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Influence of nonionic branched-chain alkyl glycosides on a model nano-emulsion for drug delivery systems

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ABSTRACT

The effect of incorporating new nonionic glycolipid surfactants on the properties of a model water/nonionic surfactant/oil nano-emulsion system was investigated using branched-chain alkyl glycosides: 2-hexyldecyl-β(/α)-D-glucoside (2-HDG) and 2-hexyldecyl-β(/α)-D-maltoside (2-HDM), whose structures are closely related to glycero-glycolipids. Both 2-HDG and 2-HDM have an identical hydrophobic chain (C16), but the former consists a monosaccharide glucose head group, in contrast to the latter which has a disaccharide maltose unit. Consequently, their hydrophilic–lipophilic balance (HLB) is different. The results obtained have shown that these branched-chain alkyl glycosides affect differently the stability of the nano-emulsions. Compared to the model nano-emulsion, the presence of 2-HDG reduces the oil droplet size, whereas 2-HDM modify the properties of the model nano-emulsion system in terms of its droplet size and storage time stability at high temperature. These nano-emulsions have been proven capable of encapsulating ketoprofen, showing a fast release of almost 100% in 24 h. Thus, both synthetically prepared branched-chain alkyl glycosides with mono- and disaccharide sugar head groups are suitable as nano-emulsion stabilizing agents and as drug delivery systems in the future.

1. Introduction

Natural glycolipids are interesting for studies on bio-mimicking due to their special role in membranes since these are known to influence membrane functionality [1,2]. This feature is related to their amphitropic liquid crystalline properties [3] given by the sugar moiety and the hydrophobic alkyl chains. Thus these amphiphilic surfactants exhibit interesting phase behaviour, such as the formation of different thermotropic phases, in addition to the expected lyotropic phases [4]. Since natural glycolipids are difficult to synthesize or to extract from natural sources, their synthetic counterparts obtained by straightforward synthesis have moved into the focus of research [5–12]. Like their natural analogues, synthetic glycolipids are non-toxic, biocompatible and biodegradable. Hence, they are suitable for various pharmaceutical applications.

Among the synthetic glycolipids, branched-chain glycolipids provide a closer alternative to natural ones, which usually possess double branched-chains, for example sphingolipids and glycoglycerol lipids [13,14]. Different types of branched-chain glycolipids have been studied, such as 1,2-dialkyl/diacyl-glycerol-based glycolipids [10,11] or 1,3-glycosyl-glycerol-based glycolipids [7,15]. In the present investigation, Guerbet alcohol-based glycolipids prepared [5,16,17] using the Lewis acid glycosidation method [4,18] were studied. Guerbet glycosides were prepared by using a protected sugar with a Guerbet alcohol. The latter is an industrial material and was first synthesized by Guerbet in 1905 [19]. The Guerbet glycosides may be viewed as Guerbet sugars, an addition to the Guerbet materials including the alcohol, ester and acid, all of which have been used in many industrial applications [20]. In this particular preparation, the sugar glycosides were anomeric mixtures containing 90% β-anomer products. Two derivatives were selected, both having the same chain lengths, but different sugar head groups, leading to different polarities and HLBs. The first one was based on glucose (2-hexyldecyl-β(/α)-D-glucoside), abbreviated as 2-HDG and the second one was based on maltose (2-hexyldecyl-β(/α)-D-maltoside), abbreviated as 2-HDM. The chemical structures of the glucoside and maltoside derivatives are given in Fig. 1.

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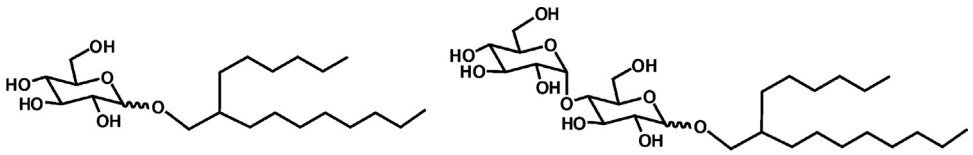

(a) (b)

Fig. 1. Chemical structures of (a) 2-hexyldecyl-$\beta(/\alpha)$-D-glucoside (2-HDG) and (b) 2-hexyldecyl-$\beta(/\alpha)$-D-maltoside (2-HDM).

Previous studies have shown that 2-HDG and 2-HDM possess rich phase behaviours [5]. Thermotropic and lyotropic liquid crystalline phases were observed, and self-aggregation in diluted aqueous dispersions reported [21,22]. Here we report on the effect of incorporating Guerbet glycosides in the model system of water/nonionic surfactant/oil nano-emulsion, with the inclusion of an active ingredient (a drug).

