Expert Opinion

informa
healthcare

From conventional towards new – natural surfactants in drug delivery systems design: current status and perspectives

Snežana Savić†, Slobodanka Tamburić & Miroslav M Savić
University of Belgrade, Institute of Pharmaceutical Technology and Cosmetology, Faculty of Pharmacy, Belgrade Vojvode Stepe 450, 11221 Belgrade, Serbia

Importance of the field: Surfactants play an important role in the development of both conventional and advanced (colloidal) drug delivery systems. There are several commercial surfactants, but a proportionally small group of them is approved as pharmaceutical excipients, recognized in various pharmacopoeias and therefore widely accepted by the pharmaceutical industry.

Areas covered in this review: The review covers some of the main categories of natural, sugar-based surfactants (alkyl polyglucosides and sugar esters) as prospective pharmaceutical excipients. It provides analysis of the physicochemical characteristics of sugar-based surfactants and their possible roles in the design of conventional or advanced drug delivery systems for different routes of administration.

What the reader will gain: Summary and analysis of recent data on functionality, applied concentrations and formulation improvements produced by alkyl polyglucosides and sugar esters in different conventional and advanced delivery systems could be of interest to researchers dealing with drug formulation.

Take home message: Recent FDA certification of an alkyl polyglucoside surfactant for topical formulation presents a significant step in the process of recognition of this relatively new group of surfactants. This could trigger further research into the potential benefits of naturally derived materials in both conventional and new drug delivery systems.

Keywords: advanced drug delivery systems, alkyl polyglucosides, conventional drug delivery systems, natural surfactants, physicochemical behavior

Expert Opin. Drug Deliv. (2010) 7(3):353-369

1. Introduction

Surfactants present one of the most important classes of pharmaceutical excipients, finding a wide range of uses in pharmaceutical preparations. Depending on the type of formulation, surfactants may play a role in solubilization or stabilization of drugs in different liquid preparations, improve physical stability and textural characteristics of semisolids, or alter the flow properties of powders and granulates in solid dosage form manufacturing [1]. Moreover, surfactants play an important role in the development of colloidal drug delivery systems, such as reverse micelles, vesicles, liquid crystal dispersions, nanoemulsions and nanoparticles [2].

In addition to their basic functions in dosage form formulation, surfactants could be included with the aim of improving the bioperformance of drugs. Depending on their structure and physicochemical properties, surfactants could alter thermodynamic activity, solubility, diffusion, disintegration and dissolution rate of a drug. By affecting these parameters, surfactants influence the rate and extent of

10.1517/17425240903535833 © 2010 Informa UK Ltd ISSN 1742-5247

Article highlights.

- There are three categories of natural surfactants: amphiphiles produced by yeast or bacteria, amphiphiles containing a natural polar headgroup and amphiphiles containing a natural hydrophobic tail.
- Research is particularly intensive in the area of sugar-based surfactants (alkyl polyglucosides (APGs) and sugar esters)), which are of pharmaceutical importance as prospective, and recently FDA-approved, pharmaceutical excipients for conventional and novel drug delivery systems.
- APGs and sugar esters exhibit peculiar physicochemical behavior (pH stability/sensitivity, specific interfacial properties/adsorption phenomenon and phase transition, temperature insensitivity, i.e. microemulsions forming independent on temperature...) and favorable safety profiles (particularly in dermatological and ocular use).
- In conventional drug delivery systems natural APG mixed emulsifiers favorably interact with a range of pharmaceutical excipients, forming topical vehicles of different rheological profiles, stabilized predominantly by synergistic effects of lamellar liquid crystalline (L_α) and complex lamellar gel (L_β) phases, with acceptable efficacy and safety.
- In addition, sucrose fatty acids esters (SEs), nonionics with a sucrose sub-unit as the polar headgroup, show some potential for skin penetration enhancement.
- Microemulsions, niosomes and nanoparticles present some of the novel delivery systems where the application of sugar-based surfactants has been thoroughly investigated.
- In particular, sugar surfactants have been studied in the delivery of poorly soluble drugs and peptides/proteins for oral delivery, often replacing traditional surfactants or in the combination with some of them.

This box summarises key points contained in the article.

drug absorption. Furthermore, interacting directly with biological membranes, surfactants may alter their permeability and consequently drug penetration/permeation profile, that is, their transport across the membranes. This behavior is strongly related to surfactant safety profiles, as they also have the capacity to irritate the skin and damage biological membranes [1,3].

A large number of commercial surfactants is available, but a proportionally small group of them is approved as pharmaceutical excipients, recognized in various pharmacopoeias [4-7] and therefore widely accepted by the pharmaceutical industry in the formulation of drug delivery systems. From this group, surfactants of particular pharmaceutical importance include anionic sodium lauryl sulfate (SLS/SDS) and non-ionic polyoxyethylated glycol monoethers (e.g., cetomacrogol), sorbitan esters (Span®; AkzoNobel Corporate, Netherlands) and ethoxylated sorbitan esters or polysorbates (Tween®; AkzoNobel Corporate, Netherlands).

One of the most prominent functions of surfactants is their capacity to stabilize different types of emulsion system intended for skin application [1]. Mixed emulsifiers consisting of fatty alcohols (amphiphiles) and ionic or non-ionic surfactants are probably the most commonly used emulsifiers, officially listed in many pharmacopoeias (e.g., European Pharmacopoeia 6.0 [Ph. Eur. 6.0]) [4]. The problem with these emulsifiers is their irritation potential, originating from either anionic surfactants (e.g., sodium lauryl sulfate) or ethoxylated non-ionics (e.g., polysorbates) [3,8]. Moreover, SLS is well established as a cytotoxic chemical marker [9] and *in vivo* skin irritant [10-12]. Besides this sporadically shown irritancy, there is an extra problem with mixed polyoxyethylated non-ionic systems – a very slow structuring of the emulsion systems. In this type of mixed emulsifier, surfactant is interpositioned among the amphiphile molecules, usually consisting of long chain fatty alcohols. Emulsion structuring occurs as a result of the swelling of the alcohol α-crystals, owing to the hydration of the polyoxyethylene chains of the surfactant. This process is slow and could postpone the final structuring of the emulsion system for up to 2 months, which could significantly affect its rheological properties and physical stability, and could bring about inconsistent drug availability [13]. The use of vehicles based on the conventional mixed emulsifiers, although meeting general requirements for pharmaceutical bases, is very often accompanied by adverse skin reactions [8,12], or associated with an unpleasing appearance and unacceptable skin feeling during application [14]. Overcoming the above problems is an important formulation task, which may be accomplished by adequate selection of new emulsifier systems [8,15].

Increased attention given to the environment over the past few decades has produced a growing interest in the field of natural surfactants. The term 'natural surfactants' relates in its broadest sense to surface-active substances coming from natural raw materials [10]. Generally, there are three categories of natural surfactants: amphiphiles produced by yeast or bacteria, amphiphiles containing a natural polar headgroup and amphiphiles containing a natural hydrophobic tail. Sugars and amino acids are the two most important examples of surfactant polar headgroups of natural origin [16-18]. Research is particularly intensive in the area of sugar-based surfactants, which are of pharmaceutical importance as prospective, and recently FDA-approved, pharmaceutical excipients for conventional and new drug delivery systems.

This review covers some of the main categories of sugar-based surfactants, potentially useful in pharmaceutical development, including the physicochemical background and reports of their prospective use in conventional and advanced drug delivery systems for different routes of administration.

2. Sugar-based surfactants – physicochemical behavior and safety evaluation

Interest in sugar-based surfactants is based on the fact that they are made from renewable materials and possess favorable properties for applications in various fields. For example,

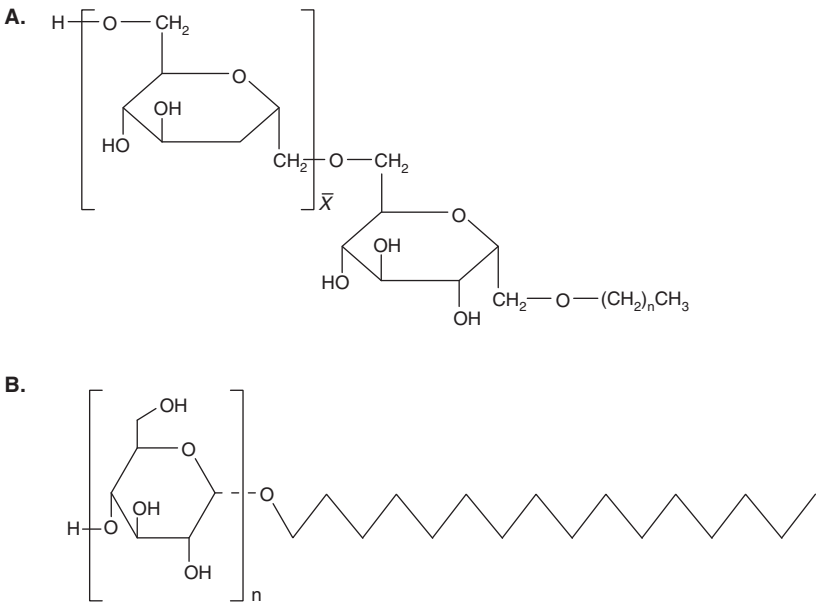

Figure 1. A. Chemical structure of alkyl polyglucosides. **B.** Chemical structure of alkyl polyglucoside surfactant cetearyl glucoside combined with cetearyl alcohol.

temperature-insensitive physicochemical characteristics present a useful property in drug formulation development. This is particularly important if one compares the sugar surfactants with well-known non-ionic alkyl polyethyleneglycol ethers, which are very sensitive to temperature changes [19]. In recent years, there has been a focus on three classes of surfactants with sugar as polar headgroups: alkyl polyglucosides (APGs, alkyl glucosides), alkyl glucamides and sugar esters [16,17].

At present, there is a very strong interest in exploring APGs (**Figure 1A**) as surfactants for several types of application. By combining a vegetable oil (e.g., palm kernel or coconut oil) and sugar (from potato, wheat or corn starch) as raw materials, it was, for the first time, possible to offer commercially significant amounts of non-ionic surfactants completely based on renewable resources, without compromising their performance. APGs are synthesized by direct reaction of glucose with fatty alcohol, using a large excess of alcohol in order to minimize sugar oligomerization. With regard to their ecological, toxicological and dermatological properties, APGs can be considered surfactants with extraordinary product safety [19].

APGs show peculiar physicochemical behavior. They are stable at high pH and sensitive to low pH, where they hydrolyze to sugar and fatty alcohol. A sugar unit is more water soluble and less soluble in hydrocarbons than the corresponding polyoxyethylene unit; hence, APGs are more hydrophilic than their polyoxyethylene-based surfactant counterparts (e.g., polysorbates). This makes the physicochemical behavior of APGs in oil–water systems distinctly different from that of conventional non-ionics. It affects their interfacial properties (water–air, water–oil and water–solid interfaces), as well as their behavior in solutions, that is, phase behavior [20,21].

