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The usefulness of sugar surfactants as solubilizing agents in parenteral formulations

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Abstract

The usefulness of sugar surfactants as solubilizing agents was assessed and compared to commercial polyoxyethylene-based surfactants. The sugar surfactants examined comprised of monosaccharides or disaccharides with alkyl chains ranging from C_8 to C_{12}. Each surfactant was investigated with respect to solubilization capacity for felodipine and haemolytic activity. The haemolytic activity was determined using a static method in which surfactant solutions were added to fresh dog blood. The polyoxyethylene-based surfactants were found to be more suitable as solubilizing agents than the sugar surfactants due to better solubilization capacities combined with lower haemolytic activities. The sugar surfactants caused severe haemolysis below or at the critical micelle concentration, in contrast to the polyoxyethylene-based surfactants that are nonhaemolytic in this concentration range. The structure-related variations in haemolytic activity are probably due to variations in the surfactants partition coefficients for the distribution equilibrium between the aqueous phase and the cell membrane. Longer alkyl chains cause higher haemolytic activity, while larger saccharide groups lower the activity. The clear difference between sugar and polyoxyethylene surfactants, which are considerably less haemolytic, is due to a combination of low critical micelle concentrations and presumably low degrees of partitioning of the latter surfactants into the cell membranes.

Keywords: Sugar surfactant; Haemolysis; Solubilization

1. Introduction

Surfactants find one of their major pharmaceutical uses as solubility enhancers in aqueous formulations. This approach is termed solubilization and has been described extensively before (Yalkowsky, 1999). The selection of surfactant depends largely on the route of administration and the surfactant concentration. For parenteral formulations, only nonionic surfactants are generally used. Beside phospholipids, the group of acceptable surfactants for this purpose has been limited to polyoxyethylene-based surfactants.

Recently, interest in the use of alternative surfactants has grown. Existing nonionic surfactants for parenteral formulations suffer from several major drawbacks. They may cause a range of adverse responses (Attwood and Florence, 1983), haemolysis and release of histamine being perhaps the most severe. The commercial surfactant products generally consist of complex mixtures of different components, mainly with varying degrees of ethoxylation, which complicates chemical analysis and handling of product specifications. There are also environmental

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concerns of using presently accepted surfactants since they are manufactured from petrochemical products.

Sugar surfactants (Claesson and Kjellin, 2002) are a class of surfactants whose hydrophilic part consists of or is derived from a carbohydrate group. The sugar group, being a naturally occurring compound, is likely to be nontoxic. Furthermore, it is produced from renewable resources and is readily biodegradable. The sugar surfactants have drawn great attention as alternatives in many industrial applications, but the number of reports on their use in pharmaceutical applications is limited (Lerk et al., 1996; Uchegbu and Vyas, 1998; von Rybinski and Hill, 1998).

The aim of this work was to assess the usefulness of a number of simple sugar-based surfactants as solubilizers in parenteral formulations, and compare this group of surfactants with existing polyoxyethylene-based surfactants. Here we have focused on the most restricting property of the surfactants for this application, their ability to cause haemolysis. Another important aspect is the capacity to solubilize sparingly soluble substances (Yalkowsky, 1999). Those two properties are for many surfactants conflicting. Hence, the solubilization capacity for a model substance, felodipine, has also been determined. Felodipine, being a neutral and lipophilic molecule with a very limited aqueous solubility, is a good model substance for solubilization studies (von Corswant et al., 1998). The substance is stable in solution, the aqueous solubility is independent on pH, and it is readily solubilized in surfactant systems.

Several different methods, both static and dynamic, for determining the haemolytic activity of surfactants have been proposed (Krzyzaniak and Yalkowsky, 1999). The dynamic methods, in which a surfactant solution is added to a flowing blood stream, probably bear greatest relevance for the physiological situation. However, a less labor intensive static method was employed in the present study. Clearly, the obtained data cannot be interpreted in terms of haemolysis in humans after parenteral administration but the method is satisfying for comparing haemolytic activity of different surfactants.