Nano-emulsions are dispersions of two immiscible liquids generally stabilized by surfactant molecules with droplet size in the nanometer range, typically less than 200 nm [23]. Due to the small droplet size, nano-emulsions are stable against sedimentation or creaming, and visually they appear transparent to translucent [23]. Unlike microemulsions, which are thermodynamically stable and form spontaneously, nano-emulsions being thermodynamically unstable require energy input for their preparation. Nano-emulsion preparation is usually divided into two main methodologies: the high-energy (e.g. high pressure homogenization) and the low-energy emulsification methods. Of the latter, the most common are the phase inversion temperature (PIT) method introduced by Shinoda [24,25] and the phase inversion composition (PIC) method [23,26]. In this work, nano-emulsions were prepared using the PIC method. The preparation method consists of maintaining the temperature constant, but changing the composition during emulsification (e.g. by adding water to an oil–surfactant mixture to obtain O/W nano-emulsions). Different methods of addition, progressive and at-once addition [27–31] as well as through two-step methods [32–34] have been reported. In general, after the phase inversion, low polydispersity oil (or water) droplets are formed in water (or oil). It has been described that nano-emulsion main breakdown process is due to Ostwald ripening [35,36] where molecular diffusion of the disperse phase from the small droplets to the bigger ones takes place as a consequence of the difference in Laplace pressure (i.e. different solubility) of droplets of different size. The stability of nano-emulsions against Ostwald ripening can be increased by reducing the polydispersity to a minimum and by using very low solubility oil in the continuous phase [23,37].

In our investigation, the selected reference O/W nano-emulsion system was the water/Cremophor® EL/medium-chain triglyceride oil system. Using this system as a reference, we have studied the effect of adding Guerbet branched-chain alkyl glycoside surfactants on oil droplet size, the long-term stability and the release properties of a model drug. The selection was made considering the stability of the nano-emulsions system [29] and the suitability of the system components for pharmaceutical and cosmeceutical applications. Indeed, Sadurni et al. [29] reported nano-emulsion formation by the PIC method in the water/Cremophor® EL/MCT oil system at water contents above 50% and oil/surfactant weight ratios between 10/90 and 60/40. Droplet size was highly dependent on the oil/surfactant ratio and no phase separation or other destabilization signs were observed in nano-emulsions with low oil/surfactant weight ratios. The incorporation of small concentrations of Guerbet branched-chain alkyl glycosides in such a model nano-emulsion system is expected to have an influence on emulsion properties. Recently, a patent was filed for an industrial formulation using Guerbet glycosides as additives [38]. The study may contribute to the basic knowledge of Guerbet branched-chain alkyl glycosides and of nano-emulsion formulations, which consequently lead to their use in practical applications.

2. Materials and methods

2.1. Materials

All chemicals were of analytical grade and used as received. De-ionized filtered water (Milli-Q®, Millipore) was used in all formulations. Cremophor® EL (Crem EL), a polyethylene glycol (35 OE) castor oil, with hydrophilic–lipophilic balance lying between 14 and 16, was obtained from BASF, Germany. Medium-chain triglyceride oil (MCT oil) was purchased from Fagron Iberica, S. A. U. Ketoprofen (2-(3-benzoylphenyl)-propionic acid) was purchased from Sigma, potassium dihydrogen phosphate, orthophosphoric acid and methanol were purchased from Merck, while anhydrous dibasic sodium phosphate was obtained from Fluka. Dialysis bags were made of regenerated cellulose by Cellu·Sep (molecular weight cut-off of 12,000–14,000 Da). 2-Hexyldecyl-$\beta(/\alpha)$-D-glucoside (2-HDG) and 2-hexyldecyl-$\beta(/\alpha)$-D-maltoside (2-HDM) were synthesized following the protocol described by Hashim et al. [5].

2.2. Nano-emulsion preparation

Nano-emulsions were prepared by the phase inversion composition (PIC) method consisting of the stepwise addition of water to a mixture of oil (medium-chain triglycerides) and nonionic surfactants (either Cremophor® EL or mixed Cremophor® EL/2-HDG or Cremophor® EL/2-HDM). Nano-emulsions with 90 wt% of water and different oil–surfactant ratios (40/60, 50/50, 60/40) were prepared. A sample preparation was performed at 25.0 °C and the resulting nano-emulsions were kept at 25.0 °C and 37.0 °C.

2.3. Nano-emulsion characterization

The oil droplet radius was determined by dynamic light scattering (DLS) using a 3D-Photon Correlation Spectrometer (PCS) from LS INSTRUMENTS. Triplicate readings of 200 s were recorded at an angle of 90°. The radius was obtained by a manual exponential fitting of the first cumulant parameter. The measurement temperatures (25.0 °C and 37.0 °C) were maintained by a decalin bath, which matched the refractive index of glass and therefore did not interfere with the measurements.

A JEOL JEM-1400 Cryogenic Transmission Electron Microscope (Cryo-TEM) (Jeol Ltd., Tokyo, Japan) with voltage acceleration of 80–200 kV was used for nano-emulsions imaging and droplet size determination. 5 μL of the sample was placed on a QUANTIFOIL® R 1.2/1.3 grid and the excess was eliminated with Whatman N°1 paper. The vitrification was done with a Cryo Preparation Chamber (CPC) from Leica by immersing the grid in liquid ethane.

2.4. Nano-emulsion stability

Long-term stability was assessed by changes in droplet size (by DLS) and by light backscattering. Light backscattering was performed with a TURBISCAN MA 2000 Stability Analyser (France) equipped with a 850 nm LASER and two detectors for recording backscattered light (135°), as well as transmission (0°). Backscattering was recorded as a function of sample height for 24 h.