Understanding adsorption behavior of sugar surfactants is necessary in order to control wetting, dispersion and detergency processes. These processes are particularly important in suspension stabilization, including the production nanodispersed systems, yet there are very few studies on APGs' adsorption on solids. An investigation into adsorption of three APGs, differing in chain length from $C_{8/10}$ to $C_{12/14}$, on titanium dioxide has shown their ability to adsorb efficiently onto the solid surface, at least in the form of monolayer, in a manner comparable to SLS [20]. The adsorbed amount of APGs increased with surfactant concentration in the solution, and was highest in the case of APG $C_{12/14}$ water solution [20].

Regarding their phase behavior, it is well known that sugar surfactants form both thermotropic liquid crystalline phases in their pure state on heating and lyotropic liquid crystalline phases on addition of solvent (e.g., water). In water solutions, APGs first aggregate into micelles and this micellar phase region is usually large. As opposed to polyoxyethylene-based non-ionics, which have two micellar phases (dilute and concentrated), APGs build different types of micelle in these regions. The dilute phase consists of micelles with aggregation number in the range 200 – 400, whereas the concentrated phase contains larger aggregates, probably branched micelles, which form a network through entanglement. In addition, APGs are capable of building mixed micelles with anionic surfactants (e.g., SLS) in water, which could solubilize different polar oils more efficiently than individual surfactant systems. The solubilization capacity of APGs has been shown to increase with increase in their chain length [22-28].

The normal pattern of liquid crystalline phases is present at higher APG concentrations [20]. A characteristic feature of the liquid crystalline region, which appears at higher APG

concentrations, is that the borders between the different crystalline phases in the temperature versus surfactant concentration diagram are almost vertical, indicating a temperature-independent behavior. This is very different from the behavior of polyoxyethylene-based non-ionics and presents a significant advantage of APGs in the formulation of drug delivery systems whose preparation procedure requires a strong control of the temperature. Generally, both thermotropic and lyotropic liquid crystalline phases behavior are influenced by the sugar surfactant's structure, especially the alkyl chain length, the increase of which results in greater thermal stability of both phases. In lyotropic liquid crystals, an increase of the alkyl chain length leads to destabilization of the hexagonal in favor of the lamellar phase, which is particularly interesting for pharmaceutical systems. The addition of fatty alcohols as a third component to APG/water mixtures leads to the appearance of different lamellar phases over the entire concentration range. Consequently, APGs with a chain length of $C_{12/14}$ or longer, combined with long chain fatty alcohols, are particularly interesting for the formulation of drug delivery systems relying on lamellar liquid crystalline phases to stabilize their structure [20,21,24-26].

Rheological characterization of $C_{12/14}$ APG/water mixtures with up to 15% (w/w) APG indicates a linear increase in viscosity with APG concentration, up to almost its lyotropic phase. This is the result of steric hindrance, which exists during shear stress application to the system, consisting mostly of overlapping rod-like micelles. In the case of longer alkyl chains, even in significantly lower concentrations, APG-fatty alcohols/water binary systems show distinct viscoelastic behavior, mostly due to the presence of lamellar liquid crystalline or lamellar gel crystalline phases. These systems also show plastic or pseudoplastic flow behavior, with moderately pronounced thixotropy, a property desirable for viscous liquid dispersions or semisolids [20,21].

Another favorable property of APG surfactants is their ability to form microemulsion systems, almost independent on temperature. Contrary to the ethoxylated non-ionic surfactants that create microemulsions in combination with water and oil in a process strongly dependent on temperature (phase inversion temperature [PIT] phenomenon) [20,21], no temperature-dependent phase inversion can be expected to occur in APG-containing emulsions. Instead, APG microemulsions could be formulated by careful selection of suitable surfactant/co-surfactant combinations and ratios, as well as optimal contents of water and oil phases, in a tailor-made formulation fashion [29,30].

In addition to APGs, there is now considerable interest in sugar esters, particularly esters of glucose and sucrose, which show physicochemical behavior similar to APGs. For example, recent studies [31-33] have investigated the liquid crystal structural variability of water/sucrose laurate/ethoxylated mono- or di-glyceride/caprylic capric triglyceride systems, with and without ethanol, using the methods of small angle X-ray scattering (SAXS) and polarization microscopy. Lamellar (L_α) liquid crystals detected in the systems differed in the size of their hydrophobic compartments and the thickness of hydrophilic mantle of the lamellae, depending on the presence and content of alcohol in the system [31-33].

Concerning the safety profiles of sugar surfactants, considerable work has been performed on their suitability for dermatological use [34-36]. Based on acute oral and dermal toxicity tests, as well as on assays for local compatibility, APGs are not considered to be toxic or harmful, although undiluted material is classified as skin and eye irritant. Data from human repeated patch test (HRIPT) showed no sensitizing effects. A recent comparative study has assessed the ocular and dermal irritation potential of a range of 18 surfactants, starting from SLS and 9 commonly used traditional anionics, 1 cationic and 4 amphotheric surfactants and ending with 4 APG-type natural surfactants (coco glucoside, lauryl glucoside, decyl glucoside and a mixture of sodium lauryl glucose carboxylate and lauryl glucoside), using the same stock solution of surfactant for each evaluation [36]. The ocular irritation potential of surfactants was investigated using the red blood cell test (RBC), the hen's egg test-chorioallantoic membrane (HET-CAM) and the Skinethic® (SkinEthic Laboratories, Nice, France) ocular tissue model. The skin irritation potential was assessed based on data obtained from human studies using a 24-h epicutaneous patch test (ECT) and a soap chamber test (SCT), followed by transepidermal water loss (TEWL) measurements. Considering ocular irritation, all three tests pointed to 'non irritating to slight irritating' classification for all examined APGs. The same finding was obtained for dermal irritation potential study in all APGs [36].

In vitro tests with APGs did not display any potential for gene and chromosome mutations [37]. No systemic toxicity was found in a sub-chronic oral toxicity study in which male and female Wistar rats received a daily dose of 1000 mg/kg (body weight). Consequently, this dose was defined as 'no observed adverse effect level' (NOAEL). In-depth ecological studies have proved that APGs are ultimately biodegradable and do not bioaccumulate [37]. Also, recent studies were performed to investigate developmental toxicity to the unborn, reproductive toxicity and possible modulatory effects on endocrine activity [38]. Two *in vitro* screening test systems were used to investigate the endocrine modulating potential of APGs. No indications were observed for any estrogenic or antiestrogenic effects in an MCF-7 E-Screen assay and a Reporter gene assay using luciferase-transfected MCF-7 cells. APG concentrations exceeding the effective concentration of estradiol by a factor of 1000 did not reveal any indication for estrogenic activity. In a combination assay investigating the effects of estradiol in the presence of APGs, no antiestrogenic potential was observed. In one-generation screening assay in rats, no effects on the fertility were observed up to the highest dose of 1000 mg/kg (body weight) a day of APG. Therefore, for the APGs' embryo/fetotoxicity, the teratogenicity and the maternal toxicity a NOAEL of 1000 mg/kg (body weight) a day was established [38].

3. Natural surfactant-based conventional topical vehicles for different model drugs

Emulsion systems used in dermopharmacy as drug carriers have to fulfill several requirements, including acceptable physical stability, chemical inertness, satisfactory safety profile and drug delivery efficacy, reaching at the same time optimal sensory attributes (e.g., cohesiveness, spreadability, rub-out, after-feel sensation) (cf. [39,40]). Most 'ready to use' pharmaceutical vehicles are based on traditional ionic or ethoxylated non-ionic emulsifiers, or their mixtures with long chain fatty alcohols (mixed emulsifiers). For example, Ph. Eur. 6.0 recognizes only two mixed emulsifiers, both of them of anionic type: cetostearyl alcohol (type A), emulsifying and cetostearyl alcohol (type B), emulsifying, with a minimum of 7% (w/w) sodium cetostearyl sulfate (SCS) and 7% (w/w) of SLS, respectively [4]. However, as mentioned above, SLS is a well-established cytotoxic marker [9] and an *in vivo* skin irritant, causing skin barrier impairment and resulting in a variety of dermatological ailments that could affect the patient's quality of life [10-12].

There is a growing need, therefore, for a new group of safe and effective surfactants in regular pharmaceutical practice. For a new surfactant to be considered as a reliable pharmaceutical excipient for topical products, some critical data are required, including a comprehensive physicochemical characterization in a variety of different formulations, a study of the impact of its formulation on the *in vitro* release/permeation of drugs and their *in vivo* efficacy, and a safety evaluation. Consequently, to establish the viability of topical vehicles based on natural surfactants as prospective 'ready to use' pharmaceutical bases, a detailed investigation of their key properties has to be performed. This includes colloidal structure characterization of the new vehicles and the physical stability study, followed by an evaluation of their effects on the bioavailability of different topical drugs and their skin safety profile.

At present, the most exploited natural surfactant in the formulation of topical vehicles is the APG-type surfactant cetearyl glucoside combined with cetearyl alcohol (**Figure 1B**) (hydrophilic–lipophilic balance [HLB] ~ 6). This combination has recently been certified by the FDA as a pharmaceutical excipient, under the name Alkyl glucoside (Sepineo SE® 68, Seppic, France) [41].

The headgroup moiety of this sugar-based emulsifier contains several free hydroxyl groups, which bind water and could provide extra skin moisturization, having an impact on the stratum corneum (SC) pliability and penetration potential of drug and cosmetic actives [12]. In line with these expectations, the first published study pointed to the significantly better skin hydration, barrier improving and non-erythematic potential of creams based on cetearyl glucoside and cetearyl alcohol (Alkyl glucoside) compared with the commonly used polyoxyethylene non-ionic emulsifiers [42], but did not provide an insight to the colloidal structure of the samples. Studying the mesomorphic behavior of a new surfactant material in the systems similar to real pharmaceutical vehicles is necessary in order to assess its possible use. This is particularly important for APGs, as more information is available on thermotropic and lyotropic properties of polyglucosides with disaccharide than with monosaccharide headgroups (e.g., cetearyl glucoside) [24,25]. This lack of data is the consequence, at least partly, of their insolubility in water owing to a high Kraft point.

To evaluate the structure–property relationships in systems based on cetearyl glucoside and cetearyl alcohol, recent studies in the authors' laboratories [43,44] have assessed a series of binary (emulsifier/water) and ternary systems (emulsifier/water/oil) prepared using fixed ratios of components and medium chain triglycerides as oil phase. Test samples were characterized using the techniques of polarization and transmission electron microscopy (PLM, TEM), small and wide-angle X-ray diffraction (SAXD and WAXD), continual and oscillatory rheology and thermal analysis – differential scanning calorimetry (DSC) and thermogravimetry (TGA) [43,44]. The results showed that cetearyl glucoside and cetearyl alcohol, despite its low HLB value, enables the stabilization of multiphase oil-in-water (o/w) emulsion systems by synergistic effects of viscoelastic hydrophilic and lipophilic gel networks, as well as by lamellar liquid crystalline bilayers surrounding the oil droplets [43-52], which corresponded with an earlier study [13]. The existence of these structures was detected using the PLM, TEM, X-ray diffraction techniques and DSC (**Figure 2A – F**) in a systematic evaluation of binary and ternary systems. It was assumed that the lamellar hydrophilic gel phase consisted of mixed cetearyl glucoside/cetearyl alcohol crystalline bilayers, entrapping the water by hydrogen bonding. Therefore, it was proposed that the gel phase was stabilized by steric hindrance. The addition of oil to the binary system of fixed emulsifier/water ratio (1:10.43) was shown to affect both the bilayer thickness (SAXD measurements) and the amount of interlamellarly fixed water. Moreover, using the TGA technique, a specific pattern of water distribution within the systems was observed (**Figure 2G**), implying the existence of four water fractions within this colloidal structure: i) free ('bulk') water; ii) water entrapped within the lipophilic gel phase ('secondary' water); iii) water interlamellarly fixed between crystal lipid bilayers (hydrophilic gel phase); and iv) water interlamellarly fixed between lipid bilayers, existing in the form of liquid crystals [43,44]. The above findings have indicated a certain solubilization potential of the APG mixed emulsifier, as well as the possibility of increasing the hydration potential of topical vehicles by the incorporation of oil up to the level allowed by the system's physical stability. It was reasonable to assume that the existence of 'depot' water within the colloidal structure could contribute to skin barrier improvement and enhance the moisturization properties of creams based on APG mixed emulsifiers [43,44].