The haemolytic activity of polyoxyethylene-based surfactants has been the topic of a number of publications (Kondo and Tomizawa, 1968; Zaslavsky et al., 1978; Azaz et al., 1981; Fukuda et al., 1987; Miyajima et al., 1987; Trägner and Csordas, 1987; Ohnishi and Sagitani, 1993; Vinardell and Infante, 1999), whereas sugar surfactants have been less investigated in this respect (Reinhart and Bauer, 1995). The diversity of methods employed for the haemolysis studies makes a direct comparison of surfactants in different reports difficult. Furthermore, the attempts to correlate the haemolytic activity to surfactant properties such as the critical micelle concentration (*cmc*) (Miyajima et al., 1987; Trägner and Csordas, 1987; Ohnishi and Sagitani, 1993; Reinhart and Bauer, 1995) or the hydrophile–lipophile balance (HLB) (Zaslavsky et al., 1978; Fukuda et al., 1987; Miyajima et al., 1987; Ohnishi and Sagitani, 1993) have failed. Hence, the haemolytic activity of a surfactant cannot be assessed based on such data. Here we report comparable haemolysis data for a few common polyoxyethylene-based surfactants and a number of typical sugar surfactants. Sugar surfactants previously not studied are also included in the present work.

2. Materials and methods

2.1. Materials

^{14}C-labeled felodipine with specific radioactivity of 667 MBq/mol and 96% radiochemical purity was obtained from AstraZeneca AB. Polyoxyethylene (10) isooctylphenyl ether (Triton® X-100), polyoxyethylene (23) lauryl ether (Brij® 35), polyoxyethylene (20) stearyl ether (Brij® 78), *N*-octanoyl-*N*-methylglucamine (Mega-8), and *N*-decanoyl-*N*-methylglucamine (Mega-10) were purchased from Sigma–Aldrich Sweden AB; *n*-octyl β-D-glucopyranoside (C_8G_1), *n*-octyl β-D-maltopyranoside (C_8G_2), and *n*-dodecyl β-D-maltopyranoside ($C_{12}G_2$) from Calbiochem Corp., La Jolla; and sucrose monododecanoate (SMD) from Fluka Chemie AG, Buchs, Switzerland. Solutol® HS15 was obtained from BASF AB. Prof. Vulfson, Institute of Food Research, Reading, UK kindly provided lactose monododecanoate (LMD). The commercial polyoxyethylene surfactants are not isomerically pure but consist of diverse collections of homologous surfactants. Thus, for Triton® X-100, Brij® 35, and Brij® 78 we have used the average molecular weights provided by the supplier. In the estimation of the molecular weight of Solutol® HS15, we have accounted for the fraction of free polyethylene glycol,

which is up to 35% (w/w) according to the supplier, and only considered the major components of the surfactant mixture. It should be noted that for this particular product the molecular weight is indeed a rather coarse estimation, which may have poor physical relevance. Therefore, data of Solutol® HS15 should be seen as indicative only.

For each haemolysis experiment, a volume of fresh blood not exceeding 10 ml was collected from adult Beagle dogs. The study was approved by the Animal Ethics Committee of Gothenburg (ethics approval number, 120200).

2.2. Solubilization capacity

For the determination of the solubilization capacity, each surfactant was dissolved in normal saline (0.9% NaCl in water) in three to four different concentrations at or above the corresponding *cmc*. An excess of ^{14}C-labeled felodipine was added to each surfactant solution and the samples were allowed to equilibrate for at least 48 h in room temperature. The samples were filtered to remove undissolved material and the concentration of solubilized felodipine was determined by means of scintillation detection. No radiochemical degradation could be observed during the experiments.

The solubilization capacity (κ) was calculated as the slope of the solubilization curve in the linear region

$$\kappa = \frac{\Delta S_{\text{felodipine}}}{\Delta C_{\text{surfactant}}},$$

where $S_{\text{felodipine}}$ is the concentration of solubilized felodipine and $C_{\text{surfactant}}$ is the surfactant concentration.

2.3. Haemolytic activity

The surfactants were dissolved and diluted in normal saline (0.9% NaCl in water). A total of 100 μl of surfactant solution was added to 400 μl of fresh blood. Immediately after addition, the blood/surfactant mixtures were gently agitated for 2–3 s. The samples were further incubated by shaking for 10 min in a water bath at 37 °C. After incubation, the intact red blood cells were separated from the supernatant by centrifugation for 6 min at 3000 × *g* and 5 °C. The supernatant was removed and analyzed with respect to hemoglobin in a Cobas Bio spectrophotometer, Hoffman La Roche & Co. Typically, five to six different concentrations were tested in triplicate for each surfactant. Prior to testing, the surfactant concentration region was adjusted to give approximately 0–10% haemolysis.

Six control samples, corresponding to the basal haemolysis, were prepared by adding 100 μl of normal saline to 400 μl blood. The total amount of hemoglobin was determined after complete lysis of the red blood cells. A total of 400 μl blood was added to 3600 μl distilled water, and the mixture was incubated for 30 min to allow for complete haemolysis. The controls were then analyzed with respect to hemoglobin.

