

Evaluation of microcapsules` release properties influenced by core composition

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INTRODUCTION

In recent years more and more active ingredients are known which exhibit low bioavailability due to their low solubility and/or permeability. Incorporation of such drugs in self-(micro)emulsifying systems (S(M)ES) offers several advantages for their delivery, the main one being faster drug dissolution and absorption. S(M)ES are mixtures of oil, surfactant and hydrophilic co-surfactant, capable of forming fine o/w (micro)emulsion upon gentle agitation provided by the digestive motility of the stomach and intestine. The spontaneous formation of a microemulsion upon S(M)ES dilution with intestinal fluids advantageously delivers the drug in its dissolved form all over its transit through gastrointestinal tract thus avoiding drug dissolution step and providing a large interfacial surface area for drug absorption. Apart from solubilization, the presence of lipid and surfactants in the formulation also help to improve bioavailability (Porter CJH, 2007). Incorporation of S(M)ES into a solid dosage form, such as microcapsules and microspheres would offer an important advantage from the viewpoint of patient compliance as well as dosage form preparation. Microparticulate drug delivery systems are widely used in pharmacy. They exhibit several advantages over single unit drug delivery systems, namely no dose dumping and larger surface area, allowing faster drug dissolution. Further, use of biodegradable substances has safety benefits (Homar M, 2007).

The aim of the current study was to evaluate the ability of microcapsules with S(M)ES in the core to enhance the dissolution rate of furosemide, the class IV drug according to BCS.

MATERIALS AND METHODS

Materials: S(M)ES were composed of medium chain triglyceride Mygliol 812[®] (Hüls, Germany) or isopropyl myristate (IPM) (Fluka, Chemie GmbH, Switzerland) as lipophilic phase, caprylocaproyl macroglycerides Labrasol[®] (Gattefosse, France) or polyoxyethylene (20) sorbitan monopalmitat Tween 40[®] (Fluka, Chemie GmbH, Switzerland) as surfactant and polyglyceryl-6 dioleate Plurol Oleique[®] (Gattefosse, France) or glyceryl caprylate Imwitor 308[®] (Condea Chemie GmbH, Germany) as cosurfactant. Pectin (Genu[®] pectin type LM-104 AS-Z) was used as polymer matrix (CP Kelco, Denmark) and low-viscosity chitosane as coating polymer (Fluka, Germany). Furosemide and lactose (mesh 200) as shell phase additive were kindly provided by Lek Pharmaceuticals d.d.. White wax (Lex d.d., Slovenia) and colloidal silica (Aerosil 200, Degussa, Dusseldorf, Germany) were used as the S(M)ES thickening agents.

Preparation of S(M)ES: System I was prepared by blending the Labrasol[®] and Plurol oleique[®] in a 4:1 mass ratio to obtain the surfactant mixture. The ratio was determined previously by Špiclin et al. (2003). Mygliol 812[®] was then added in different mass ratios (12, 20, 30 wt.%). System II was prepared by pre-blending the Tween 40[®] and Imwitor 308[®] in a 1:1 mass ratio; IPM was then added in

different mass ratios (20, 40 or 60 wt.%) to obtain desired S(M)ES composition. Prepared blends were then mixed to give homogeneous S(M)ES. Optimal system was mixed for 24 hours with 0.5 wt.% of CaCl₂ and thickened with white wax or colloidal silica in 2-6 wt.% concentration. To prepare drug loaded S(M)ES furosemide was added to already prepared systems at 1 wt. % concentration prior thickening.

Determination of solubilization capacity: The saturated solubility of furosemide in the S(M)ES of different compositions was determined by adding excess drug and stirring continuously for at least 72 h at ambient temperature to reach equilibrium. The supernatant was filtered with a 0.45 µm membrane filter and analyzed by HPLC after appropriate dilution with a mixture (80:20 v/v) of acetonitrile and bidistilled water.

Rheological studies: Rheological characterization was performed using a controlled stress rheometer (Haake RS 150, ThermoHaake, Germany), equipped with a cone and plate sensor system (C 60/4). Tests were carried out under destructive shear conditions at 20±1°C. Flow curves were measured by stress sweep tests.

In vitro dissolution test: The drug release studies were conducted using USP dissolution rate test apparatus (apparatus 2, 75 rpm, 37 ± 0.5°C) (VK7000, VanKel, USA) for 4 h in pH 3 hydrochloric acid aqueous solution and pH 6.8 phosphate buffer (900 ml). At the predetermined intervals (hours) 10 ml sample aliquots were withdrawn, filtered through a 0.45 µm membrane filter and assayed by HPLC method. Cumulative percentages of the drug dissolved from the products were calculated and plotted vs. time.

RESULTS AND DISCUSSION

One of the most important considerations when formulating a self-emulsifying formulation is avoiding precipitation of the drug on dilution in the gut lumen *in vivo*. Therefore, the system used should have high solubilization capacity for the drug, ensuring its solubilization in the resultant dispersion.

The qualitative compositions of S(M)ES were selected on the basis of our previous work (Špiclin P, 2003; Podlogar F, 2004). Results from solubility studies for two systems of different qualitative composition and with different oil phase/surfactants ratios are reported in Figure 1. As seen from the figure, the pure surfactants mixture (Labrasol[®]/Plurol Oleique[®] = 4/1) showed the highest solubilization capacity for furosemide (~100 mg/ml), followed by self-emulsifying mixtures with different content of Miglyol 812[®]. The solubilisation capacity of systems composed of IPM/Tween 40[®]/Imwitor 308[®] is considerably lower. Due to high solubilisation capacity (~86 mg/ml) and large area where microemulsions are formed upon dilution, as obtained in the phase diagram system composed of 12 % Miglyol 812[®] and 88% Labrasol[®]/Plurol Oleique[®] mixture was selected as core phase for the production of microcapsules. Previously we have determined the internal structure of the systems formed upon dilution of S(M)ES with aqueous phase and confirmed their stability (Zvonar A, 2008).