Such colloidal structure was reflected on the rheological behavior of the systems, which have shown 'shear-thinning'

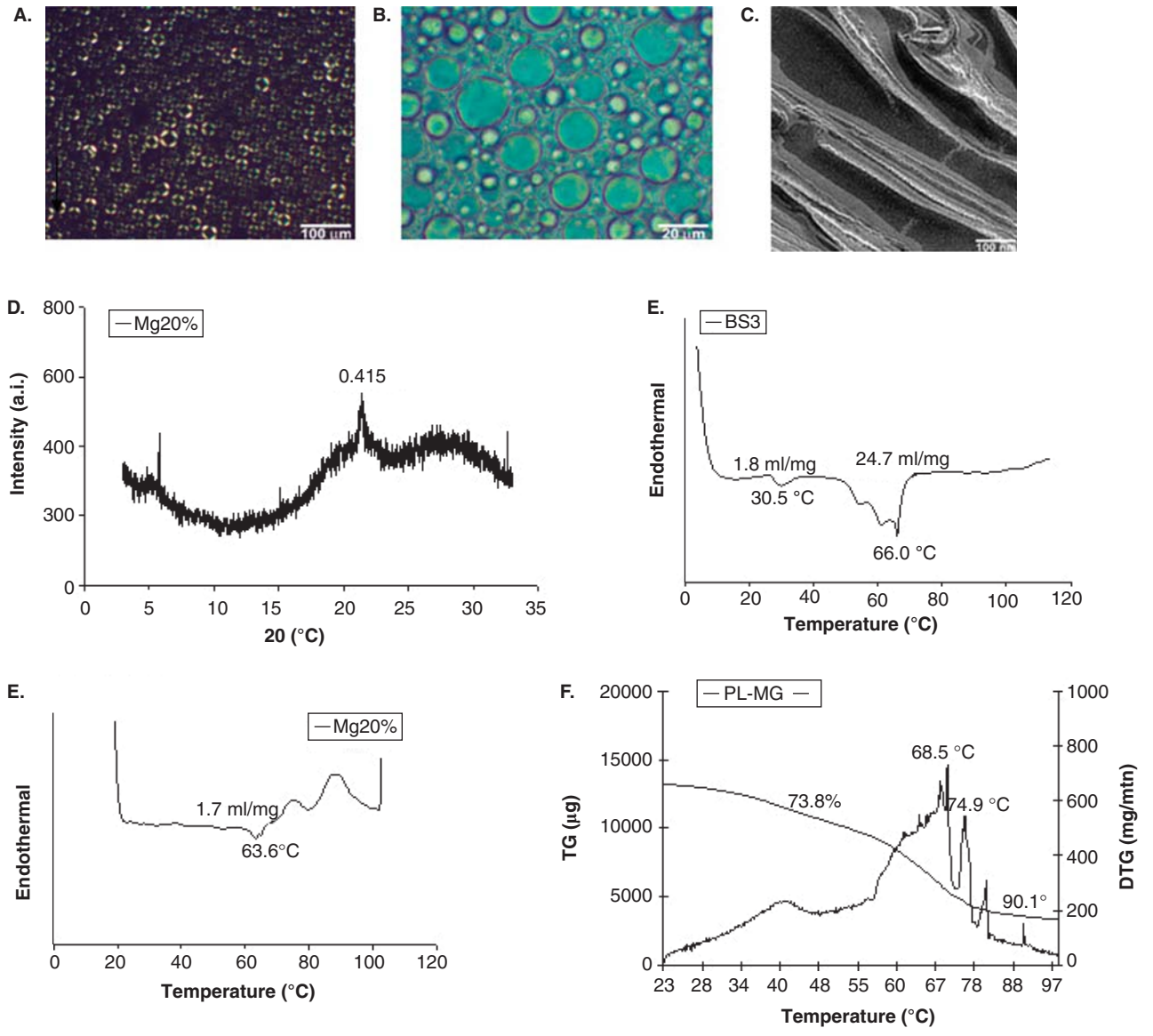

Figure 2. Physicochemical/structural characterization of different binary (emulsifier/water) and ternary (emulsifier/water/oil) systems based on APG surfactant cetearyl glucoside combined with cetearyl alcohol. A. PLM of ternary system (prospective 'ready to use' pharmaceutical base) with 7.26% (w/w) emulsifier and 20% (w/w) of medium chain triglycerides with several distorted Maltese crosses, a sign for lamellar liquid crystalline and lamellar gel crystalline mesophases as dominant structures in the emulsion system. **B.** OLM of the same sample with well-developed gel structure in the continual phase of the emulsion system. **C.** TEM micrograph of the same sample with wide planar lamellar sheets creating the lamellar gel phase. **D.** WAXD pattern of the same model pharmaceutical base with a single sharp reflection at 0.415 nm, confirming predominant presence of α-crystalline gel phase within the system. **E.** DSC graph representing phase transitions in a binary system with fixed emulsifier/water ratio (1:10.43). **F.** DSC scan of ternary system (model pharmaceutical base) with the same emulsifier/water ratio and 20% (w/w) of medium chain triglycerides, depicting phase transitions in the system; both scans show predominant presence of lamellar gel phase within the structure. **G.** Pattern of TGA for the same sample shows temperature-dependent water evaporation rate from the system, indicating complex structure and four different fractions of water: free ('bulk') water; water entrapped within the lipophilic gel phase ('secondary' water); water interlamellarly fixed between crystal lipid bilayers (hydrophilic gel phase); and water interlamellarly fixed between lipid bilayers, existing in the form of liquid crystals.

APG: Alkyl polyglucoside; DSC: Differential scanning calorimetry; OLM: Ordinary light micrograph; PLM: Polarization micrograph; TEM: Transmission electron microscopy; TGA: Thermogravimetry analysis; WAXD: Wide-angle X-ray diffraction.

pseudoplastic behavior with slightly to moderately pronounced thixotropy [43,44]. When assessed by oscillation tests, the systems based on APG mixed emulsifier showed viscoelastic behavior, with distinct elastic (G′) over viscous modulus (G″). Moreover, the uniform packing of the oil droplets has positively affected the textural, aesthetic and application properties of the vehicles. As a result of the above studies, the authors chose the cream with the emulsifier/water ratio of 1:10.43 and 20% (w/w) medium chain triglycerides as an optimal model formulation for further investigations [43,44].

The above results are in line with the Gel network theory proposed by Eccleston and co-workers [13,47] and Junginger [48], which explains the stability mechanism of emulsions based on traditional mixed emulsifiers (emulsifying waxes) of either ionic or non-ionic nature. The above results have also allowed a step forward in the understanding of gel phase formation. According to the theory, this process is governed by different swelling mechanisms, depending on the type of surfactant and its charge. The lamellar gel crystalline phase could be stabilized by either electrostatic or steric repulsions. With polyethoxylated non-ionic emulsifiers, the swelling is due to the hydration of polyoxyethylene (POE) chains, which are proposed to be orientated into the interlamellarly fixed water in 'zig-zag' formation. With APG mixed emulsifier, the lamellar gel crystalline phase seems to be stabilized mainly by hydrogen bonding of water to the monosaccharide hydroxyl moieties, causing a specific conformation that could be assigned as steric hindrance. This type of gel phase gives the continuous phase its structure ('self-bodying action'), contributing to the oil droplets' immobilization and the reduction in flocculation and coalescence [13]. In addition, detailed rheological studies have shown that the hydration process of the APG monosaccharide headgroups and the resulting swelling of fatty amphiphiles happen during emulsification and cooling, meaning that the structuring is completed within 48 h of sample preparation [43,44,53-55]. This is a considerable advantage of APG mixed emulsifiers over conventional POE non-ionic mixed emulsifiers (e.g., cetomacrogol 1000 and polysorbate emulsifying waxes, official in British Pharmacopoeia and USP/NF). It is known that pharmaceutical emulsions containing non-ionic emulsifying waxes often show considerable structural changes on storage, sometimes changing from milky liquid to a semisolid. As mentioned already, these changes are produced by delayed (prolonged) hydration of POE groups and consequent swelling of fatty alcohols. These variations in rheological properties are undesirable not only from an aesthetic viewpoint, but also because they may result in inconsistent drug bioavailability profiles [13].

Another relevant study [56] was concerned with the development of a time-saving rheological method for stability assessment of highly viscous pharmaceutical o/w emulsions. The samples were divided into two groups, the first one based on 5% (w/w) sorbitan stearate/polysorbate 20 combination, further thickened with 0.6% (w/w) of Carbopol® 980 (Carbomers, Ph. Eur. 6.0; Lubrizol, USA), and the second one based on 5% (w/w) of two different APG mixed emulsifiers: cetearyl glucoside and cetearyl alcohol; or coco-glucoside and cetearyl alcohol, without any extra thickener. Three types of natural oil were used as emulsion oil phases, in the concentration of 20% (w/w): olive, apricot kernel and sweet almond oil, respectively. Emulsions were stored for 6 months at 25 and 50°C and characterized by steady-state flow (yield stress and apparent viscosity) and oscillatory measurements (elastic and viscous moduli, loss tangent – tan δ and yield stress), as well as microscopic techniques, in 1-month intervals. All emulsions studied were stable at 25°C during the entire experiment. However, authors reported destabilization of emulsions based on coco-glucoside and cetearyl alcohol after 3 months of storage at 50°C, irrespective of oil type, whereas emulsions based on Span 60/Tween 20/Carbopol 980 were generally more stable. The second APG mixed emulsifier (cetearyl glucoside and cetearyl alcohol) provided better stabilization of the systems than the first one, but not enough to consider them physically stable pharmaceutical emulsions. However, this study did not take into account the influence of emulsifier concentration on rheological behavior, or the costabilizing capacity of Carbopol 980 in the systems based on combination of traditional non-ionics.