The degree of haemolysis due to the surfactant activity (%*H*) was calculated according to

$$\%H = \frac{\text{Hb} - \text{Hb}_0}{\text{Hb}_{\text{tot}}} \times 100\%,$$

where Hb is the amount of released hemoglobin in each sample, Hb_0 the amount released due to basal haemolysis (negative control), and Hb_{tot} is the total amount of hemoglobin in the blood.

The haemolysis data presented in this report are shown in a similar fashion for all surfactants. The degree of haemolysis is plotted as a function of the surfactant concentration in the mixture of blood and surfactant solution. In a diagram constructed in this way, the position of the haemolysis curve indicates the haemolytic activity of the surfactant. When comparing a number of surfactants with regard to their haemolytic activity, the order of activity is given by the relative order of the haemolysis curves.

It should be noted that only haemolysis levels below approximately 15% have been determined. Hence, the erythrocytes are affected only to a minor degree of the surfactants in this concentration region. This fact implies that the erythrocytes are in excess of the surfactants in the haemolysis experiments. Hence, the natural variations in the number of erythrocytes between blood samples will have only very small effects on the haemolysis curves. For our purposes it is not crucial to know the relative amounts of surfactant to erythrocytes. If the details of the haemolysis mechanism were to be fully investigated, the relative amount of surfactant to erythrocytes would be important.

3. Results

Although the solubilization capacity (κ) of a surfactant is strongly influenced by the substance that is solubilized, general conclusions regarding the solubilizing properties of the surfactant may still be drawn from solubilization data of only one substance. Here we have used felodipine as a model compound with poor aqueous solubility, 0.8 mg/l or 2 μM (von Corswant et al., 1998), to determine the solubilization capacities. Fig. 1 shows the solubilization curves of felodipine for all the sugar surfactants in this study. In Fig. 2 are shown the corresponding curves for the polyoxyethylene-based surfactants. Clearly, the concentration of felodipine in the surfactant solutions are several orders of magnitude higher than the aqueous solubility. The κ's are determined from the slope of the linear parts of each curve. The solubilization capacities of all surfactants are summarized in Table 1.

The haemolysis curves of the polyoxyethylene-based surfactants are shown in Fig. 3. Clearly, the haemolytic activity of the surfactants varies considerably. The individual order of the haemolysis curves indicate that the haemolytic activity increases in the following order

Table 1
Felodipine solubilization capacities (κ) of various surfactants

Surfactant	κ (mol/mol)
Brij® 78	0.233
Brij® 35	0.166
Solutol® HS15	0.163
Triton® X-100	0.107
$C_{12}G_2$	0.0673
Mega-10	0.0318
LMD	0.0308
SMD	0.0289
C_8G_1	0.0184
C_8G_2	0.0175
Mega-8	0.0153

$$\text{Solutol}^{®}\ \text{HS15} < \text{Brij}^{®}\ 35 < \text{Brij}^{®}\ 78 < \text{Triton}^{®}\ \text{X-100}.$$

As described before, the molar concentration of Solutol® HS15 cannot be defined exactly due to the complexity of the product. Hence, the position of the haemolysis curve along the concentration axis may be shifted although the shape of the curve is correct. Despite this uncertainty it is quite clear that this product is much less haemolytic than the other polyoxyethylene-based surfactants.

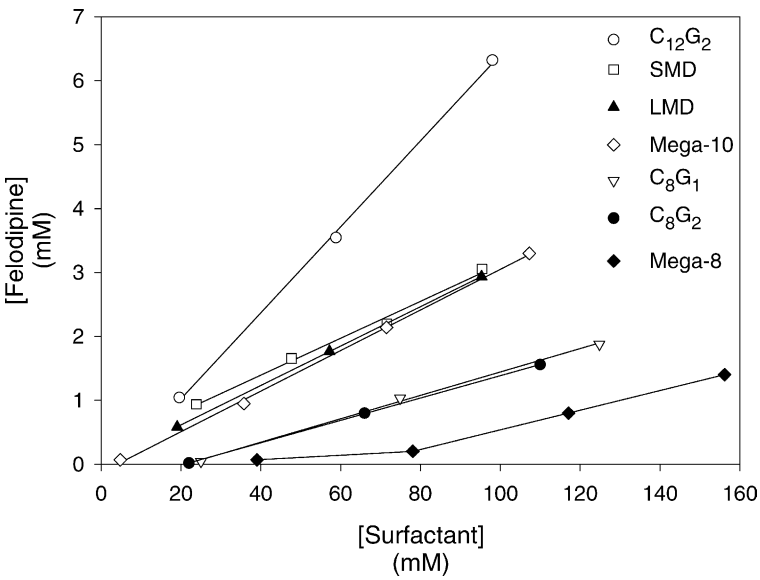

Fig. 1. Solubilization of felodipine by sugar surfactants.

