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Rapid communication

Applicability of sucrose laurate as surfactant in solid dispersions prepared by melt technology

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ABSTRACT

This study focused on an investigation of the applicability of sucrose laurate as surfactant in solid dispersions. Although this surfactant has a US Drug Master File, it has not been used so far in internal pharmaceutical products. High drug-loaded solid dispersion systems consisting of gemfibrozil as a model drug and PEG 6000 as a carrier, with or without sucrose laurate (D1216), were prepared by the melting method. Cytotoxicity studies on Caco-2 monolayer cells were also performed, in order to gain information on the applicability of D1216 in oral formulations. The results showed that the presence of the surface-active agent did not affect the solid-state characteristics of the model drug significantly. A markedly improved dissolution of gemfibrozil from the ternary solid dispersion systems was observed as compared with the binary solid dispersion systems. The optimum concentration range of the D1216 in the formulations was determined to be 5–10%. The effective final concentrations of D1216 in the dissolution experiments proved to be non-toxic towards CaCo-2 cells. The results suggest the potential use of D1216 in innovative internal pharmaceutical formulations.

The poor water solubility of drug substances and their low rates of dissolution in the aqueous gastrointestinal fluids often lead to insufficient bioavailability, and this remains a problem to the pharmaceutical industry. Solid dispersions of hydrophobic drugs in water-soluble carriers have attracted considerable interest as a means of improving dissolution behaviour, and hence enhancing bioavailability. Water-soluble carriers such as high-molecular-weight polyethylene glycols (PEGs) and polyvinylpyrrolidones (PVPs) have been most commonly used for solid dispersions (Bikiaris et al., 2005; Craig and Newton, 1991; Leuner and Dressman, 2000; Saharan et al., 2009; Serajuddin, 1999). The use of surfactants with solubilizing properties, such as polysorbates, poloxamers, Gelucires (polyethylene glycol glycerides), sodium lauryl sulfate or vitamin E TPGS have also attracted considerable interest recently (Dehghan and Jafar, 2006; Jagdale et al., 2010; Liu and Wang, 2007; Mura et al., 1999; Okonogi and Puttipipatkhachorn, 2006; Owusu-Ababio et al., 1998; Sethia and Squillante, 2002; Vasconcelos et al., 2007). As described in the review by Vasconcelos et al. (2007), the third-generation solid dispersion systems contain a surfactant carrier, or a mixture of amorphous polymers and surfactants as carriers. These third-generation solid dispersions are intended to achieve the highest degree of bioavailability for poorly soluble drugs. The inclusion of surfactants in the solid dispersions may help to avoid drug recrystallization and to stabilize the systems (Vasconcelos et al., 2007).

Sucrose esters (SEs) are widely used in the food and cosmetics industries, and there has recently been great interest in their applicability in different pharmaceutical fields. They are biodegradable, natural, non-ionic surface-active agents consisting of sucrose as hydrophilic moiety and fatty acids as lipophilic groups (Abd-Elbary et al., 2008; Csóka et al., 2007; Ganem Quintanar et al., 1998; Okamoto et al., 2005; Otomo, 2009; Ntawukulilyayo et al., 1993; Shibata et al., 2002).

In an earlier study we investigated, the structure and thermal behaviour of SE in order to predict their applicability in hot melt technology (Szűts et al., 2007). Our results revealed that SEs are semicrystalline carriers, with both amorphous and crystalline regions. During the preparation of solid dispersions, the drugs are built into the amorphous phases of the SEs (Szűts et al., 2008). In melt technology, mainly the lipophilic SEs may be suggested as carriers. They display characteristic melting, whereas SEs with high or moderate HLB values only soften during heating (Szűts et al., 2007). It has also been found that hydrophilic SEs exhibit gelling behaviour at body temperatures, which can influence the drug release (Szűts et al., 2010a,b). In view of these results, the applicability of hydrophilic SEs alone as carriers in hot melt technology is not suggested. Dispersion or dissolution of the drugs in the softened SEs is difficult, and a high amount of swelling SEs can reduce the rate of dissolution of a drug.