2.5. Incorporation of drug into nano-emulsions

Ketoprofen (KT) was incorporated into the oil/surfactant mixtures prior to the addition of water to form the nano-emulsions. The samples were homogenized with a vortex mixer and then kept in a water bath at 25.0 °C. Different weight percentages of drug were tested and the stabilities were examined by visual observation for at least 24 h. The optimized percentage of drug which could be incorporated was determined by the stability of the drug in nano-emulsion against precipitation.

2.6. In vitro drug release experiments

About 3.0 g of nano-emulsion containing ketoprofen was filled in a dialysis bag and immersed for 24 h in a receptor solution (130 mL) consisting of a phosphate buffer solution at pH 7.4 (considered to be the pH of blood). The diffusion cells consisted of three cylindrical thermo-jacketed glass vessels connected to a water bath set at 25.0 °C and closed to avoid loss of receptor solution by evaporation. The receptor solution was stirred with a magnetic stirrer. Aliquots of receptor solution were withdrawn for the determination of released drug concentration and analyzed by HPLC. The chromatographic system consisted of a UV detector set at 260 nm wavelength and connected to a Waters 1500 Series HPLC pump equipped with a 5 mm × 15 cm × 0.46 cm Spherisorn ODS column. Ketoprofen analysis was carried out at room temperature with a 6:4 methanol:water (v/v) mobile phase that was adjusted to a pH of 1.50 with ortho-phosphoric acid. 20 μL of sample was injected at a flux rate of 1 mL·min^{-1}. The retention time was 8 min. The aliquot withdrawn was replaced with the same volume of receptor solution in order to maintain the volume of the receptor solution constant. The volume of receptor solution used ensured sink conditions throughout the diffusion experiments, i.e. the concentration of the drug in the receptor solution was not higher than 10% of its solubility in this medium.

3. Results and discussion

3.1. Nano-emulsion formation

The influence of glycolipids (2-HDG and 2-HDM) in O/W nano-emulsions of the model system based on water, Cremophor® EL (a commercial nonionic surfactant) and medium chain triglycerides was first tested in samples with 90 wt% water, oil/surfactant ratios of 40/60, 50/50 and 60/40 and Crem EL/glycolipid ratios of 95/5 and 90/10. Independently on the Crem EL/glycolipid ratio, the nano-emulsions with 60/40 and 50/50 oil/surfactant ratio were more opaque than those with a ratio of 40/60. A more opaque appearance usually indicates bigger oil droplet size and consequently lower stability. Indeed, creaming of 2-HDG and 2-HDM nano-emulsions with oil/surfactant ratio 50/50 or higher was observed after several days. Light scattering measurements of nano-emulsions with a 60/40 oil/surfactant ratio could not be performed due to the high opacity of the samples. These preliminary results allowed selecting the optimum oil/surfactant ratio (40/60) for further investigations (considering application suitability, nano-emulsions with lower surfactant concentrations, high oil/surfactant ratio, are preferred).

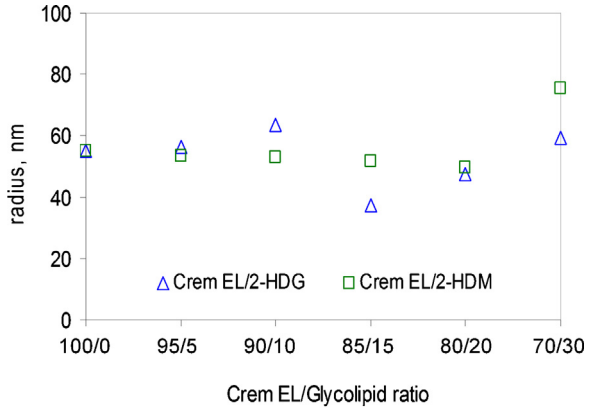

Fig. 2. Influence of Crem EL/glycolipid ratio on oil droplet radius at 25.0 °C.

The effect of Crem EL/glycolipid weight ratio (from 95/5 to 70/30) on nano-emulsions with a 40/60 oil/surfactant ratio was determined at 25.0 °C. Fig. 2 shows nano-emulsion droplet radius as a function of Crem EL/glycolipid ratio, measured by dynamic light scattering after preparation.