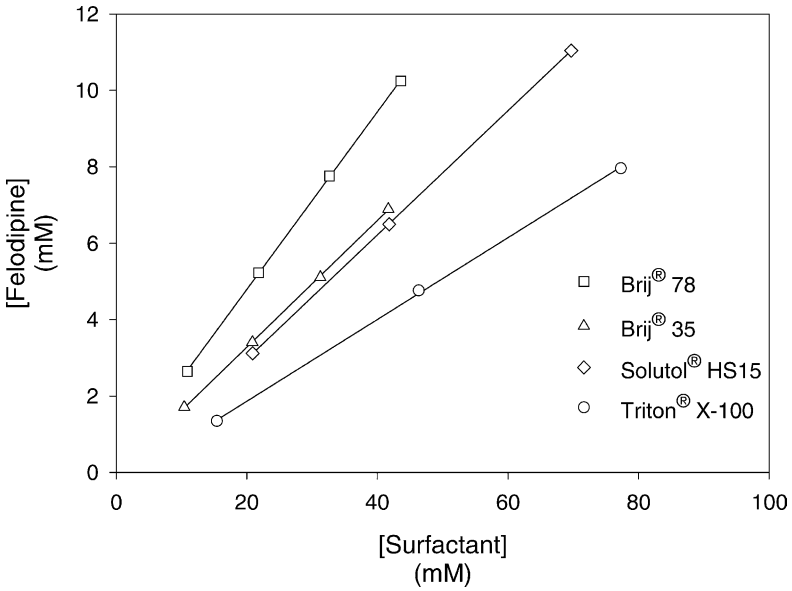

Fig. 2. Solubilization of felodipine by polyoxyethylene-based surfactants.

The haemolysis curves of sugar surfactants with a dodecyl group, $C_{12}G_2$, SMD, and LMD, are shown in Fig. 4. For those surfactants the hydrophobic groups are identical, but the polar headgroups have slightly different structures. Furthermore, the disaccharides, maltose, sucrose, and lactose, are attached to the hydrocarbon chains by different bonds. In the case of $C_{12}G_2$ the two moieties of the molecule are connected

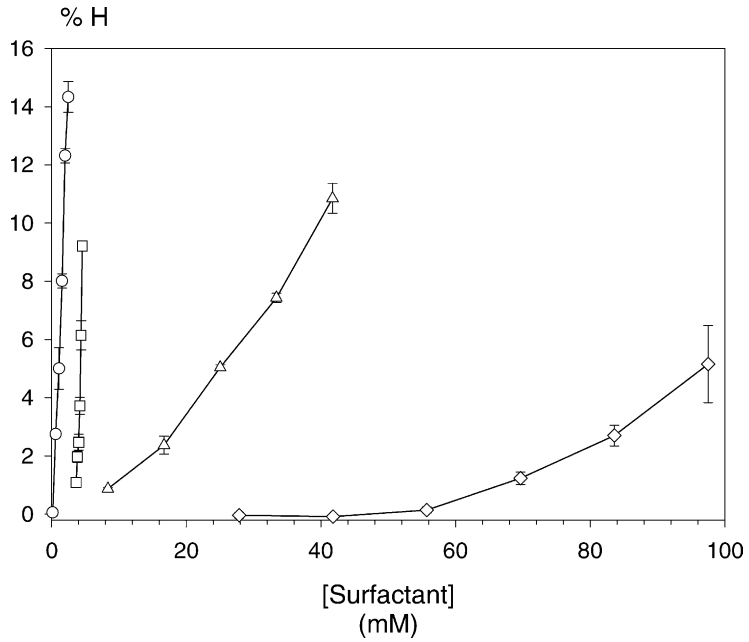

Fig. 3. Haemolysis curves of Triton® X-100 (○), Brij® 78 (□), Brij® 35 (△), and Solutol® HS15 (◇).

