 2 (Fig. 4). To improve calixarene nanoemulsion efficiency for uranium extraction at an acidic pH, 2 mg g^{-1} calixarene loaded nanoemulsion was prepared with a pH 5 acetate buffered water phase (named afterwards the buffered nanoemulsion). Buffering the nanoemulsion aqueous phase did affect neither the entrapment of calixarene nor other physical characters of the nanoemulsion as attested by stability monitoring studies in terms of size, zeta potential and pH which indicate that both buffered and non-buffered nanoemulsion were not destabilized after 6-month storage at room temperature. The efficacy of the buffered nanoemulsion was then compared to the one of the non-buffered calixarene nanoemulsion under static condition (Fig. 5). In the case of uranium-contaminated solution at pH 5, the buffered calixarene nanoemulsion was found to be as efficient as the non-buffered one with uranium extraction yield of about 87%. In the case of a contaminated solution at pH 2, the uranium extraction yield by the non-buffered nanoemulsion decreased to about 10% while the pH 5 buffered calixarene nanoemulsion extracted 65.8 ± 2.3% of the uranium from the acidic contaminated solution. The calixarene nanoemulsion efficacy can thus be significantly improved in case of acidic contaminated solution by buffering the aqueous phase of the nanoemulsion.

3.3.3. *Calixarene:uranium molar ratio*

All experiments were conducted with a calixarene:uranium molar ratio of 10,000 representing a sufficient calixarene excess to ensure good uranium extraction by calixarene molecules (Boulet et al., 2006). The present experiment consists in determining the minimal calixarene:uranium molar ratio which is required to reach the optimal efficiency of the 2 mg g^{-1} calixarene loaded nanoemulsion under 1 h static contact with uranium-contaminated solution. For this purpose, different calixarene:uranium ratios have been tested, keeping the nanoemulsion:contaminated solution volumes ratio equal to one (Table 2).

As it can be observed in Fig. 6, the 2 mg g^{-1} calixarene loaded nanoemulsion shows an optimal uranium extraction yield of approximately 80% until a calixarene:uranium molar ratio value of 32, which corresponds to uranium-contaminated solution of 12.5 mg l^{-1}. At a calixarene:uranium molar ratio of 16 (*i.e.*, uranium concentration of the contaminated solution of 25 mg l^{-1}), the calixarene nanoemulsion efficiency is divided by two and becomes nil for smaller calixarene:uranium molar ratios. To obtain a quantitative uranium extraction rate in liquid-liquid extraction experiments under similar conditions, the molar ratio was shown to be much higher than 10,000 (Baglan et al., 1997; Boulet et al., 2006), which shows the interest of our emulsified system.

3.3.4. *Optimal calixarene concentration in the nanoemulsion*

In this part of the study, the calixarene:uranium molar ratio was also varied but with uranium concentration of the contaminated solution kept at 25 mg l^{-1}. The calixarene concentration of the nanoemulsion was increased from 2 to 8 mg g^{-1} in order to determine the optimal calixarene concentration that ensures the best uranium extraction rate. The percentage of extracted uranium was almost doubled for a calixarene concentration increase from 2 to 4 mg g^{-1} (Fig. 7). However, the use of 8 mg g^{-1} calixarene loaded nanoemulsion does not allow to improve the nanoemulsion efficiency. This suggests that the additional quantity of calixarene

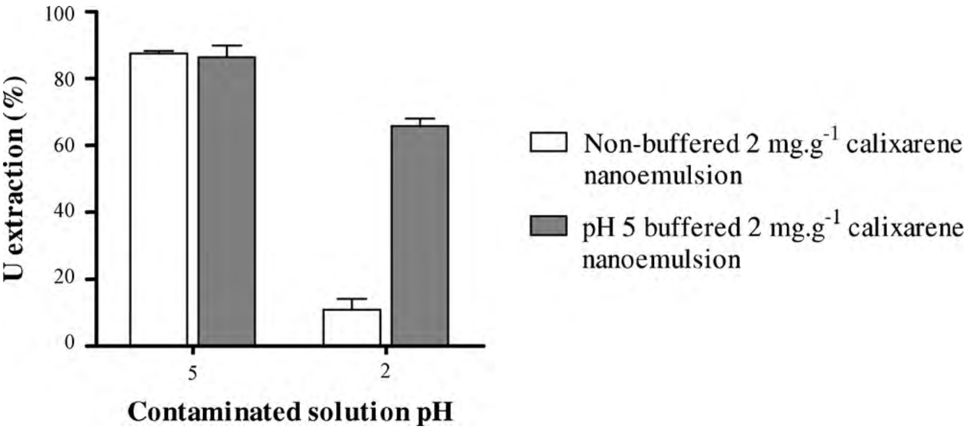

Fig. 5. Percentage of uranium extracted from pH 2 and pH 5 contaminated solutions by pH 5 buffered and non-buffered 2 mg g^{-1} calixarene loaded nanoemulsions. Experimentations were conducted during 1 h under static contact with a calixarene nanoemulsion volume three times higher than the contaminated solution one and 10,000-fold calixarene molar excess.