The oil droplet radius was significantly influenced by 2-HDG, producing an increase in radius at low 2-HDG concentrations (up to a Crem EL/2-HDG ratio of 90/10). However, the radius decreased with a further increase in 2-HDG concentration, the smallest radius observed being at a Crem EL/2-HDG ratio of 85/15. Finally, on increasing the composition of 2-HDG, to 20 and 30 wt% in the surfactant mixtures used, the radius increased again. It has to be mentioned that destabilization was observed shortly after the preparation of nano-emulsions with a Crem EL/2-HDG ratio of 80/20 and higher. Therefore, the increase in size at high Crem EL/2-HDG ratios was due to the destabilization process. On the other hand, the presence of 2-HDM did not influence significantly the droplet size of the nano-emulsions up to a Crem EL/2-HDM ratio of 80/20. At a higher Crem EL/2-HDM ratio (70/30), the rapid increase in droplet radius after nano-emulsion preparation was attributed to its low stability. The fact that the incorporation of 2-HDM in the system had practically no effect on nano-emulsion droplet size could be an indication that it did not act as a co-surfactant (e.g. having no strong effect on the interfacial film properties). In contrast, the pronounced effect of 2-HDG can be attributed to a stronger effect on the interfacial properties of the model system and hence the reduced droplet size. Nevertheless, other factors played a role causing droplet size increase at low 2-HDG concentrations (counterbalancing the interfacial tension reduction). Furthermore, 2-HDM has a bulkier head group and greater hydrophilic–lipophilic balance (HLB = 12) than does 2-HDG (HLB = 9). The 2-HDG is more lipophilic which induces higher curvature elastic strength to promote curve phases, as was evidenced in its phase behaviour study [22]. The surfactant packing parameters for 2-HDG and 2-HDM are 1.45 and 1.05, respectively [22]. However, it was observed that both surfactants destabilized the nano-emulsions when the Crem EL/glycolipid ratio was 70/30 by forming a more opaque solution which indicates bigger droplet size.

3.2. Nano-emulsions stability

Nano-emulsions with 85/15 ratio of Crem EL/glycolipid (2-HDG/2-HDM) were chosen for further stability tests, based on the results above. Since a significant reduction of oil droplet radius was observed from the Crem EL/2-HDG nano-emulsion system, an increase in stability was expected. Additionally, to investigate the influence of branched-chain alkyl glycosides on the nano-emulsion system, the effect of temperature during storage of the

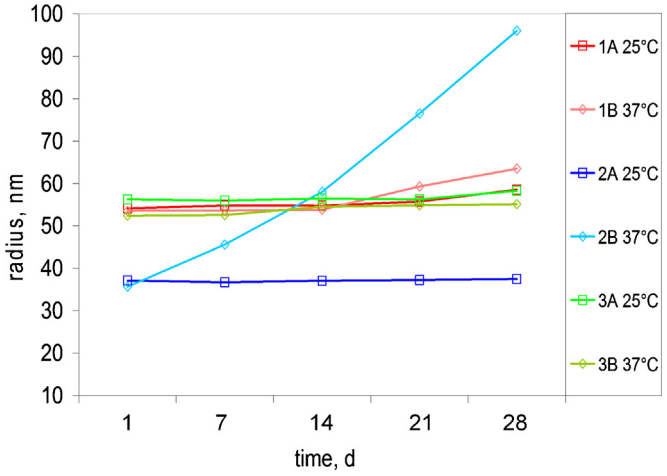

Fig. 3. Oil droplet radius (nm) of water/surfactant/MCT oil nano-emulsions as a function of time at different storage temperatures. Nano-emulsions with Crem EL (1A and 1B), 85/15 Crem EL/2-HDG (2A and 2B) and 85/15 Crem EL/2-HDM (3A and 3B). The preparation temperature was 25.0 °C, whereas the storage temperatures were 25.0 °C (A) and 37.0 °C (B). Water content was fixed at 90 wt%, whereas oil/surfactant ratio was 40/60.

nano-emulsions was also tested. Therefore, nano-emulsions were prepared at 25.0 °C and subsequently stored at 25.0 °C (room temperature) and also at 37.0 °C (body temperature) to study their suitability for pharmaceutical or cosmetic applications.

Fig. 3 shows the oil droplet radius of Crem EL, Crem EL/2-HDG and Crem EL/2-HDM nano-emulsions as a function of time at preparation temperature of 25.0 °C and two storage temperatures of 25.0 °C and 37.0 °C. The nano-emulsions of the model system, without glycolipid surfactant, were not significantly influenced by the storage temperatures. After 14 days, a small increase of droplet radius was observed in both Crem EL nano-emulsions, being the most stable the one stored at 25.0 °C (1A). Compare to the other nano-emulsion systems, the Crem EL/2-HDG nano-emulsion exhibited the smallest initial droplet radius. The storage temperature had also influenced the stability of Crem EL/2-HDG nano-emulsions. The size of nano-emulsions stored at 25.0 °C (2A) did not change within the experimental observation period of 4 weeks, whereas the nano-emulsions stored at 37.0 °C (2B), showed a rapid increase in size. This might be because 2-HDG was more lipophilic and did not stabilize the nano-emulsions at higher temperatures. Another possible explanation was the destabilizing effect of the surfactant layer at the water–oil interface at a higher temperature. However, due to small droplet size, the nano-emulsions were still stable against creaming or sedimentation.