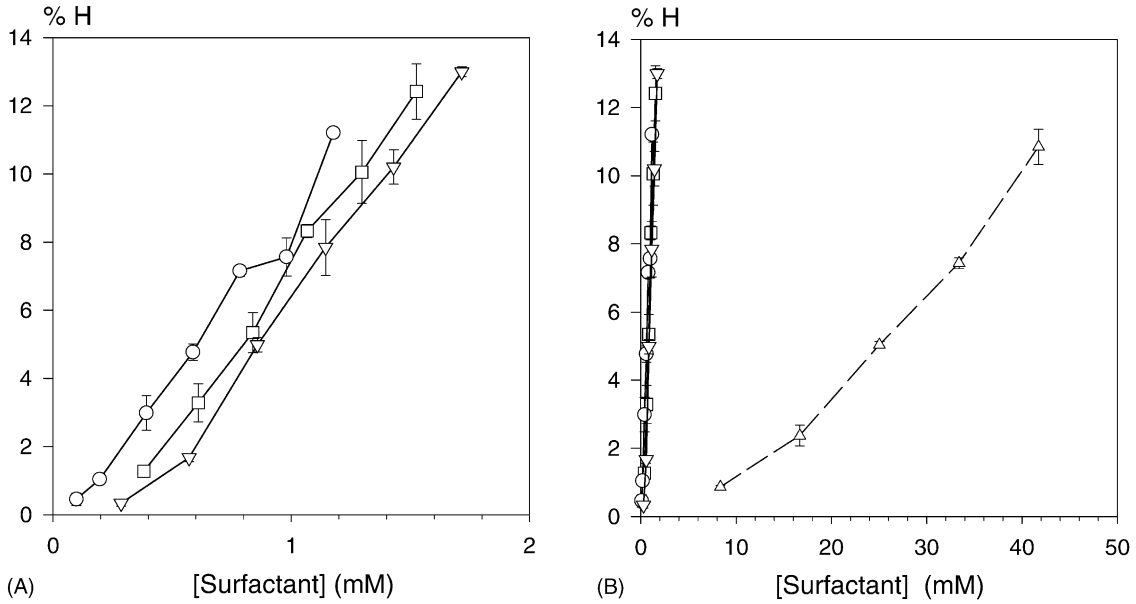

Fig. 4. (A) Haemolysis curves of $C_{12}G_2$ (○), SMD (□), and LMD (▽). (B) Comparison of the haemolysis curves of C_{12} sugar surfactants and the corresponding polyoxyethylene C_{12} surfactant Brij® 35 (dashed line).

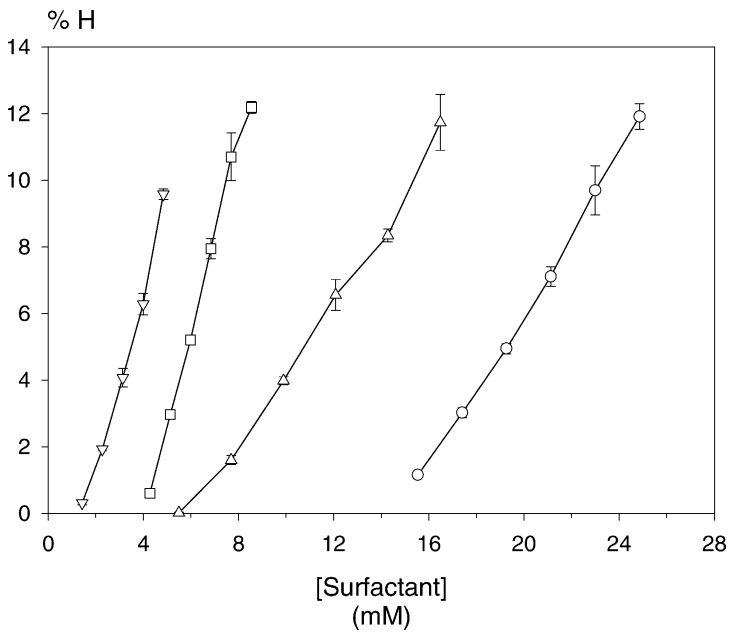

Fig. 5. Haemolysis curves of Mega-10 (▽), C_8G_1 (□), C_8G_2 (△), and Mega-8 (○).

by an acetal link, whereas the other two surfactants are esters.

Those small structural differences between the dodecyl sugar surfactants had a substantial influence on the solubilization capacities (Fig. 1). Similar structural effects could not be observed for the haemolytic activity. Instead, the haemolysis curves of the three surfactants almost coincided (Fig. 4A). However, it should be noted that these surfactants are clearly more haemolytic than the corresponding polyoxyethylene dodecyl ether, Brij® 35 (Fig. 4B).