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The aim of the present study was to evaluate the applicability of hydrophilic sucrose ester as surfactant in third-generation solid dispersion systems together with a polymer. As carrier, the commonly used PEG 6000 was chosen, with which the hydrophilic (HLB = 16) sucrose laurate showed the best miscibility among the evaluated sucrose esters (sucrose-stearate, -palmitate and -laurate). Although this surfactant has a US Drug Master File, it has so far not been used in internal pharmaceutical products. In this work, studies on the cytotoxicity of sucrose laurate on Caco-2 monolayer cells were also performed, in order to gain information on its availability in oral formulations.

Gemfibrozil (GEM), a poorly water-soluble (29.1 μg/ml at pH = 6.2 ± 0.1) model drug, was supplied by TEVA (Hungary). PEG 6000, the carrier used in our experiments, was from Hungaropharma (Hungary). Sucrose laurate D1216 (HLB = 16) was kindly provided by Harke Pharma GmbH (Germany).

During the sample production, 40% w/w of GEM was always applied. In the case of the binary systems, PEG 6000 was heated at 70 °C in a sand bath and, after melting, the appropriate amount of GEM was added. In dispersions incorporating surfactant (1%, 5%, 10% or 15% w/w), D1216 was dissolved in the melted carrier prior to the addition of GEM. The molten mixture was stirred manually for 15 min, to achieve homogeneous dispersion of the drug. The melts were quickly cooled to −10 °C in a freezer, after which the solidified samples were pulverized in a mortar and sieved to 200 μm.

The physical states of the GEM in the different samples were evaluated by XRPD with a Miniflex II X-ray Diffractometer (Rigaku Co. Tokyo, Japan), where the tube anode was Cu with Kα = 1.5405 Å. Patterns were collected with a tube voltage of 30 kV and a tube current of 15 mA in step scan mode (4°/min). The instrument was calibrated by using Si.

The release of the model drug was studied by using Pharmatest equipment (Hainburg, Germany) at a paddle speed of 100 rpm. 100 ml artificial enteric juice with a pH of 6.8 (±0.05) at 37 °C (±0.5 °C) was used. The concentration of GEM was determined spectrophotometrically at 276 nm (Unicam UV/vis spectrophotometer). The dissolution experiments were conducted in triplicate.

The statistical test ANOVA was used to compare the results of dissolution data. The difference between samples was deemed statistically significant if the 95% confidence intervals for the means did not overlap ($p < 0.05$).

The effect of D1216 on living cells was tested by using the human colon carcinoma cell line CaCo-2 (ATCC, USA), a model of the intestinal epithelium (Breemen and Li, 2005). Cells were grown in Eagle's minimal essential medium (MEM, Invitrogen) supplemented with 15% foetal bovine serum (Lonza, Switzerland) and 1% Na-pyruvate (Sigma, Hungary). Confluent monolayers were obtained in 96-well plates (Orange Scientific, Belgium) 3 days after cell seeding. For toxicity experiments, Dulbecco's Modified Eagle's medium (DMEM) without phenol red was used as assay medium. Two different cytotoxicity tests were performed. The lactate dehydrogenase (LDH) assay detects cell damage and death by measuring the release of the cytoplasmic enzyme LDH from cells due to plasma membrane disruption. The LDH levels in culture medium were determined with a commercially available kit (Cytotoxicity Detection Kit LDH, Roche, Switzerland). An increase in the number of dead or membrane-damaged cells results in an increase in LDH activity in the cell-free culture supernatant. Cytotoxicity was calculated as a percentage of the total LDH release from cells treated with 1% Triton X-100 as detergent. The MTT test measures cell viability, because only living and metabolically active cells can convert the yellow tetrazolium salt (MTT, Sigma M5655) into insoluble purple formazan crystals. The extent of dye conversion was determined spectrophotometrically by measuring the absorbance at 570 nm. In the MTT assay, a decrease in dye reduction correlates to the cell damage. Viability was calculated as a percentage of the number of untreated control cells. All experiments were repeated at least three times; the number of parallel wells for each treatment and time point varied between 4 and 8.