On the other hand, the droplet size and the stability of the Crem EL/2-HDM nano-emulsions (3A and 3B) were slightly influenced by the storage temperatures in the 4 weeks, similar to the results obtained by the Crem EL nano-emulsion only. Thus, the Crem EL/2-HDM nano-emulsions were stable within the storage time. It was noted that the 2-HDM surfactant was able to stabilize the nano-emulsions at a higher range of temperatures compared to the 2-HDG. This observation was supported by the fact that the phase diagrams of maltosides were usually found to be temperature insensitive [7]. In a maltoside, the disaccharide unit has 8 OHs that strongly bind the self-assembly through intra-layer sugar–sugar hydrogen bonds compare to a glucoside that has only 4 OHs [6]. This also explains the previous observations, where 2-HDM surfactants (two glucose units) did not significantly affect the interfacial film properties of the model system. In contrast, 2-HDG (one glucose unit) had a stronger effect as a co-surfactant resulting in a pronounced reduction of the droplet size. Therefore, increasing the sugar head group's size and polarity but maintaining the same

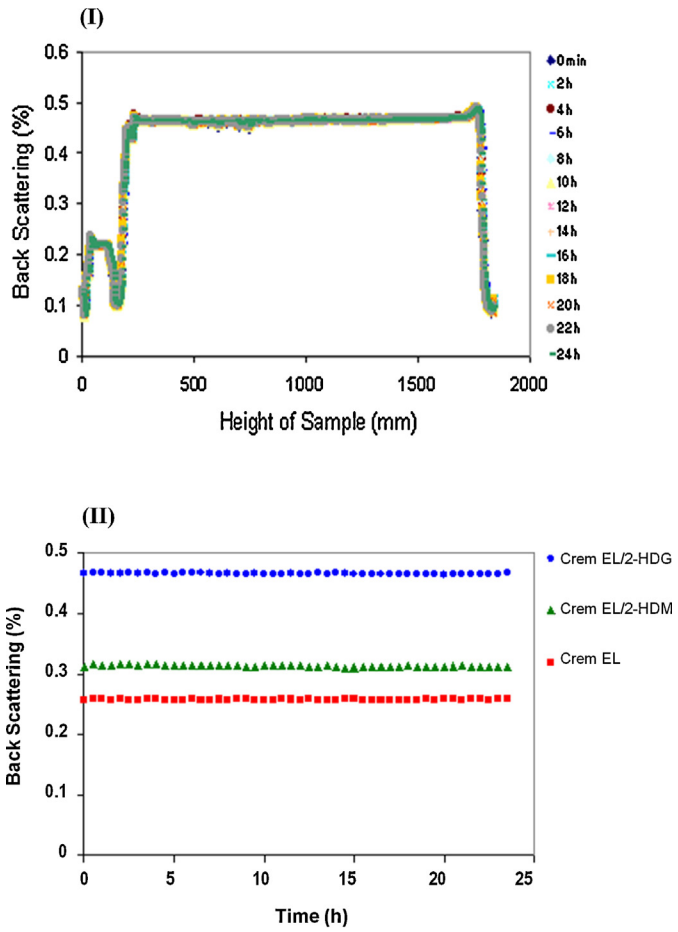

Fig. 4. (I) Backscattering (%) of Water/Crem EL/2-HDG/MCT oil (2A) nano-emulsions as a function of sample height (mm) at 25.0 °C. Data were given for different periods of time up to 24 h. Water content was fixed at 90 wt%, whereas oil/surfactant ratio was 40/60 and Crem EL/Glycolipid ratio was 85/15. (II) Backscattering (%) at a fixed sample height (1000 nm) of Crem EL (1A), Crem EL/2-HDG (2A) and Crem EL/2-HDM (3A) nano-emulsions as a function of measurement time.

branched-chain alkyl length alter the emulsion droplet size and stability similar to that of the conventional surfactants with a long chain poly(oxyethylene)ether [25,29].

The stabilities of three nano-emulsions prepared and stored at 25.0 °C were also investigated by light backscattering measurements. In all three samples, Crem EL only (1A), Crem EL/2-HDG (2A) and Crem EL/2-HDM (3A) nano-emulsions, the backscattering signal did not change during the 24 h. Fig. 4I shows the exemplary backscattering intensity in %, measured hourly, of the Crem EL/2-HDG nano-emulsion as a function of sample height. The fact that no change was observed implied that the droplet radius and droplet number did not change during the 24 h of measurements. Moreover, since changes of the backscattered light intensity could be detected also for particle migration (creaming or sedimentation), which was not visible to the naked eye, the complete overlap of the backscattering curves in Fig. 4I over 24 h indicated long-term stability.

For a better visualization, the backscattering at a fixed sample height of 1000 mm was plotted as a function of time (Fig. 4II). The backscattering remained constant for all nano-emulsion systems over 24 h of measurements. The differences in backscattering intensity can be explained by the differences in the oil droplet size. In principle, backscattering uses multiple scattering. Therefore, the more particles there are in the sample, the higher the backscattering intensity will be. The compositions of the three nano-emulsions