Fig. 5 shows the haemolysis curves of Mega-10, Mega-8, C_8G_1, and C_8G_2. The hydrophobic groups of these surfactants are composed of octyl (C_8) groups except for Mega-10, which is a decyl (C_{10}) chain surfactant. The figure clearly shows that both the hydrocarbon chain length and the structure of the polar headgroup influence the haemolytic activity. From Fig. 5 it is evident that the C_{10} surfactant is more haemolytic than the C_8 surfactants. However, they are less haemolytic than the C_{12} sugar surfactants in Fig. 4.

The haemolytic activity of the sugar surfactants increases in the following order

$$\text{Mega-8} < C_8G_2 < C_8G_1 < \text{Mega-10} < \text{LMD, SMD, } C_{12}G_2.$$

4. Discussion

A prerequisite for surfactant solubilization of a substance is that micelles are present in the aqueous phase. From this it follows that the ability of a surfactant to solubilize a sparingly soluble substance is not only governed by the solubilization capacity but also the *cmc* of the surfactant. This fact is well illustrated for the octyl chain surfactants in Fig. 1 but it is true for all surfactants. Clearly, there is a critical surfactant concentration for each surfactant below which the felodipine concentration is equal to the aqueous solubility of the compound. Those critical concentrations are as expected close to the *cmc*'s of the surfactants. The *cmc*'s of the surfactants in this study are given in Table 2 for comparison.

The structural factor that has the strongest impact on the solubilization capacity (κ) is the hydrocarbon chain length (Yalkowsky, 1999). The κ's for felodipine reported here follow this general rule well. The surfactant with the longest hydrocarbon chain, 18 carbons in Brij® 78, also has the highest capacity. In fact, this is the highest solubilization capacity ever observed for felodipine. Similarly, the surfactants with the lowest capacity are found among the octyl chain surfactants, Mega-8, C_8G_1, and C_8G_2. The reason κ increases with increasing hydrocarbon chain length is that the micelles become larger with increasing length. The nonpolar core of the micelles becomes larger and the radius of curvature of the micelle surface increases, both favoring the dissolution of solutes in the interior of the micelles.

There are only minor differences in κ between the sugar surfactants, with the exception of $C_{12}G_2$. Although the explanation for the higher capacity of this surfactant can only be tentative, the result suggests that the headgroup structure has significance for the solubilization of felodipine. This conclusion also finds support in the κ of Brij® 35, another dodecyl chain surfactant, which is considerably higher than for other surfactants with the same hydrocarbon chain length. The headgroup structure probably influences the geometry of the micelles rendering them a higher solubilizing capacity. It is also likely that this structural effect contributes to the generally higher solubilizing

Table 2
Reported values of the critical micelle concentrations in pure aqueous solutions of the investigated surfactants

Surfactants	*cmc* (mM)	References
SMD	0.455 0.339 (25 °C)	Herrington and Sahi (1986); Claesson and Kjellin (2002)
LMD	0.427 (25 °C)	Drummond and Wells (1998)
C_8G_1	20 25 (22 °C)	Kameyama and Takagi (1990); Claesson and Kjellin (2002)
C_8G_2	19.1 (25 °C)	Boyd et al. (2000)
$C_{12}G_2$	0.15 0.185 (25 °C)	Aoudia and Zana (1998); Claesson and Kjellin (2002)
Mega-10	5.5 (25 °C)	Aveyard et al. (1998)
Mega-8	74 (25 °C)	Harada and Sahara (1994); Kawaizumi et al. (1998)
Brij® 35	0.068 (22 °C)	Patist et al. (2000)
Brij® 78	0.0071 (22 °C)	Patist et al. (2000)
Triton® X-100	0.20 (22 °C)	Patist et al. (2000)

capacities of polyoxyethylene-based surfactants compared to sugar surfactants.

It should be noted that the localization of the solubilized drug in the micelles probably plays an important role for the effects of surfactant structure on solubilization. For instance, it is most likely that the headgroup structure has a stronger influence on the solubilization capacity for a drug that is localized at the surface rather than in the interior of the micelles. However, the localization of the drug in the micelles cannot be determined from the present data.

In order to assess the usefulness of a surfactant as a solubilizer for pharmaceutical use one also needs to consider unwanted effects, such as haemolysis. The polyoxyethylene surfactants in this study are reasonably good solubilizers, possibly with the exception of Triton® X-100, since they have high solubilizing capacities and possess relatively low haemolytic activities. It is illustrating to compare the concentration at which the haemolysis commences for each surfactant with the respective *cmc*. From the *cmc*'s in Table 2 and the haemolysis curves in Fig. 3 it is obvious that the concentration of each polyoxyethylene surfactant needs to be higher or much higher than the corresponding *cmc* before the haemolysis becomes measurable. The fact that the reported *cmc*'s were determined at both lower temperatures and ionic strength than for the experiments performed here does not alter this conclusion. The *cmc*'s of polyoxyethylene surfactants are known to decrease at elevated temperatures (Jönsson et al., 1998c) and increased salt concentrations (Carale et al., 1994), which strengthens this conclusion. The practical implication of this observation is that these surfactants are able to solubilize substances without necessarily causing any haemolysis.