A further study from the authors' laboratories [57] proceeded in assessing cetearyl glucoside and cetearyl alcohol as a prospective pharmaceutical excipient. It was of interest to find out whether a combination of a mild natural surfactant with established pharmaceutical excipients could provide a suitable topical pharmaceutical base with satisfying physical stability. Five different oils of pharmacopoeial quality were used in the concentration of 20% (w/w): decyl oleate, medium chain triglycerides, isopropyl myristate, dimethicone and light liquid paraffin, with polarity indices of 18.7, 21.3, 24.2, 26.6 and 43.7 mN/m, respectively. The emulsifier/water ratio was 1:10.43, as established previously [43]. In addition to different oils, three pharmacopoeial coemulsifiers/costabilizers were used: two lipophilic – glycerol monostearate and cetearyl alcohol; and one hydrophilic – xanthan gum. Using PLM, TEM, pH, conductivity and thermogravimetry measurements and rheological, droplet size and polydispersity index analysis, the colloidal structure and physical stability of a range of emulsion systems were evaluated. To assess physical stability, the samples were subjected to a rigorous temperature cycle stress test (CST), that is, 10 consecutive cycles of 12 h at -75 and +40°C, alternately.

The results have shown that natural APG mixed emulsifier interacts favorably with a range of pharmaceutical excipients, forming semisolid topical vehicles of different rheological profiles, stabilized predominantly by synergistic effects of lamellar liquid crystalline (L_α) and complex lamellar gel (L_β) phases. It was shown that oils of ester type with medium polarity and a nonpolar mineral oil form stable emulsion vehicles, unlike silicone oil, which forms unsuitable systems with this APG emulsifier. Concerning the choice of

coemulsifiers/costabilizers, it was found that fatty alcohols also strengthen the primary viscoelastic α-crystalline gel network, whereas hydrophilic xanthan gum competes with APG surfactant for water, causing the loss of interlamellarly fixed ('depot') water within the system. The respective merits of medium polarity oils of ester type and long chain fatty alcohols in the formulation of stable APG-based topical vehicles were discussed. Owing to the differences they impart to the colloidal structure, different oils have shown variations in the potential for prolonged skin moisturization and the impact on drug release and skin penetration profiles [57].

The above findings have contributed to our understanding of the microstructure of sugar surfactant-based pharmaceutical carriers, essential in order to optimize the formulation and manufacture of both conventional and new drug delivery systems for dermal application. In addition to good physical and chemical stability and aesthetic appeal, a topical system must also be non-irritating to the skin and, where appropriate, capable of incorporating buffers, co-solvents, antioxidants, extra polymeric stabilizers and preservatives. Thus, surfactant has to be prospectively useful in many complex formulations containing a variety of model drugs and interacting auxiliary substances [13].

Regarding the above requirements, some recent studies focused on the *in vitro*/*in vivo* skin performance (efficacy and safety) of different APG-based topical vehicles containing several model drugs, which varied in molecular size, solubility, pK_a values and ionic strength, for example, urea, caffeine, salicylic acid, diclophenac sodium, diclophenac diethylamine and hydrocortisone [58-64]. These emulsion systems were compared either mutually or with a well-established pharmaceutical base of pharmacopoeial quality (e.g., non-ionic hydrophilic cream [NHC], official in German Pharmacopoeia, 2006) [58-64].

The first in this series was a study [58] dealing with physicochemical and *in vitro* characterization of cetearyl glucoside and cetearyl alcohol-based o/w emulsions containing 5% (w/w) emulsifier (Seppineo SE 68), 40% (w/w) cetearyl octanoate (Lanol® 1688, Seppic, France) as an oil phase and 3% (w/w) salicylic acid (SA) as a model drug. Active substance (SA) was incorporated into emulsion systems in three different ways: i) in the lipophilic phase at 70°C, at the beginning of the preparation; ii) in the emulsion, during the emulsification process at 70°C, in the middle of preparation; and iii) at the end of emulsion preparation, at 35 – 40°C. The emulsion systems obtained were stable, showing a characteristic lamellar liquid crystalline phase, with acidic active substance predominantly present in the internal phase of emulsions. *In vitro* release profiles of SA were not significantly influenced by droplet size and viscosity of the formulation or by the mode of its incorporation into the system. Drug dissolution was mostly controlled by the colloidal structure of the systems, that is, by mesophase created by the APG surfactant/fatty amphiphiles/water/oil phase interaction, irrespective of the way SA was incorporated into the system.

In subsequent studies [59,60], the *in vitro*/*in vivo* permeation of hydrocortisone (HC) was investigated from several different cetearyl glucoside and cetearyl alcohol-based formulations, comparing them with the pharmacopoeial base (non-ionic hydrophilic cream, DAB 2006). The aim of these studies was to relate the previously established information on the colloidal structure of APG-based emulsion systems [43,44], particularly its water distribution mode, with *in vitro* and *in vivo* bioavailability data of commonly used topical drug hydrocortisone at 1% (w/w) [65-70]. It is known that skin hydration level affects not only skin texture and appearance, but also its barrier properties, that is, skin penetration/permeation coefficients of both polar and nonpolar actives. In fact, water is considered to be a natural penetration enhancer [71-73]. Therefore, it was reasonable to assume that, by affecting skin hydration level to a different extent, different vehicles would affect the penetration of actives they carry.

A vehicle may affect the skin moisture content through an occlusive effect produced by its lipid ingredients, or by controlling the mode of water distribution within the system [71-73]. On the basis of previous results, it was proposed that the water distribution mode could be enhanced by increasing the interlamellarly fixed water, which may serve as a formulation reservoir ('depot') for controlled skin hydration [43,44]. An assumption was made that such a structure may be the result of the mesomorphic behavior of APG mixed emulsifier [24,25], which in turn positively affects other formulation properties important for dermatological use (e.g., physical stability and rheological performance) [43,44]. In the authors' study, a range of emulsion formulations with a fixed emulsifier/water ratio (1:10.43) and a varied content/composition of oil phase were used. The variations in the oil phase were: 10% (w/w) versus 20% (w/w) of medium chain triglycerides, 1.5% (w/w) cetearyl alcohol added into the basic formulation versus no addition, or 20% (w/w) of one of the following: medium chain triglycerides, isopropyl myristate or light liquid paraffin. Test sample were subjected to the physicochemical characterization using microscopic techniques, WAXD, rheological and TGA analysis, and compared with the pharmacopoeial base (NHC), consisting of 10% cetearyl alcohol, 25% white petrolatum, 5% polysorbate 60, 10% glycerol and 50% water [59,60]. *In vitro* HC permeation was followed through the cultivated artificial skin constructs (ASC) using Franz diffusion cells, whereas *in vivo* HC skin penetration was performed according to the FDA-recommended skin blanching assay [74-78] for the evaluation of corticosteroid bioavailability. Alongside the evaluation of pharmacodynamic activity of HC from the test APG-based vehicles, a study of skin irritation potential was carried out. Placebo bases were also investigated, using a 24-h occlusion test, by assessing transepidermal water loss (TEWL), as a measure of skin barrier integrity, stratum corneum hydration (SCH) and erythema index (EI), as a direct measure of skin irritation. These parameters, known to be relevant for drug

release [76,77,79,80], were measured before sample application and 1 h after occlusion was removed.

It was shown that both the rheological profile of the vehicle and the thermodynamic activity of suspended HC had a significant influence on the *in vitro* permeation of drug in an infinite dose test. A higher amount of HC permeated *in vitro* from APG-based vehicles than from the model pharmaceutical base (NHC) (**Figure 3A**). Unexpectedly, this *in vitro* finding was accompanied with a more pronounced increase in TEWL and less marked blanching action of HC tested *in vivo* after a 24-h occlusion (**Figure 3B**), particularly from the selected vehicle (7% of the APG mixed emulsifier and 20% of medium chain triglycerides). However, taking into account *in vitro* HC data (massive drug permeation after 8 h of experiment) and the well-established fact that maximum blanching effect for most topical corticosteroids is reached between 10 and 18 h after application, it is almost certain that the observed effect was the result of the HC waning phase [59]. Comparing the influence of different polarity oils on *in vivo* HC skin absorption from the APG vehicles revealed that medium chain triglycerides could retard the HC skin permeation, whereas isopropyl myristate and nonpolar light liquid paraffin promoted HC skin permeation. The mechanism was either a direct interaction with SC lipid lamellae or an indirect one, by improving skin hydration.

In conclusion, the APG formulation containing 7% of the APG mixed emulsifier, 20% of medium chain triglycerides and preserved purified water up to 100% has shown promising characteristics, including good HC release and favorable *in vivo* skin safety profile [59,60]. This makes it suitable for the possible model of a new 'ready to use' pharmaceutical base.

To assess application characteristics of the APG mixed emulsifier cetearyl glucoside and cetearyl alcohol (Sepineo SE 68) in topical formulations, it was necessary to combine it with a range of common pharmaceutical excipients, as well as some typical model drugs, whose release behavior from topical systems was already known [81-83]. In further studies, the composition of an APG-based model vehicle was varied either by the use of different types of oil [63] or by the incorporation of some commonly used co-solvents and penetration enhancers, such as propylene glycol (PG) or glycerol (GL) [64]. Two model drugs, differing in their pK_a values and ionic strength (diclophenac sodium [DC] and caffeine [CF], respectively), were added to the model bases. It was of interest to assess to what extent and by which mechanism the two polyols affect the colloidal emulsion structure formed by cetearyl glucoside and cetearyl alcohol, and how that affects its *in vitro*/*in vivo* skin performance and *in vitro* permeation of DC and CF.

An *in vitro* permeation study was again performed through the human reconstructed skin model (artificial skin constructs [ASCs]). Following up on some conflicting literature data on excipient/skin and excipient/ASC interactions [65-69], the study was also concerned with the suitability of ASC for the prediction of *in vivo* drug behavior. In addition, an evaluation of the safety profiles of test vehicles was performed *in vitro* using an alternative method for skin irritation test (cytotoxicity assay) [84,85], and *in vivo* using the method of skin bioengineering (TEWL, skin hydration, erythema index) [76,77,79].

The results show that the addition of polyol (20% of propylene glycol and glycerol, respectively) significantly affected the colloidal structure of a simple APG-based o/w emulsion with medium chain triglycerides. The effect was dependent on the type of polyol used and, to some extent, on the type of model drug (DC versus CF). The incorporation of glycerol led to larger variations in the colloidal structure of the vehicle, whereas propylene glycol produced a stronger hydrophilic lamellar gel phase, with a larger proportion of interlamellar PG/water mixture, probably entrapping part of the dissolved drug [64].

It was found in the above studies that the *in vitro* permeation of both DC and CF through the ASC membrane (infinite dose approach) was dependent on the rheological properties of the vehicles. Enhanced permeation profiles of both drugs from PG-containing formulations coincided with a bigger increase in TEWL observed *in vivo*, confirming the penetration/permeation enhancer effect of PG. Glycerol did not affect the skin barrier significantly, although a marked increase in skin hydration was detected. The study findings suggest that GL acts as a permeation-retarding rather than permeation-enhancing excipient in this type of topical vehicle [64].

In vitro skin irritation testing has demonstrated the mild nature of the APG emulsifying mixture and the absence of negative effects of added polyols or different oils on cell viability, at concentrations corresponding to therapeutic concentrations (**Figure 4A**, **B**). This result, along with the low erythema index found in all cases, supports the use of cetearyl glucoside and cetearyl alcohol as a suitable pharmaceutical excipient (FDA certified in 2008), especially as an alternative to traditional mixed emulsifiers [63,64].