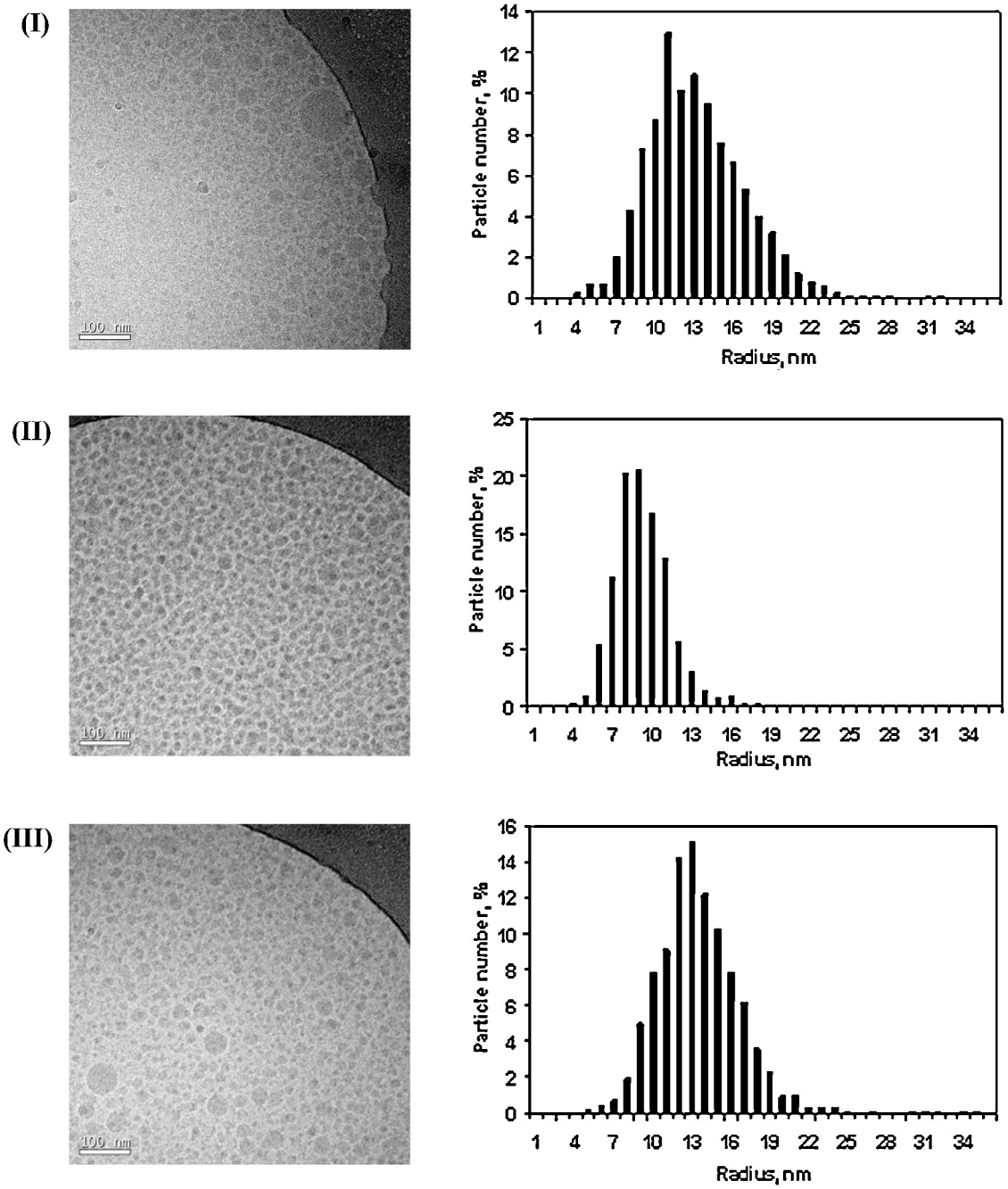

Fig. 5. Nano-emulsion droplets size images under cryo-TEM and the size distributions of ternary (I) Water/Crem EL/MCT oil (II) Water/Crem EL/2-HDG/MCT oil and (III) Water/Crem EL/2-HDM/MCT oil at 25.0 °C.

tested by light backscattering were identical except for the surfactant ratio. As mentioned above, the oil droplet size of the Crem EL/2-HDG nano-emulsion was much smaller than those of the other two. Consequently, for the same oil volume fraction, the number of oil droplet must be higher for the Crem EL/2-HDG nano-emulsion as indicated by the higher backscattering intensity. Therefore, the backscattering intensity in Fig. 4 confirmed the results obtained by DLS (Fig. 3).

3.3. Nano-emulsion characterization

Cryo-TEM micrographs were used for visualization of the nano-emulsions prepared and stored at 25.0 °C. Fig. 5 shows the electron micrographs and the corresponding size distribution obtained by statistical analysis of the nano-emulsions with Crem EL only (1A), Crem EL/2-HDG (2A) and Crem EL/2-HDM (3A). The mixed Crem EL/glycolipid ratio was 85/15. A narrower size distribution was observed for the Crem EL/2-HDG (2A) nano-emulsion compared to Crem EL (1A) and Crem EL/2-HDM (3A) nano-emulsions, implying its uniform nature (Fig. 5). In addition, the number of droplets in the Crem EL/2-HDG nano-emulsion seemed to be higher than that in the Crem EL and Crem EL/2-HDM nano-emulsions, which was in agreement with the results from the light backscattering measurements (Fig. 4).