The sugar surfactants in this study are not equally suitable as solubilizers in pharmaceutical applications as the polyoxyethylene surfactants. The sugar surfactants tend to be more haemolytic than their polyoxyethylene-based counterparts, best illustrated in Fig. 4 by SMD, LMD, $C_{12}G_2$ and Brij® 35. This fact, combined with rather poor solubilization capacities, limits the use of the present sugar surfactants as solubilizers.

The comparison between the *cmc*'s and the haemolysis curves in Figs. 4 and 5 reveals that this type of surfactants causes substantial cell damage at concentrations close to or even below their *cmc*'s. Once again the reported *cmc*'s are determined under different experimental conditions than here. The effects of elevated temperature and higher ionic strength are not fully known for these surfactants. However, temperature effects are generally regarded as marginal (Sulthana et al., 2000; Kjellin et al., 2001; Claesson and Kjellin, 2002). The presence of salt is likely to lower the *cmc*'s of all sugar surfactants (Claesson and Kjellin, 2002) but probably not more than 20–25% (Zhang et al., 1996; Miyagishi et al., 2001). Consequently, the short-chain, C_8–C_{10}, sugar surfactants cause substantial haemolysis already in the pre-micellar concentration region. For the dodecyl chain surfactants, micelles have just started to form in the aqueous phase when the haemolytic process commences.

It is obvious from this study that the haemolytic activity of nonionic surfactants increases with increasing hydrocarbon chain length. It is likely that this trend continues also beyond C_{12} chain lengths, although no general conclusion can be drawn from the limited data presented here. It has also been reported that the toxicity of surfactants reaches a maximum at C_{12}–C_{14} chains (Schott, 1973; Ferguson and Prottey, 1976).

To better understand the widely different haemolytic behaviour of sugar surfactants and polyoxyethylene-based surfactants we need to elaborate on the haemolysis mechanism. It has previously been suggested that the haemolytic process is initiated by the absorption of surfactant molecules onto the surfaces of the red blood cells at low surfactant concentrations (Kondo and Tomizawa, 1968; Bonsall and Hunt, 1971; Zaslavsky et al., 1978; Miyajima et al., 1987). In more recent reports on the molecular interactions between surfactants and lipid bilayers (Inoue et al., 1988; Edwards and Almgren, 1991; Edwards and Almgren, 1992; Wenk and Seelig, 1997; de la Maza et al., 1998; López et al., 1998) this step is viewed as a surfactant partition equilibrium between the aqueous phase and the membrane. The partitioning of surfactant molecules into the lipid bilayer causes a slight growth of the vesicle accompanied by a leakage of material from the vesicle interior. At higher surfactant concentrations the cell membranes disrupt, the surfactant solubilizes the lipids of the membrane and mixed micelles are formed. At this stage the leakage of entrapped substances is almost instantaneous.

The surfactant concentrations in this study are not sufficient to completely solubilize the erythrocyte

membrane lipids. Here only the initial phase of the haemolytic process has been in focus. The effect on the cell membrane is in this region highly dependent on the distribution of the surfactant to the membrane. Therefore, it is relevant to discuss the structural surfactant effects in terms of the partition equilibrium and its corresponding partition coefficient (K) defined as (Schurtenberger et al., 1985)

$$K = \frac{S_B}{S_W L},$$

where S_B is the concentration of surfactant incorporated into the bilayers, S_W the surfactant monomer concentration in the aqueous phase, and L is the lipid concentration.

According to the suggested models, the leakage of hemoglobin from the erythrocytes increase with increasing surfactant concentration in the membranes, in this case being the S_B-to-L ratio. Hence, surfactants with a high affinity to the cell membrane, i.e. surfactants with large partition coefficients K, will be more haemolytic. Following this line of reasoning it is tempting to conclude that the structure–property relation regarding haemolytic activity of surfactants is reflected in the partition coefficients. Only very few studies on the structural effects on K exist to confirm this statement, but it has been shown for alkyl glucosides that K increases steeply with increasing alkyl chain length (de la Maza et al., 1998). This is completely congruent with the results of the C_8-/C_{10}-/C_{12}-chain sugar surfactants reported here.