Sucrose fatty acid esters (SEs), non-ionics with a sucrose subunit as the polar headgroup, have recently been investigated *ex vivo* as penetration enhancers [86,87]. From the series of SEs tested, only sucrose laureate was found to increase the passage of lidocaine hydrochloride through buccal and palatal mucosae [87]. Similarly to APGs, SEs are considered to be nontoxic and biodegradable; they are approved by FAO/WHO as food additives. As SEs are not skin irritants, they are also suitable for topical therapeutic and cosmetic applications. Their use in dermatology has become even more promising since it was established that some SEs, such as laurate and ricinoleate, have the ability to form liquid crystals and microemulsions [31].

In a related study [86], two SEs, sucrose oleate (O) and sucrose laureate (L), were evaluated as prospective penetration enhancers using the following approach: i) the influence of SEs on the skin barrier function was measured by the TEWL method; and ii) the impact of SEs on the percutaneous

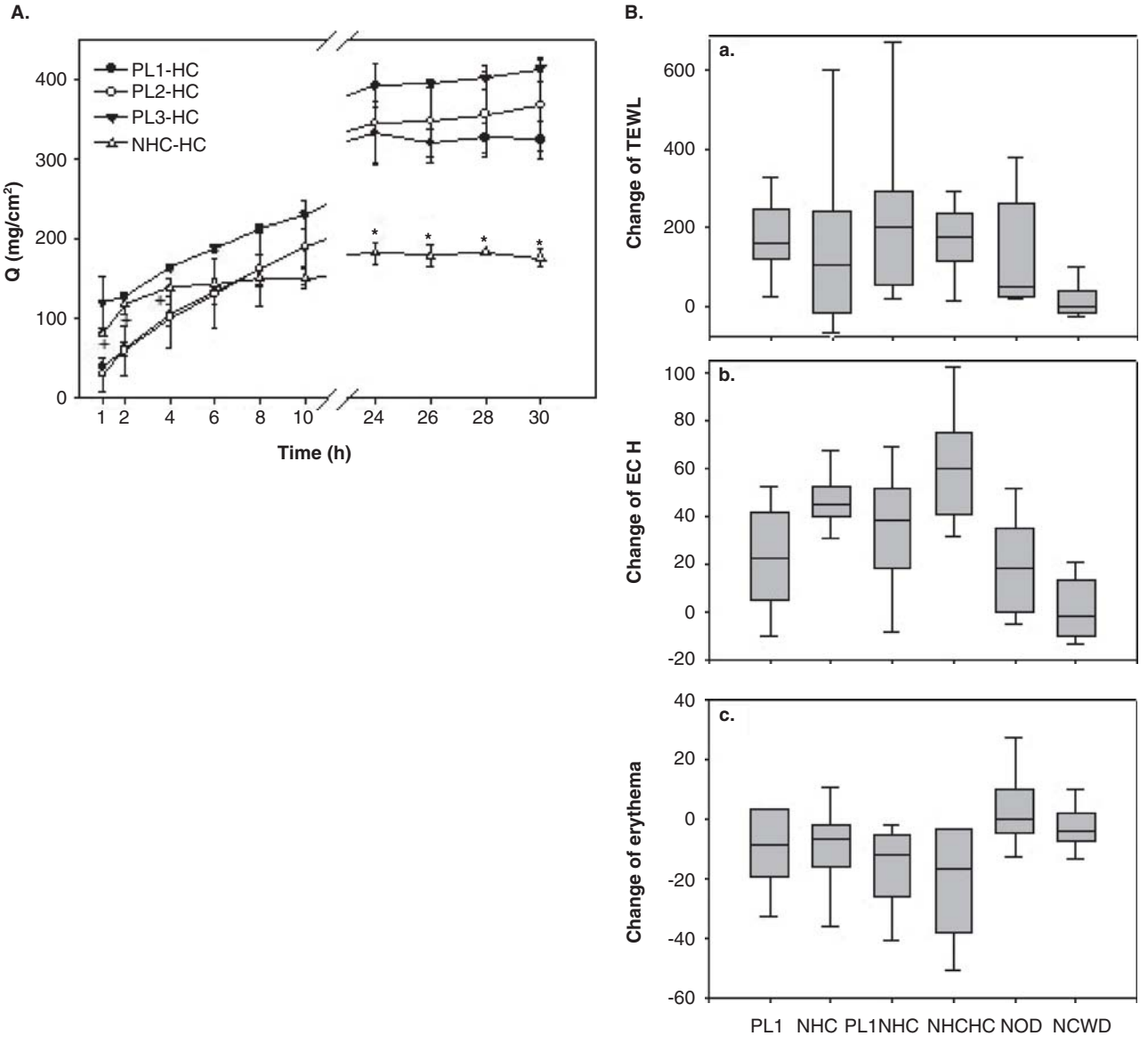

Figure 3. A. *In vitro* permeation profiles of 1% (w/w) HC from different vehicles based on APG surfactant cetearyl glucoside combined with cetearyl alcohol (PL1-HC, PL2-HC and PL3-HC) compared with official pharmaceutical base (NHC, DAB 2006). The study was performed using Franz diffusion cells, with ASCs as membranes in an infinite dose experiment. **B.** *In vivo* evaluated pharmacodynamic effect of HC (skin blanching assay) from prototype pharmaceutical base containing APG surfactant cetearyl glucoside combined with cetearyl alcohol in parallel with official NHC base containing Polysorbate 60. At the same time, skin irritation and moisturizing potential of both samples were compared. The graph shows the influence of placebo (PL1 and NHC) and active samples with 1% HC (w/w) (PL1-HC, NHC-HC) on (**a**) TEWL, (**b**) SC hydration and (**c**) skin blanching (erythema index). Parameters are expressed as per cent change on the second versus first day, and plotted as vertical bars with medians, 25th and 75th percentile (10th and 90th percentile as error bars). The effects of placebo and active samples were compared mutually and related to non-treated controls, under and without occlusion (NCO and NCWO), using the Wilcoxon test.

*$p < 0.05$ NHC-HC compared with PL1-, PL2- and PL3-HC.

Bars = ± s.d., +$p < 0.05$ PL1- and PL2-HC compared with PL3-HC.

APG: Alkyl polyglucoside; ASCs: Artificial skin constructs; HC: Hydrocortisone; NHC: Non-ionic hydrophilic cream; SC: Stratum corneum; TEWL: Transepidermal water loss; Q: Permeated amount of drug/area (μg/cm^2).

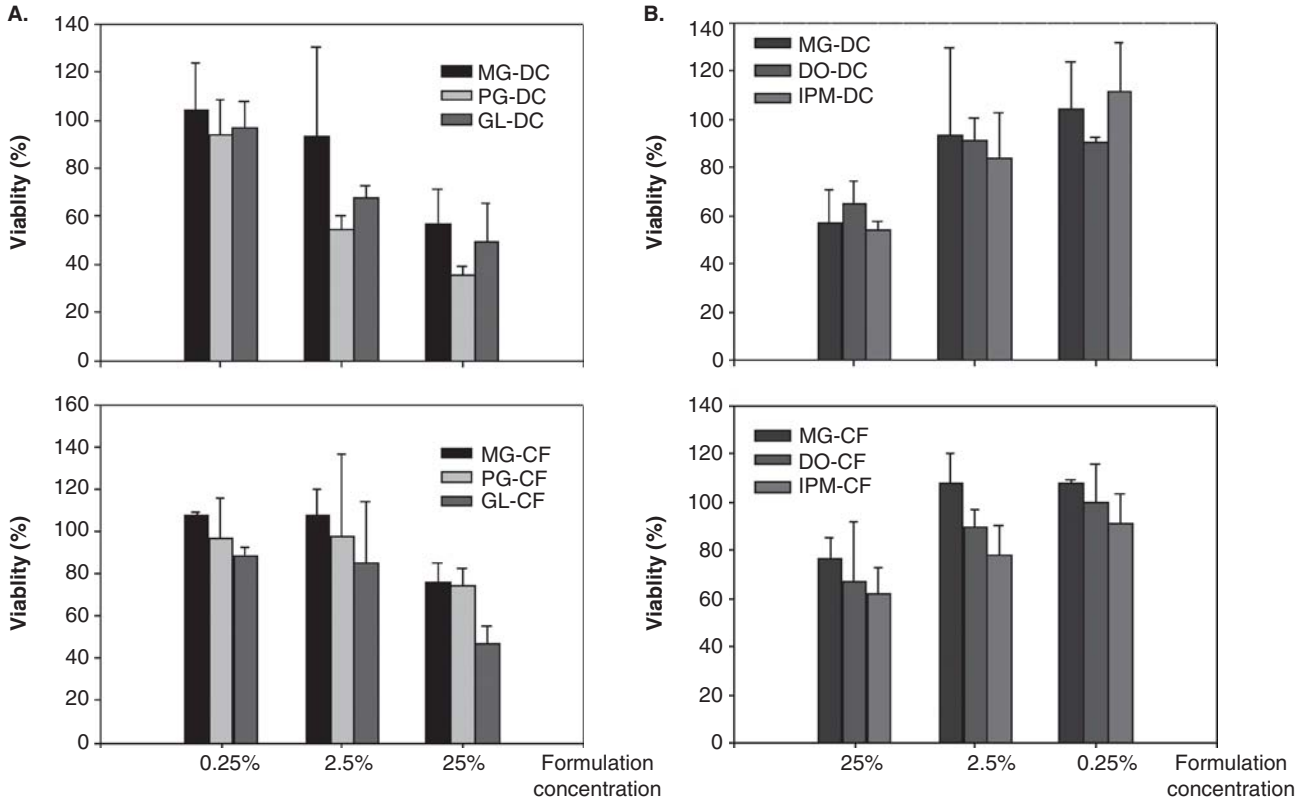

Figure 4. *In vitro* skin irritation test (a cytotoxicity assay): formulation concentration versus viability histograms. A. Topical vehicles based on APG surfactant cetearyl glucoside combined with cetearyl alcohol containing two alternative polyols (20% (w/w) of PG or GL). **B.** Topical vehicles based on APG surfactant cetearyl glucoside combined with cetearyl alcohol with three different oil phases (medium chain triglycerides versus decyl oleate versus isopropyl myristate). In both cases (**A** and **B**) samples contained two model drugs, DC or CF, and showed high compatibility with the artificial skin.

APG: Alkyl polyglucoside; CF: Caffeine; DC: Diclofenac sodium; GL: Glycerol; PG: Propylene glycol.

penetration of 4-hydroxybenzonitrile (4-HB, a model penetrant) was examined by ATR-FTIR spectroscopy combined with tape-stripping method. Subjects were treated topically with water or Transcutol® (TC) solutions containing sucrose oleate or sucrose laureate at two different concentrations (2 and 10%), respectively. Transcutol (monoethyl ether of diethylene glycol) was chosen for its well-known ability to increase drug solubility in the skin. ATR-FTIR spectra and TEWL were recorded before the treatment, 5 min after removal of the samples and then every hour during the following 4 h [86].