The mean droplet radius of the Crem EL nano-emulsion was about 12–13 nm, while those of the Crem EL/2-HDG and Crem EL/2-HDM nano-emulsions were about 8–9 nm and 13–14 nm, respectively. The same trend of droplet radius was observed by the

dynamic light scattering experiment. Of the three nano-emulsion systems, the oil droplet radius of Crem EL/2-HDG nano-emulsion was the smallest, whereas those for both the Crem EL and Crem EL/2-HDM nano-emulsions were nearly similar, but greater than the former. Moreover, the size distribution of the Crem EL nano-emulsion was wider than that of the Crem EL/2-HDM. This fact explains the slightly lower long-term stability, since higher polydispersity (wide distribution) enhances particles' agglomeration and Ostwald ripening process [37]. As expected, the mean oil droplets radii obtained from Cryo-TEM were smaller (Fig. 5) compared to that from the dynamic light scattering experiment (DLS) (Fig. 3), since the droplet radius from DLS is a hydrodynamic radius, defined as the actual object's radius plus a strongly bound water shell moving with the object through the continuous phase. The OH groups in sugar molecules strongly bind to the water molecules through the inter-molecular interaction (hydrogen bonding). On the other hand, in the Cryo-TEM measurement (freezing), the continuous aqueous phase of the nano-emulsion systems is removed, leading to a smaller droplet radius (the object's actual radius). As a consequence, the hydrodynamic radius measured by DLS is usually bigger than the actual radius observed by electron micrographs.

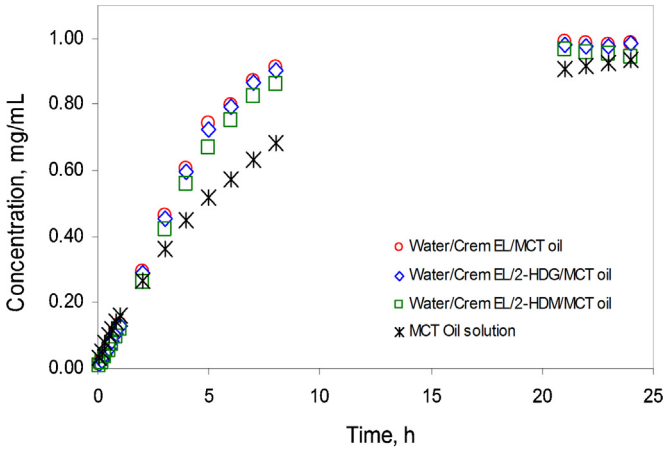

Fig. 6. Release profile of ketoprofen from the MCT oil solution and from the three nano-emulsions: Water/Crem EL/MCT oil, Water/Crem EL/2-HDG/MCT oil and Water/Crem EL/2-HDM/MCT oil as a function of time at 25.0 °C. The nano-emulsion composition was 90 wt% water content, whereas O/S and Crem EL/Glycolipid ratios of 40/60 and 85/15, respectively.

3.4. Drug incorporated nano-emulsion

The optimized percentage of drug incorporated was determined by the stability of the drug in the nano-emulsion against precipitation. The amount of ketoprofen incorporated in nano-emulsions (0.5 wt% in the final composition) was selected, taking into account the drug solubility in the nano-emulsion components and the accomplishment of sink conditions in the receptor solution (i.e. the concentration of the drug in the receptor solution was not higher than 10% of its solubility in this medium). From observation, the drug incorporated in the nano-emulsion system was unstable and precipitated after a few hours, if the percentage used was higher than this amount.

3.5. In vitro release experiments

The release of 0.5 wt% ketoprofen (KT), an oil soluble drug, from the three nano-emulsions to a receptor solution was determined as a function of time during 24 h by the dialysis bag method, as described in the experimental section. Although dialysis membranes may influence the release behaviour of molecules [39,40] it is not likely to occur in this study since the membrane molecular