The sugar surfactant results also indicate that the structure of the hydrophilic headgroup influence the haemolytic activity. Although the study is limited to only monosaccharides and disaccharides, the activity appears to decrease with increasing size of the sugar group. This observation is also in line with previous findings (Reinhart and Bauer, 1995). Another structure-related difference in the haemolytic activity is that between surfactants with a closed pyranoside rings (e.g. C_8G_1) and a straight polyhydroxylated chain (e.g. Mega-8). The surfactant with the more flexible headgroup is less haemolytic. Further, more systematic, investigations are needed to fully establish the influence of the headgroup structure and whether this is reflected in the partition coefficient.

In the partition equilibrium view, a lowering of the monomer concentration (S_W) should reduce the deteriorating effects on the lipid membranes since the S_B-to-L ratio also becomes low. This might appear contradictory to the behaviour of the sugar surfactants. For a series of pure sugar surfactants with varying chain lengths a decrease in S_W, caused by the lowering of the *cmc*, is accompanied by an increase in haemolytic activity. The explanation to this effect is probably that the driving force for micellization, i.e. the low aqueous solubility of the hydrophobic moiety of the surfactant (Evans and Wennerström, 1994), also gives rise to large partition coefficients (K). Consequently, increasing the chain length results in lower S_W and larger K. Our results suggest that the effect of increasing chain length on K is larger than that on S_W. Support for this conclusion can be found in previously published data on alkyl glucosides (de la Maza et al., 1998). Using those data it can be shown that the product $K \times S_W$ increases with increasing hydrocarbon chain length, i.e. the influence on K dominates over that on S_W.

Using similar arguments one can speculate on the reason for the exceptionally low haemolytic activities for the polyoxyethylene-based surfactants. The surfactants used here are much less haemolytic than the sugar surfactants, although the *cmc*'s are very low. This unexpected behaviour may be due to the fact that the polyoxyethylene-based surfactants used here are not isomerically pure. Such mixtures are bound to form mixed micelles when dissolved in aqueous solutions. It is well known that only minor amounts of surfactants with low *cmc*'s strongly influence the *cmc* of the mixture and that the mixed micelles are enriched in those more hydrophobic surfactants (Jönsson et al., 1998b). Hence, it is possible that, due to the presence of minor amounts of hydrophobic components, the reported *cmc*'s of the technical grade products are lower than the *cmc* of the pure stated major component of each product. For example, the *cmc* of Brij® 35 (68 μM) is probably lower than the *cmc* of the stated major component, polyoxyethylene (23) lauryl ether ($C_{12}E_{23}$). Furthermore, the *cmc*'s of the pure surfactants $C_{12}E_5$ (65 μM), $C_{12}E_6$ (68 μM), $C_{12}E_7$ (69 μM), and $C_{12}E_8$ (71 μM) (Jönsson et al., 1998a) indicate that the *cmc* of $C_{12}E_{23}$ is indeed somewhat higher than the reported value for Brij® 35. Consequently, the partition coefficient of the major component of Brij® 35 is probably smaller than the low *cmc* indicates. Furthermore, S_W of this component is lower at *cmc* than would be

expected for the pure surfactant. For technical grade products the surfactant partition into the lipid membrane may, therefore, be weak due to the combination of both low S_W and low K.

Although the monomer concentration in theory is constant at concentrations above the *cmc*, it probably increases slightly as the total concentration increases. At concentrations much higher than the *cmc*, the monomer concentration of the polyoxyethylene-based surfactants in the aqueous phase becomes sufficiently high to push the S_B-to-L ratio into the cell-damaging region. At this point also this group of surfactants cause haemolysis.

The degree of changes in the lipid membrane structure caused by the incorporation of a surfactant and the following effects of those changes are specific to each surfactant. It should be noted that there are probably differences between different surfactants when it comes to the effects on the bilayer structure. However, the data presented here do not allow any further investigation of such effects.

5. Conclusions

The comparison of surfactants in the present work show that the commercial polyoxyethylene-based surfactants are more suitable as solubilizing agents, in particular in parenteral formulations, than the sugar surfactants. The sugar surfactants have poor solubilization capacities and are relatively haemolytic. The behaviour of this group of surfactants needs to be improved to make them more useful. In this study, it is indicated that introducing longer alkyl chain lengths enhances the solubilization capacity. Prolonging the chain will give rise to a higher haemolytic activity, which may be compensated for by increasing the size of the sugar group or possibly by making the headgroup more flexible by ring-opening of the saccharide.

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