It was demonstrated that the penetration of 4-HB was enhanced in the presence of SE and TC, which appeared to interact synergistically and modify the skin barrier, promoting the penetration of 4-HB. It was significant that TEWL remained unaltered after application of all tested formulations. Of the two SEs studied, the laureate ester (C_{12}), in combination with TC was significantly more effective that its oleate (C_{18}) analogue [86]. This indicated that the effect of sucrose esters was dependent on the chain length as a dominant structural parameter, a relationship also found in traditional non-ionics.

4. New drug delivery systems based on natural surfactants

In addition to conventional pharmaceutical forms, the prospective use of sugar-based surfactants was also considered in advanced drug delivery systems for different routes of administration. In recent years, several studies dealing with the application of APGs or sugar esters in the design of modern pharmaceutical forms have been performed.

Manconi *et al.* [88] evaluated the use of two APG mixtures in the formulation of multilamellar (MLV) and unilamellar (ULV) vesicles (niosomes). These niosomes were used as carriers for tretinoin, using both saturated and unsaturated solutions of the drug. Commercial APG mixtures used were octyl-decyl polyglucosides (Oramix®CG110, Seppic, Italy) and decyl polyglucoside (Oramix®NS10, Seppic, Italy). Positively and negatively charged vesicular formulations were prepared using either stearylamine or dicetylphosphate as charge inducers. Alongside APG-based niosomes, the niosomes made with polyoxyethylene-4 lauryl ether (Brij® 30) and liposomes made with soy phosphatidylcholine (P90) were also prepared and studied. All vesicles were characterized by

TEM and optical and polarization microscopy for their formation and morphology, and by dynamic laser scattering (DLS) for particle size distribution. The effect of the vesicular incorporation of tretinoin on its (*trans*)dermal delivery through the newborn pig skin was also investigated *in vitro* using Franz diffusion cells, in comparison with commercial formulation of the drug (RetinA®). *In vitro* permeation results have shown that the composition of niosomes was very important for the cutaneous or transdermal delivery of a lipophilic drug such as tretinoin. It was shown that a very hydrophilic octyl-decyl polyglucoside (HLB = 16) could improve diffusion of tretinoin through the pig skin [88]. On the other hand, Brij 30 and decyl polyglucoside (HLB = 9 and 11, respectively) niosomes have shown the ability to enhance greatly drug cutaneous retention, particularly if compared with the commercial formulation RetinA and P90 liposomes. Therefore, it was concluded that APGs present an interesting class of amphiphiles for niosomes formation, which could, depending on their structure, improve transdermal or cutaneous delivery of niosomal tretinoin [88].

Junginger's research group has studied the feasibility of a peroral vaccine delivery system based on non-ionic sugar surfactant vesicles (niosomes), using female BALB/c mice for *in vivo* antibody production [89]. The vesicles were prepared from cholesterol (purity > 95%), dicetyl phosphate and sucrose ester surfactants (Wasag®7 and Wasag®15, Schmidt, NL) at a molar ratio of 5:1:4. Wasag7 consists of 70% stearate sucrose ester and 30% palmitate sucrose ester (total HLB = 7), whereas Wasag15 consists of 30% stearate sucrose ester and 70% palmitate sucrose ester (total HLB = 15). These sucrose esters were chosen for their ability to form gel state bilayers at 37°C, their easy biodegradability and very low toxicity. Ovalbumin was encapsulated in two different formulations of niosomal vaccines. The specific antibody titers within the serum, saliva and intestinal washings were monitored by ELISA on days 7, 14, 21 and 28 after intragastric administration. Only encapsulation of ovalbumin into Wasag7 niosomes resulted in a significant increase in antibody titers; the application of the more hydrophilic Wasag15 niosomal vaccine did not have a significant effect [89].

Different types of sucrose fatty acids ester were also used in a study dealing with transdermal therapeutic systems (TTS) for a water-soluble β-blocker, metoprolol [90]. Metoprolol was used as a model drug with short biological half-life, with the intention to prolong its delivery by TTS. Various types of TTS, including matrix and membrane-controlled, were used in the study. The membrane was made from methacrylic polymer (Eudragit® NE) of pH-independent permeability, which could provide diffusion-controlled drug release. Sucrose fatty acid esters of different fatty acid chain length and consequently different HLB values were studied in terms of effect on the metoprolol release from TTS. The main rationale for using SEs was their desirable dermal profile and a wide range of possible HLB values, asserted as an advantage over the traditional ionic and polyethoxylated non-ionic surfactants. The following Ryoto® (Mitsubishi-Kagaku Foods Corporation, Japan) sugar esters were used: sucrose stearate (S-370, S-970, S-1670, with HLB values 3, 9 and 16, respectively), sucrose oleate (O-1570, unknown HLB), sucrose palmitate (P-1570, HLB = 15), sucrose laurate (L-1695, HLB = 16) and sucrose myristate (M-1695, HLB = 16). Different mathematical models were applied for the evaluation of various release profiles. The results of the *in vitro* studies indicated that SEs of shorter fatty acid chains and higher HLB values have contributed to a 10-fold increase in drug release. It was concluded that the use of SEs in transdermal therapeutic systems to control drug release and cutaneous absorption was promising [90].

Patel and Joshi [91] have investigated mixed surfactant systems consisting of SLS and APGs (C_{10} APG, C_{12} APG and $C_{12/14}$ APG) as carriers for solid dispersions, that is, their effect on dissolution rate of poorly soluble drugs. Aceclofenac, a non-steroidal anti-inflammatory agent, was used as a model drug with limited water solubility. Mixed surfactant systems were characterized by critical micellar concentration, zeta-potential and β-parameter calculations, whereas solid mixtures were characterized by infrared spectroscopy (FTIR), X-ray diffraction studies (XRD) and scanning electron microscopy (SEM). The results showed that the dissolution rate of aceclofenac from solid dispersions increased with the increase in the APG proportion relative to SLS, with the optimum ratio of 0.2 SLS/0.8 APG in all cases. The observed effects on the dissolution rate increase were attributed to the drug–surfactant interactions, detected by FTIR, SEM and XRD methods [91].

A related study [92] evaluated the potential of an APG as an alternative surfactant/stabilizer, this time in the preparation of peptide-loaded nanoparticles. Human gel filtration fraction 2 (hGF_2) was used as a model peptide, and APG based on C_{10} fatty alcohol (decyl polyglucoside) was used as a representative surfactant. PLA (poly-DL-lactide) and PLGA (poly-DL-lactide-*co*-glucoside)-based nanoparticles were prepared and the effect of APG on particle size, entrapment efficiency and biological activity was evaluated. At concentrations as low as 0.05% (w/v), APG provided an excellent stabilization effect, resulting in nanoparticles with better encapsulation efficiency and a particle size < 450 nm. *In vitro* and *in vivo* biological activity evaluation confirmed that the peptide was compatible with the APG used. These preliminary results indicated that APGs could be used as alternative surfactants in the preparation of nanoparticles [92].

An interesting study [93] investigated the potential of two APGs, decyl glucoside (DG) and capryl-caprylyl glucoside (CCG), to form microemulsion templates, in order to produce nanoparticles as drug delivery vehicles for proteins and peptides. Two pseudo-ternary systems, comprising isopropyl myristate, soybean lecithin, water, ethanol and one of the two APGs as a surfactant, were used in the microemulsion formulation. Phase diagrams were established and the systems

were characterized using polarization microscopy, viscosity, conductivity measurements, electron microscopy, differential scanning calorimetry and self-diffusion NMR. As a result, an area of isotropic, monophasic systems was identified as a solution-type microemulsion region. Poly(alkylcyanoacrylate) nanoparticles were then prepared by interfacial polymerization from selected microemulsions. They were monodisperse and ranged from 145 to 660 nm in size, depending on the type of monomer (ethyl (2) or butyl (2) cyanoacrylate) and the microemulsion template used. Generally, larger nanoparticles were formed by butyl (2) cyanoacrylate. Insulin added as a model protein did not alter the physicochemical behavior of the microemulsions or the morphology of the nanoparticles. However, insulin-loaded nanoparticles in the CCG-containing system decreased in size when using butyl (2) cyanoacrylate. The study showed that microemulsions containing sugar-based surfactants of APG type were suitable formulation templates for the production of peptide-loaded nanoparticles.

Another study [94] presents the results related to the possible use of sucrose esters in the preparation of matrices for nanodispersions. These are lipid-based drug delivery systems (LDDS), widely used to improve drug solubility and absorption, but also for controlled release applications [95]. In LDDS formulations, which require a high input of energy during production, glycerides and phospholipids are usually the dominant lipid ingredients. However, this approach commonly brings about chemical and physical instability and problems with drug incorporation into nanoparticles. Sucrose esters were recognized as suitable alternative excipients for the preparation of LDDS matrices. The above-mentioned study [94] was focused on the mixture of mono- and di-esters of sucrose and stearic acid (Ryoto sugar ester SE S1170F), with well-balanced hydrophilic and lipophilic properties (HLB = 11). SE matrices were prepared using two alternative methods, hot and cold dispersion techniques, and characterized using light microscopy, rheometry, electron paramagnetic resonance spectroscopy (EPR), DSC, photon correlation spectroscopy (PCS) and TEM [94,96]. Based on the results obtained, it was suggested that SEs were promising ingredients for the production of nanoscaled systems. Using only gentle heat and moderate shear stress proved sufficient for the production of nanosized, physiologically acceptable SE dispersions, free of organic solvents. Formulations were stable over several months, with colloidal structure consisting of coexisting micelles and lamellae of different types, depending on the manufacturing procedure used [94].

A very recent study [97] gives further insight into APG use in the formulation of microemulsion as a vehicle for ascorbic acid. APG-based surfactants were chosen for their outstanding biodegradability, excellent dermatological properties and good surface-active characteristics. The last property is particularly related to the almost temperature-independent phase behavior of APGs. It was assumed that APGs, combined with suitable co-surfactants, could form microemulsion systems with very low interfacial tension, largely electrolyte and temperature insensitive, using a rapid and easy procedure. Decyl glucoside (Cognis, Germany) was used in the study, combined with sorbitan monolaurate as co-surfactant and dioctylcyclohexane and mineral oil as lipophilic components. Ascorbic acid was incorporated into three chosen microemulsion systems, and its *in vitro* transdermal penetration was studied through pig ear skin, using Franz diffusion cells. The quantity of ascorbic acid was determined in each skin layer separately (stratum corneum, epidermis and dermis) after 1, 3, 5, 7, 10 and 14 h, using phosphate buffer (pH ~ 2.5) as receptor medium. The results show that APG-containing microemulsions provide good protection and stability for the inherently highly unstable ascorbic acid. The epidermis was the main location for ascorbic acid penetrating from microemulsions, which is important for its whitening action and use in hyperpigmentation treatment. Stable TEWL values indicated a lack of barrier impairment after the application of APG microemulsions.

5. Expert opinion

There is a relatively small number of traditional surfactants with pharmacopoeial status (Ph. Eur., USP/NF, BP) that are deemed suitable for inclusion in pharmaceutical dosage forms. They include: sodium lauryl sulfate, cetrimide, benzalconium chloride, sorbitan esters with saturated and unsaturated fatty acids, polysorbates, macrogol ethers and esters, poloxamers, as well as some of their mixtures (mixed emulsifiers, emulsifying waxes).