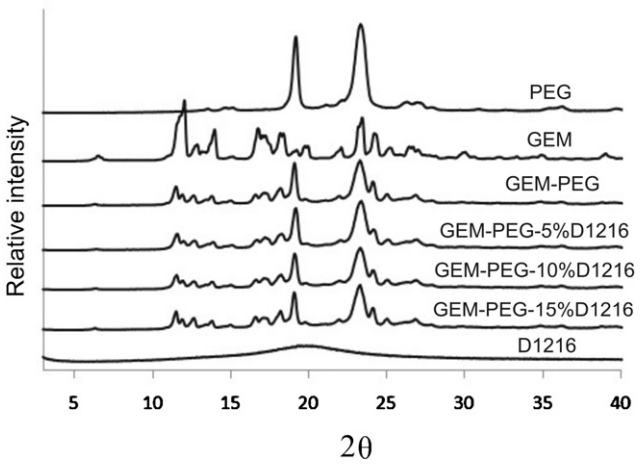

Fig. 1. X-ray power diffraction data of pure materials and solid dispersion systems.

An earlier study revealed that the hydrophilic sucrose stearate and sucrose palmitate do not melt during heating, but only soften (Szűts et al., 2007). In consequence of this thermal behaviour, the distribution of a drug in their melts is difficult, and can result in an inhomogeneous product. Hence, in the present study, the applicability of sucrose laurate as a surfactant was examined in a third-generation solid dispersion system. The solid dispersions were prepared by the melting method, containing GEM as model drug and PEG 6000 as carrier, with or without D1216 as surfactant. In the ternary solid dispersion systems, when D1216 was used up to 15%, a homogeneous melt could be formed.

Intact GEM and PEG 6000 displayed identical sharp XRPD peaks at various values of 2θ, while the X-ray pattern of D1216 exhibited an amorphous, broad halo (Fig. 1). In order to determine the crystallinity degree of drug in solid dispersions, the intensity of the most characteristic peak of GEM (intensity: 7767 at $2\theta = 12.06$) was evaluated in the various systems. The XRPD pattern of GEM binary solid dispersions demonstrated the diffraction peak of the crystalline drug. This suggested that GEM existed in the crystalline state in the solid dispersion system. However, the intensity of the peaks of crystalline GEM in the solid dispersions was significantly lower than that of the intact drug, indicating a lower degree of crystallinity of GEM in the binary solid dispersion system (inten-

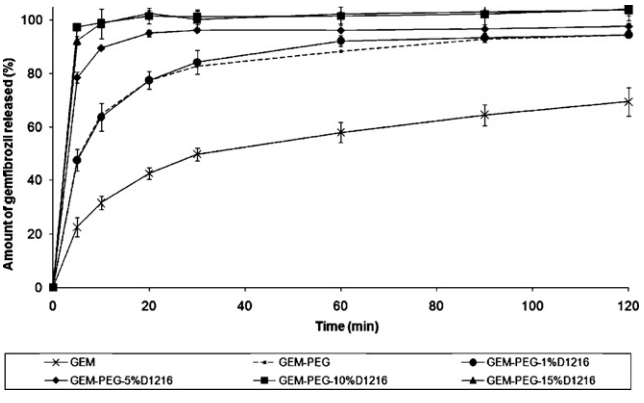

Fig. 2. Dissolution curves of GEM and solid dispersion systems containing various concentrations (0, 1, 5, 10 and 15%) of D1216 as surfactant.

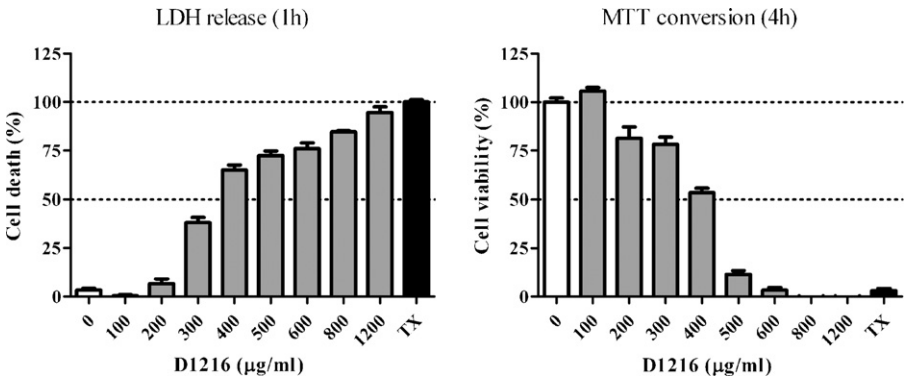

Fig. 3. Cytotoxicity measurements on various concentrations of D1216 on Caco-2 epithelial cells by LDH release after treatment for 1 h with D1216, and MTT dye conversion following treatment for 4 h (means ± SD, $n = 8–4$).