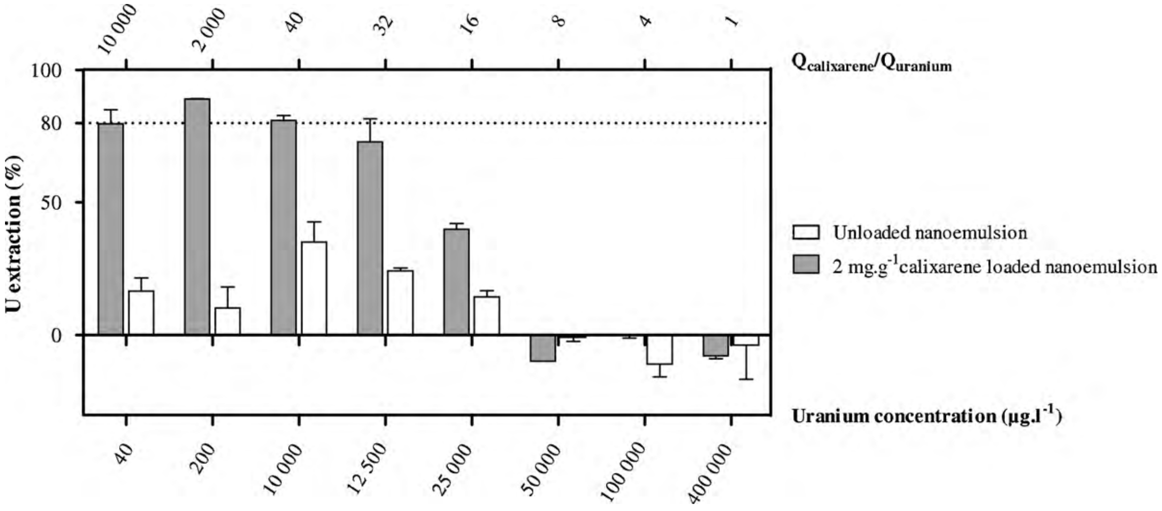

Fig. 6. Percentage of uranium extracted from a contaminated solution by unloaded and 2 mg g^{-1} calixarene loaded nanoemulsions as a function of the uranium concentration in the contaminated solution (μg l^{-1}). Experimentations were conducted during 1 h under static condition with equal volumes of nanoemulsion and pH 5 contaminated solution. $Q_{\text{calixarene}}/Q_{\text{uranium}}$ is the calixarene:uranium molar ratio.

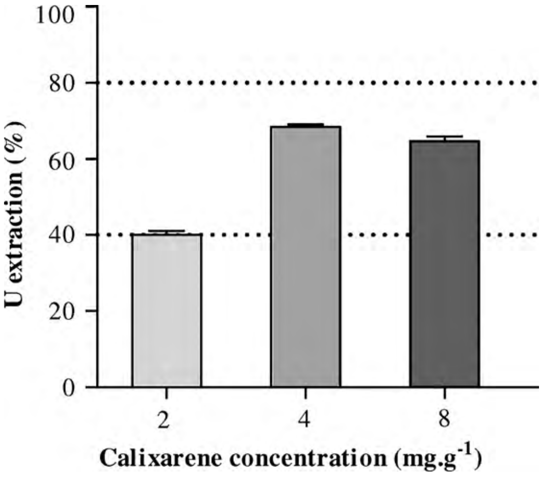

Fig. 7. Percentage of uranium extracted from a contaminated solution by calixarene loaded nanoemulsions as a function of the calixarene concentration in the nanoemulsion. Experimentations were conducted during 1 h under static condition with 25 mg l^{-1} contaminated solution of pH 5, equal volumes of nanoemulsion and contaminated solution and 10,000-fold calixarene molar excess.

in this nanoemulsion is not available for the chelation of uranium, which is in agreement with the characterization of the nanoemulsion that showed, using optical microscopy, the presence of calixarene crystals in the nanoemulsion aqueous phase from a calixarene concentration of 6 mg g^{-1} (Spagnul et al., 2010). Therefore, it appears that the 4 mg g^{-1} calixarene concentration seems to be close to the optimal nanoemulsion calixarene concentration.

4. Conclusions and perspectives

The aim of this work was to study the ability of a calixarene nanoemulsion to extract uranyl ions from an aqueous contaminated solution. For this purpose, the influence of various experimental parameters on uranium extraction by calixarene nanoemulsion was determined. The *in vitro* experiments based on the use of an adapted ultrafiltration method showed that the action of the calixarene nanoemulsion is very fast and that the effect is maintained in case of small-contaminated volumes. Moreover, contaminated solution pH was found to be the most important parameter affecting the calixarene nanoemulsion efficiency. However, the use of a buffered aqueous phase in the calixarene nanoemulsion improves its efficiency in acidic conditions. Lastly, the optimal calixarene concentration in the nanoemulsion was found to be around 4 mg g^{-1}. This study has then demonstrated that the calixarene nanoemulsion is suitable for uranium extraction in static condition, which is promising for our purpose of topical application. The next step of our work will consist in evaluating the calixarene nanoemulsion efficiency in terms of uranium skin decontamination in *ex vivo* experiments on skin samples using Franz diffusion cells.

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