The list of functional pharmaceutical excipients that have obtained pharmacopoeial status is slowly getting longer, especially with ingredients first used in cosmetic formulation. Many of them are now an integral part of pharmaceutical products for different applications, prominent examples being isopropyl myristate, oleyl oleate and dimethicone. It seems likely that a similar process will be applied to 'natural surfactants', that is, derivatives of mono- or disaccharide sugars and long chain fatty alcohols/acids. Owing to the combined pressures of ecological requirements and consumer demand for 'green' products, naturally derived alkyl polyglucosides and sucrose esters have found large-scale application in various personal care and consumer products. This includes a group of sophisticated skin care products, which are expected to be not only safe and effective, but also eco-friendly and biodegradable. In fact, the safety profile of some sucrose esters is such that they are registered as food additives.

In addition to their favorable safety and environmental profiles, sugar-based natural surfactants possess a range of desirable physicochemical properties, for example, temperature insensitivity, relatively good stability in the presence of electrolytes and in different pH environments, favorable phase behavior and good skin adsorption. This makes a strong case for their use as pharmaceutical excipients for the formulation of both conventional and new drug delivery systems, in the

possible roles of emulsifiers, wetting and dispersion agents, stabilizers of colloidal dispersions, solubilizers and penetration/permeation enhancers. Data obtained so far indicate that sugar-based natural surfactants impose less damage on biological membranes than traditional surfactants.

Potential benefits in pharmaceutical formulation are the reason for a growing number of studies on sugar-based surfactants for various applications. In particular, their use has been studied in the delivery of poorly soluble drugs and peptides/proteins for oral delivery, often replacing traditional surfactants or in combination with some of them. Microemulsions, niosomes and nanoparticles present some of the new delivery systems where the application of sugar-based surfactants has been investigated.

Obtaining pharmacopoeial status for an excipient is the ultimate proof of its universal functionality, as well as its safety for human use. So far, there is a considerable body of evidence to support the safety and efficacy of topical drug delivery using naturally derived surfactants. However, more data on oral and especially parenteral delivery are still needed to assure their safe use for these applications. Recent FDA certification of cetearyl glucoside and cetearyl alcohol mixture as 'Alkyl glucoside' (2008), a surfactant intended for topical formulations (in average concentration of 5% (w/w)), has presented a significant step in the process of recognition of this relatively new group of surfactants. It is expected that this will trigger more research into the potential benefits of these naturally derived materials in both conventional and new drug delivery systems.

Declaration of interest

The authors state no conflicts of interest concerning the preparation of this manuscript.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Corrigan OI, Healy AM. Surfactants in pharmaceutical products and systems, in Encyclopedia of pharmaceutical technology. M Dekker, New York; 2002
2. Müller-Goymann CC. Physicochemical characterization of colloidal drug delivery systems such as reverse micelles, vesicles, liquid crystals and nanoparticles for topical administration. Eur J Pharm Biopharm 2004;58:343-56
3. Ashton P, Walters KA, Brain KR, et al. Surfactant effects in percutaneous absorption. II. Effects on protein and lipid structure of the stratum corneum. Int J Pharm 1992;87:265-9
4. European Pharmacopoeia 6.0, European Directorate for Quality of Medicines, Council of Europe, Strasbourg, France; 2008
5. United States Pharmacopeia/National Formulary (USP/NF); 2009
6. British Pharmacopoeia 2009 (BP 2009), British Pharmacopoeia Commission, The Stationery Office, London, UK; 2009
7. Deutsche Arzneibuch 2006 (DAB 2006), German Federal Institute for Drugs and Medicines, Bonn, 2006
8. Bárány E, Lindberg M, Lodén M. Unexpected skin barrier influence from nonionic emulsifiers. Int J Pharm 2000;195:189-95

• **Paper describing skin irritation potential of commonly used traditional surfactants.**

9. OECD (2008). OECD Guideline for the Testing of Chemicals, Draft Proposal for a New Guideline: In Vitro Skin Irritation: Human Skin Model Test. Available from: http://www.oecd.org/searchResult/0,3400,en-2649-201185-1-1-1-1-1,00.html [Last accessed 31 August 2009]
10. Bárány E. Human in vivo skin irritancy testing, in dry skin and moisturizers. CRC Press LLC, Boca Raton; 2000
11. Fluhr JW, Kuss O, Diepgen T, et al. Testing for irritation with a multifactorial approach: comparison of eight non-invasive measuring techniques on five different irritation types. Br J Dermatol 2001;145:696-703
12. Aikens PA, Friberg SE. Emulsifiers, in dry skin and moisturizers. CRC Press LLC, Boca Raton; 2000
13. Eccleston GM. . Functions of mixed emulsifiers and emulsifying waxes in dermatological lotions and creams. Colloids Surf A Physicochem Eng Aspects 1997;123/124:169-182

• **An exhaustive review on stabilization mechanisms gained by traditional mixed emulsifiers in several conventional vehicles.**

14. Al-Bawab A, Friberg SE. Some pertinent factors in skin care emulsions. Adv Colloid Interface Sci 2006;123-126:313-322
15. Williams AC, Barry BB. Penetration enhancers. Adv Drug Deliv Rev 2004;56:603-18
16. Holmberg K. Natural surfactants. Cur Opin Colloid Interface Sci 2001;6:148-59

•• **An important review on main types, structures and physicochemical characteristics of natural surfactants.**

17. Stubenrauch K. Sugar surfactants – aggregation, interfacial, and adsorption phenomena. Cur Opin Colloid Interface Sci 2001;6:160-70

•• **Physicochemical behavior of sugar surfactants.**

18. Johansson I, Svensson M. Surfactants based on fatty acids and other natural hydrophobes. Cur Opin Colloid Interface Sci 2001;6:178-88
19. Hill K. Alkyl polyglycosides: where 'green' meets performance. HPC Focus Surfactants 2008;2:18-22
20. Nickel D, Förster T, von Rybinski W. Physicochemical properties of alkyl polyglycosides, in Alkyl polyglycosides. Weinheim: VCH; 1997
21. von Rybinski W, Hill K. Alkyl polyglycosides – properties and applications of a new class of surfactants. Angew Chem Int Ed Engl 1998;37:1328-45
22. Zhang R, Marone PA, Thiyagarajan P, Tiede DM. Structure and molecular fluctuations of n-alkyl-beta-D-glycopyranoside micelles determined by X-ray and neutron scattering. Langmuir 1999;15:7510-9

23. Sierra ML, Svensson M. Mixed micelles containing alkyl glycosides: effect of the chain length and the polar head group. Langmuir 1999;15:2301-6

24. Boyd BJ, Drummond CJ, Krodkiewska I, Grieser F. How chain length, headgroup polymerization, and anomeric configuration govern the thermotropic and lyotropic liquid crystalline phase behavior and the air-water interfacial adsorption of glucose-based surfactants. Langmuir 2000;16:7359-67

25. Vill V, von Minden HM, Koch MHJ, et al. Thermotropic and lyotropic properties of long chain alkyl glycopyranosides. Part I: monosaccharide headgroups. Chem Phys Lipids 2000;104(1):75-91

•• **Phase behavior of monosaccharide surfactants.**

26. von Minden HM, Brandenburg K, Seydel U, et al. Thermotropic and lyotropic properties of long chain alkyl glycopyranosides. Part II: disaccharide headgroups. Chem Phys Lipids 2000;106(2):157-79

27. Satam RM, Sawant MR. A study of the solubilization of polar oily materials by alkyl polyglucoside and sodium dodecyl sulfate in mixed surfactant system. J Dispersion Sci Technol 2006;27(2):179-84

28. Fanun M. Liquid crystal structural variability on water/mixed nonionic surfactants/caprylic-capric triglyceride systems. J Dispersion Sci Technol 2009;30(3):289-96

29. Fukuda K, Olsson U, Ueno M. Microemulsions formed by alkyl polyglucoside and alkyl glycerol ether with weakly charged films. Colloid Surf B Biointerfaces 2001;20:129-35

30. Kluge K, Sottmann T, Stubenrauch C, Strey R. Temperature-insensitive microemulsions formulated from octyl monglucoside and alcohols: potential candidates for applications. Tenside Surf Det 2001;38:30-40

31. Mitsubishi Kagaku Food Corporation. Application of sugar esters. 2007. Available from: http://www.mfc.co.jp/english/infor.htm/ [Last accessed 31 August 2009]

32. Garti N, Clement V, Leser M, et al. Sucrose ester microemulsions. J Mol Liq 1999;80:253-96

33. Fanun M, Wachtel E, Antalek B, et al. A study of the microstructure of four-component sucrose ester microemulsions by SAXS and NMR. Colloid Surf A Physicochem Eng Aspects 2001;180:173-86

34. Matthies W, Jackwerth B, Krächter H-U. Dermatological properties of alkyl polyglycosides, in Alkyl polyglycosides. Weinheim: VCH; 1997

35. Mehling A, Hensen H. Comparative studies on the irritation potential of surfactants. Exog Dermatol 2004;3:191-200

36. Mehling A, Kleber M, Hensen H. Comparative studies on the ocular and dermal irritation potential of surfactants. Food Chem Toxicol 2007;45:747-58

• **An important insight into ocular and skin safety profiles of sugar surfactants.**

37. Aulmann W, Sterzel W. Toxicology of alkyl polyglycosides, in Alkyl polyglycosides. Weinheim: VCH; 1997

38. Messinger H, Aulmann W, Kleber M, Koehl W. Investigations on the effects of alkyl polyglycosides on development and fertility. Food Chem Toxicol 2007;45:1357-82

39. Hadgraft J. Skin deep. Eur J Pharm Biopharm 2004;58:291-9

40. Refai H, Müller-Goymann CC. The influence of dilution of topical semisolid preparations on hydrocortisone permeation through excised human stratum corneum. Eur J Pharm Biopharm 2002;54:143-50

41. Available from: http://www.seppic.com [Last accessed 31 August 2009]

42. Savic S, Tamburic S, Savic M, et al. Vehicle-controlled effect of urea on normal and SLS-irritated skin. Int J Pharm 2004;271:269-80

43. Savic S, Vuleta G, Daniels R, Müller-Goymann CC. Colloidal microstructure of binary systems and model creams stabilized with an alkylpolyglucoside non-ionic emulsifier. Colloid Polymer Sci 2005;283:439-51

• **The first paper to deal with stabilization mechanisms obtained by APGs in conventional vehicles.**

44. Savic S, Vuleta G, Milic J, et al. Structural characterisation of multiphase emulsion systems based on an alkylpolyglucoside non-ionic emulsifier. RISG La Rivista Italiana Delle Sostanze Grasse 2005;82(5):236-44

45. Fairhust C, Fuller S, Gray J, Holmes MC. Lyotropic surfactant liquid crystals, in Handbook of liquid crystals. Volume 3. Weinheim: Wiley-VCH; 1998

46. Müller-Goymann CC, Drug delivery – liquid crystals in, in Encyclopedia of pharmaceutical technology. Volume 1. Marcel Dekker, New York; 2002

47. Eccleston GM, Behan-Martin MK, Jones GR, Towns-Andrews E. Synchrotron X-ray investigations into the lamellar gel phase formed in pharmaceutical creams prepared with cetrimide and fatty alcohols. Int J Pharm 2000;203:127-39