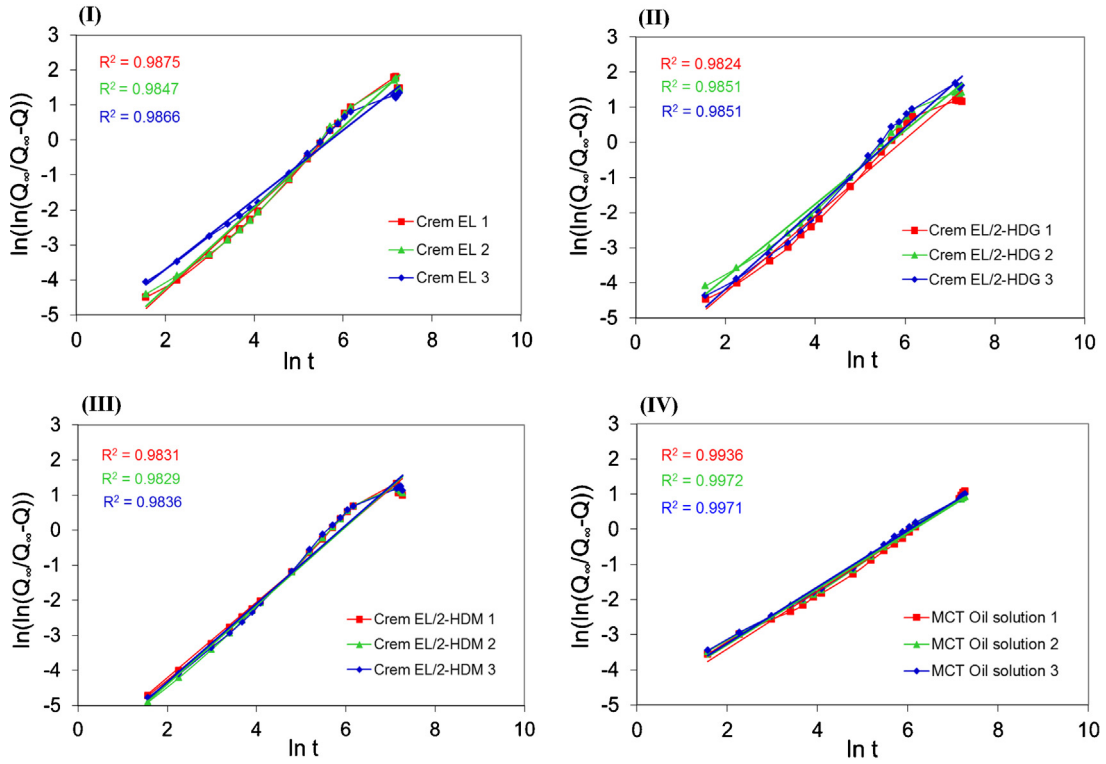

Fig. 7. Determination coefficients (R^2) of Weibull model of (I) Water/Crem EL/MCT oil (II) Water/Crem EL/2-HDG/MCT oil (III) Water/Crem EL/2-HDM/MCT oil and (IV) MCT oil solution at 25.0 °C.

weight cut-off was chosen to be much higher (12,000–14,000 Da) than the molecular weight of ketoprofen (254.28 g mol^{-1}).

The release profile of the ketoprofen (KT) from the medium-chain triglyceride oil (MCT oil) solution and from three nano-emulsions is shown in Fig. 6

Two qualitative observations can be drawn from these release profiles. Firstly, at shorter times, the release profile was approximately the same for all nano-emulsions and oil solution. Secondly, as a longer time was taken (from 3 h to 24 h), the release of ketoprofen was faster from all nano-emulsions than from the MCT oil solution. The amount of ketoprofen released after 24 h are 98.4%, 98.6%, 94.5% and 93.3% from the Water/Crem EL/MCT oil nano-emulsion, Water/Crem EL/2-HDG/MCT oil nano-emulsion, Water/Crem EL/2-HDM/MCT oil nano-emulsion and MCT oil respectively. Almost 100% ketoprofen was released from the three nano-emulsion systems by a fast mechanism. The release rate was faster compared to that of the MCT oil solution. As a consequence, these innovative nano-emulsions can be considered as promising drug delivery systems, for oral or topical administration of drugs (anaesthetic or analgesic), where a fast response is required.

In order to understand the release mechanism, the experimental results were first compared with the theoretical curves, using simulation based on Fick's second law [41]. Neither the ketoprofen oil solution nor the nano-emulsion simulated values matched the experimental points, which indicated that the lipophilic drug did not release according to a pure Fickian diffusion but through a more complex drug transport mechanism. Besides Fick's law, other mathematical functions were used, such as zero order [42,43] and first order [44,45], as well as Higuchi's law [46,47], Weibull [48–51] and Korsmeyer–Peppas model [52–55]. Examination of the linearization of the release curves with the above mentioned theories revealed that the best results were obtained with the Weibull distribution function (Fig. 7). For all three nano-emulsions, the determination coefficients (R^2) were found to be higher than 0.98.

Weibull's distribution is based on an empirical model, not deduced from any kinetic fundamental and is related to drug dissolution kinetic properties. This model permits the characterization of the drug-release process through the shape parameter β obtained from the fitting of the experimental release results [48–51,56]. In this work, the values of β were in the range of 0.75–1.01, which according to this model indicated a combined complex release mechanism in which other processes in addition to diffusion were also important.

4. Conclusions

The effect of two new synthetic branched-chain alkyl glycosides (2-HDG and 2-HDM) on the model nano-emulsions of water/Cremophor® EL/medium-chain triglyceride oil system was studied by replacing partially Cremophor® EL with sugar surfactants. In summary, the addition of 2-HDG affected the droplet radius significantly, leading to smaller droplets and higher stability at storage temperature of 25.0 °C, more than the original model (water/Cremophor® EL/medium chain triglyceride oil). On the other hand the addition of 2-HDM marginally enhanced the properties of the model nano-emulsion in terms of droplet size. However, at a higher range of temperatures, it formed a more stable nano-emulsion than with 2-HDG during the experimental time of 4 weeks. The release pattern of ketoprofen from the model water/Cremophor® EL/medium chain triglyceride oil nano-emulsions to a receptor solution was to some extent influenced by the presence of 2-HDG rather then 2-HDM. However, ketoprofen release was faster from all nano-emulsions than from a standard medium chain triglyceride oil solution. Fast release is desirable for drugs which are used for analgesic and antipyretic applications. Thus, these glycolipid stabilized nano-emulsions are interesting candidates for potential pharmaceutical applications.

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