sity: 2500 at $2\theta = 11.52$). As the drug was highly loaded into the solid dispersion, some of the GEM molecules were molecularly dispersed, and a higher amount of GEM existed in the crystalline state. The XRPD patterns of the ternary solid dispersions were similar to those of the binary system (intensities of the most characteristic peak of ternary systems: 2070 at $2\theta = 11.64$ (GEM-PEG-D1216 40-55-5), 1950 at $2\theta = 11.56$ (GEM-PEG-D1216 40-50-10) and 2452 at $2\theta = 11.52$ (GEM-PEG-D1216 40-45-15) (Fig. 1). The incorporation of D1216 up to 15% had no effect on the XRPD pattern of GEM in the solid dispersion system.

Fig. 2 illustrates that the D1216 in samples resulted in significantly higher GEM release than that of started GEM. For the 1% D1216-containing solid dispersion, the drug release was similar ($p > 0.05$) that to form the binary solid dispersion system, whereas 5% SE resulted in significantly faster release. In this case, 90% of the GEM had dissolved after 10 min. With increasing content of D1216, the dissolution rate increased further. 100% GEM release could be attained after 10 min on the use of 10% D1216 (Fig. 2). Increase of the D1216 concentration from 10% to 15% did not result in significantly faster release. Accordingly, 5–10% D1216 seems to be optimum for solid dispersions of GEM.

PEGs have been used extensively as carriers for solid dispersions due to their favourable solution properties, low melting points and low toxicity. Thanks to these characteristics, they are approved by the FDA for internal consumption.

Besides improving dissolution, surfactants can also enhance absorption, thereby increasing the bioavailibility of poorly soluble drugs (Deli, 2009). However, surfactants may be cytotoxic, which can reduce their applicability in oral formulations (Dimitrijevic et al., 2000; Ekelund et al., 2005; Kiss et al., 2010). In this study, therefore, cytotoxicity measurements were made on the human intestinal epithelial cell line Caco-2 in order to determine the maximum non-toxic concentration of D1216 as absorption enhancer. The cytotoxicity of various concentrations of D1216 in LDH tests is shown in Fig. 3. The concentration of D1216 that caused no toxicity after 1 h was below 200 μg/ml. In the MTT studies, the duration of treatment was 4 h, and significant toxicity was observed when the D1216 concentration exceeded 100 μg/ml (Fig. 3). Above 600 μg/ml D1216, high toxicity occurred, resulting in the death of Caco-2 cells (Fig. 3).

Our dissolution studies shown, that applying 5–10% D1216 was optimum for GEM solid dispersions. In these formulations, the concentrations of D1216 in the dissolution media were 83.3 μg/ml (5% D1216) and 166.7 μg/ml (10% D1216), proved to be non-toxic towards Caco-2 cells.

The cytotoxicity studies demonstrated similarly as with other surfactants, that, when the internal applicability of sucrose laurate is under consideration, the possible risk of the local effect of an increased concentration in the microenvironment of the gastrointestinal tract must be taken into account. It should be noted that the SEs are widely used in different food products, and their acceptable daily intake was set as 40 mg/kg/day. Sucrose laurate was not considered in that evaluation, but the European Food Safety Authority (EFSA) recently pointed out that the current specifications should be changed to include sucrose laurate (EFSA, 2010).

It can be concluded that the applicability of sucrose laurate in third-generation solid dispersions prepared by melt technology may be regarded as a good technique with which to accelerate the dissolution of poorly soluble drugs such as GEM. The presence of 1–15% surface-active agent did not appear to affect the solid-state characteristics of GEM significantly. The in vitro dissolution studies shown, that applying 5–10% D1216 was optimum to improve GEM release from solid dispersions. In these formulations, the concentrations of sucrose laurate in the dissolution media were 83.3 μg/ml (5% D1216) and 166.7 μg/ml (10% D1216), proved to be non-toxic towards Caco-2 cells.

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