48. Junginger HE. Multiphase emulsions, in Surfactants in cosmetics. Marcel Dekker, New York; 1997

49. Mondain-Monval O. Freeze fracture TEM investigations in liquid crystals. Curr Opin Colloid Interf Sci 2005;10:250-5

50. Makai M, Csanyi E, Nemeth Z, et al. Structure and drug release of lamellar liquid crystals containing glycerol. Int J Pharm 2003;256:95-107

51. Erös I, Kónya M, Csóka I. Study of the structure of coherent emulsions. Int J Pharm 2003;256:75-84

52. Makai M, Csanyi E, Dékány I, et al. Structural properties of nonionic surfactant/glycerol/paraffin lyotropic liquid crystals. Colloid Polym Sci 2003;281:839-44

53. Korhonen M, Lehtonen J, Hellen L, et al. Rheological properties of three component creams containing sorbitan monoesters as surfactants. Int J Pharm 2002;247:103-14

54. Robles-Vasquez O, Corona-Galvan S, Soltero JFA, et al. Rheology of lyotropic liquid crystals of Aerosol OT. II. High concentration regime. J Colloid Interface Sci 1993;160:65-71

55. Nemeth Z, Halasz L, Palinkas J, et al. Rheological behaviour of a lamellar liquid crystalline surfactant-water system. Colloid Surf A 1998;145:107-19

56. Masmoudi H, Piccerelle P, Le Dréau Y, Kister J. A rheological method to evalauate the physical stability of highly viscous pharmaceutical oil-in-water emulsions. Pharm Res 2006;23(8):1937-1947

57. Savic S, Tamburic S, Kovacevic A, et al. Natural surfactant-based emulsion systems: the influence of common pharmaceutical excipients on colloidal structure and physical stability.

J Dispersion Sci Technol 2008;29:1276-87

58. Baudonnet L, Grossiord J-L, Rodriguez F. Physicochemical characterization and in vitro release of salicylic acid from o/w emulsions prepared with Montanov 68®: effect of formulation parameters. Drug Dev Ind Pharm 2004;30 (9):975-984

59. Savić SD, Savić MM, Vesić SA, et al. Vehicles based on a sugar surfactant: colloidal structure and its impact on in vitro/in vivo hydrocortisone permeation. Int J Pharm 2006;320:86-95

60. Savic S, Savic M, Tamburic S, et al. An alkylpolyglucoside surfactant as a prospective pharmaceutical excipient for topical formulations: the influence of oil polarity on the colloidal structure and hydrocortisone in vitro/in vivo permeation. Eur J Pharm Sci 2007;30:441-50

61. Vucinic-Milankovic N, Savic S, Vuleta G, Vucinic S. The physicochemical characterization and in vitro/in vivo evaluation of natural surfactants-based emulsions as vehicles for diclofenac diethylamine. Drug Dev Ind Pharm 2007;33:1-14

62. Savic S, Tamburic S, Jancic B, et al. The impact of urea on the colloidal structure of alkylpolyglucoside-based emulsions: physicochemical and in vitro/in vivo characterization, in Colloids in cosmetic and personal care. Weinheim: Wiley-VCH; 2008

63. Savic S, Weber C, Tamburic S, et al. Topical vehicles based on natural surfactants/fatty alcohols mixed emulsifier: the influence of two polyolos on the colloidal structure and in vitro/in vivo skin performance. J Pharm Sci 2009;98(6):2073-90

- **A description of strategies in comprehensive physocochemical, *in vitro* and *in vivo* characterization of an APG as prospective pharmaceutical excipient for conventional vehicles.**

64. Savic S, Weber C, Savic M, Müller-Goymann C. Natural surfactant-based topical vehicles for two model drugs: influence of different lipophilic excipients on in vitro/in vivo skin performance. Int J Pharm 2009;381:220-30

65. Ponec M. Skin constructs for replacement of skin tissues for in vitro testing. Adv Drug Del Rev 2002;54(Suppl 1):S19-30

66. Schmook FP, Meingassner JG, Billich A. Comparison of human skin or epidermis models with human and animal skin in in-vitro percutaneous absorption. Int J Pharm 2001;215:51-6

67. Hoffmann C, Müller-Goymann CC. Use of artificial skin constructs in permeation studies of clindamycin phosphate. Pharmazie 2005;60:350-3

68. Schäfer-Korting M, Bock U, Diembeck W, et al. The use of reconstructed human epidermis for skin absorption testing: results of the validation study. ATLA 2008;36:161-87

69. Bolzinger MA, Briançon S, Pelletier J, et al. Percutaneous release of caffeine from microemulsions, emulsions and gel dosage forms. Eur J Pharm Biopharm 2008;68:446-51

70. Fang JY, Leu YL, Fang CL, Chiu HC. In vitro and in vivo evaluations of the efficacy and safety of skin permeation enhancers using flurbiprofen as a model drug. Int J Pharm 2003;255:153-66

71. Roberts MS, Walker M. Water: the most natural penetration enhancer, in Pharmaceutical skin enhancement. New York: Marcel Dekker; 1993

72. Lodèn M. Role of topical emollients and moisturizers in the treatment of dry skin barrier disorders. Am J Clin Dermatol 2003;4:771-88

73. Gloor M, Gehring W. O/W emulsions compromise the stratum corneum barrier and improve drug penetration. Pharmazie 2003;58:709-15

74. Adams WP, Singh GJP. Guidance: topical dermatologic corticosteroids: in vivo bioequivalence, Division of Bioequivalence, Office of Generic Drugs, Food and Drug Administration, 1995

75. Lehmann L, Keipert S, Gloor M. Effects of microemulsions on the stratum corneum and hydrocortisone penetration. Eur J Pharm Biopharm 2001;52:129-36

76. Clarys P, Alewaeters K, Lambrecht R, Barel AO. Skin color measurements: comparison between three instruments: the Chromameter®, the DermaSpectrometer® and the Mexameter®. Skin Res Technol 2000;6:230-8

77. Fullerton A, Fischer T, Lahti A, et al. Guidelines for measurement of skin colour and erythema. A report from the Standardization Group of the European Society of Contact Dermatitis. Contact Dermatitis 1996;35:1-10

78. Haigh JM, Meyer E, Smith EW, Kanfer I. The human skin blanching assay for in vivo topical corticosteroid assessment. I. Reproducibility of the assay. Int J Pharm 1997;152:179-83

79. Levin J, Maibach H. The correlation between transepidermal water loss and percutaneous absorption: an overview. J Control Release 2005;103:291-9

80. Zhai H, Maibach HI. Effects of skin occlusion on percutaneous absorption: an overview. Skin Pharmacol Appl Skin Physiol 2001;14:1-10

81. Panchagnula R, Salve PS, Thomas NS, et al. Transdermal delivery of naloxone: Effect of water, propylene glycol, ethanol and their binary combinations on permeation through rat skin. Int J Pharm 2001;219:95-105

82. Trottet L, Merly C, Mirza M, et al. Effect of finite doses of propylene glycol on enhancement of in vitro percutaneous permeation of loperamide hydrochloride. Int J Pharm 2004;274:213-9

83. Herkenne C, Naik A, Kalia YN, et al. Effect of propylene glycol on ibuprofen absorption into human skin in vivo. J Pharm Sci 2008;97:185-97

84. Weyermann J, Lochmann D, Zimmer A. A practical note on the use of cytotoxicity assays. Int J Pharm 2005;288:369-76

85. Vinardell MP, Mitjans M. Alternative methods for eye and skin irritation tests: an overview. J Pharm Sci 2008;97:46-59

86. Ayala-Bravo HA, Quintanar-Guerrero D, Naik A, et al. Effects of sucrose oleate and sucrose laureate on in vivo human stratum corneum permeability. Pharm Res 2003;20(8):1267-73

- **An interesting paper on sugar esters as skin penetration enhancers.**

87. Quintanar-Ganem A, Quintanar-Guerrero D, Falson-Rieg F, Buri P. Ex vivo oral mucosal permeation of lidocaine hydrochloride with sucrose fatty acid esters as absorption enhancers. Int J Pharm 1998;173:203-10

88. Manconi M, Sinico C, Valenti D, et al. Niosomes as carriers for tretinoin III. A study into the in vitro cutaneous delivery

of vesicle-incorporated tretinoin. Int J Pharm 2006;311:11-9

- **APGs as amphiphiles for the preparation of niosomes, which may considerably affect the transdermal or cutaneous delivery of tretinoin.**

89. Rentel C-O, Bouwstra JA, Naisbett B, Junginger HE. Niosomes as a novel peroral vaccine delivery system. Int J Pharm 1999;186:161-7
90. Csóka G, Marton S, Zelko R, et al. Application of sucrose fatty acid esters in transdermal therapeutic systems. Eur J Pharm Biopharm 2007;65:233-7

- **Sucrose esters as surfactants improving transdermal delivery of model drugs.**

91. Patel AR, Joshi VY. Evaluation of SLS: APG mixed surfactant systems as carrier for solid dispersion. AAPS PharmSciTech 2008;9(2):583-90
92. Patel AR, Kulkami S, Nandeker TD, Vavia PR. Evaluation of alkyl polyglucoside as an alternative surfactant in the preparation of peptide-loaded nanoparticles. J Microencapsul 2008;25(8):531-40

- **APGs as surfactants for peptide-loaded nanoparticles.**

93. Graf A, Ablinger E, Peters S, et al. Microemulsions containing lecithin and sugar-based surfactants: nanoparticle templates for delivery of proteins and peptides. Int J Pharm 2008;350:351-60
94. Youan BB, Hussian A, Nguyen NT. Evaluation of sucrose esters as alternative surfactants in microencapsulation of proteins by the solvent evaporation method. AAPS PharmSciTech 2003;5:222-30
95. Ullrich S, Metz H, Mäder K. Sucrose ester nanodispersions: Microviscosity and viscoelastic properties. Eur J Pharm Biopharm 2008;70:550-5
96. Pouton CW. Formulation of poorly water-soluble drugs for oral administration: physicochemical and physiological issues and the lipid formulation classification system. Eur J Pharm Sci 2006;29:278-87
97. Pakpayat N, Nielloud F, Fortuné R, et al. Formulation of ascorbic acid microemulsions with alkyl polyglycosides. Eur J Pharm Biopharm 2009;72:444-52

- **APG use in the formulation of microemulsions as vehicles for ascorbic acid.**

Affiliation

Snežana Savić[†1], Slobodanka Tamburić[2] & Miroslav M Savić[3]
[†]Author for correspondence
[1]University of Belgrade,
Institute of Pharmaceutical Technology and Cosmetology,
Faculty of Pharmacy,
Belgrade Vojvode Stepe 450,
11221 Belgrade, Serbia
Tel: +381 11 3951366; Fax: +381 11 3972840;
E-mail: snexs@pharmacy.bg.ac.rs
[2]University of the Arts London,
London College of Fashion,
Cosmetic Science,
20 John Prince's Street,
London, W1G OBJ, UK
[3]Institute of Pharmacology,
Faculty of Pharmacy,
Belgrade Vojvode Stepe 450,
11221 Belgrade, Serbia