Selected S(M)ES was then thickened with colloidal silica or white wax in 2-6 wt.% concentration, which allowed production of microcapsules with better furosemide encapsulation efficiency as compared with non-thickened S(M)ES (data not shown). Microcapsules were produced by vibrating nozzle technology; the shell forming phase (2% pectine solution) envelopes the core phase (furosemide-loaded S(M)ES) as they flow simultaneously through the nozzle, forming a continuous jet that is broken apart into droplets by vibration of the membrane. Formed microcapsules are collected in hardening solution (0.5M CaCl₂), where a sol-gel transition of pectin in the shell occurs. To enable

production of microcapsules with high entrapment efficiency it is important to control the flow behavior of core and shell phase.

Rheological measurements of prepared formulations demonstrated that their flow behavior depends on composition (Figure 2). Whereas non-thickened S(M)ES and those thickened with 2% colloidal silica or white wax behave like Newtonian fluids, the addition of thickening agents in 6% concentration considerably increased the viscosity of S(M)ES and changed the ideal Newtonian behavior to pseudo-plastic one. Pseudo-plastic behavior of systems containing 4% of thickening agents is only slightly expressed. S(M)ES thickened with white wax expressed lower viscosity than those thickened with colloidal silica and exhibited thixotropic behavior. Due to similar viscosities and flow properties of systems thickened with 4% colloidal silica or white wax they were selected as core forming phase for further evaluation of the influence of core phase composition on microcapsules' release properties.

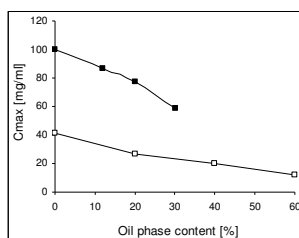


Figure 1: Furosemide loading capacity of S(M)ES (c_{max}) as a function of oil phase content in system composed of Miglyol 812®/ Labrasol®/ Plurol oleique® (■) and IPM/ Tween 40®/ Imwitor 308® (□).

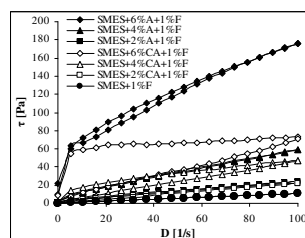


Figure 2: Rheograms of furosemide-loaded S(M)ES thickened with 2-6% colloidal silica (CS) or white wax (WW).

Results from *in vitro* drug release studies for microcapsules with S(M)ES core, thickened with 4% colloidal silica or white wax, and microspheres (without core) are reported in Figure 3a (for experiments conducted in hydrochloric acid solution with pH 3) and Figure 3b (for experiments performed in phosphate buffer solution with pH 6.8). As seen from the figures the furosemide release was faster in pH 6.8. Whereas microcapsules were already highly disintegrated after 4 hours at pH 6.8, they retained their structure throughout the dissolution test at pH 3, which is also in agreement with slower furosemide release observed. Presence of self-microemulsifying core with dissolved drug aided in the faster release of the drug from the microcapsules when compared to microspheres, where furosemide was suspended in Ca-pectinate matrix. As seen in Figure 3a up to 55% of furosemide was released from microcapsules after 4 hours, in comparison to less than 5% from microspheres in the same time intervals. This is in agreement with ability of S(M)ES to avoid drug dissolution step in the gastrointestinal tract by delivering drugs in dissolved form. From the Figure 3a it is further evident that the drug release profile was influenced by thickening agent added to self-microemulsifying core. Thickening of core with white wax resulted in slightly slower drug release (up to ~42% in 4 hours) when compared to colloidal silica (up to ~55% drug released in 4 hours). This can be explained with higher hydrophobicity of white wax that slows down the self-emulsification process and consequently drug release.

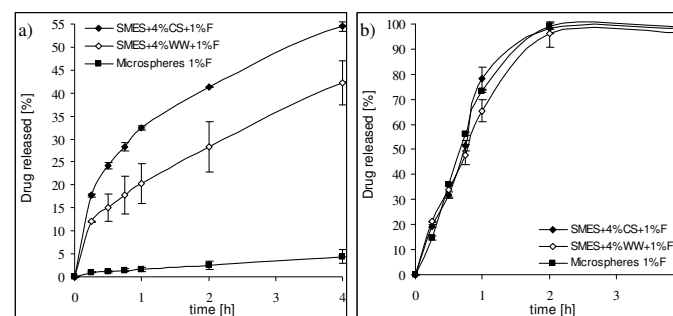


Figure 3: Percentage of furosemide released from microcapsules with S(M)ES in the core (thickened with 4% colloidal silica (CS) or white wax (WW)) or microspheres (without S(M)ES in the core) in (a) aqueous solution of HCl with pH = 3 and (b) phosphate buffer solution with pH = 6.8; n=3, furosemide loading = 1%.

CONCLUSIONS

S(M)ES offer the opportunity to deliver lipophilic drugs to the gastrointestinal tract in dissolved state, avoiding the dissolution step that can limit absorption rate of BCS Class 2 and 4 drugs. System composed of 12 % Miglyol 812® and 88% Labrasol®/Plurol Oleique® mixture and thickened with 4% colloidal silica or white wax were selected as core forming phase with regard to high solubilization capacity for furosemide and appropriate flow behavior. S(M)ES retained their unique properties upon incorporation into microcapsules as the release rate of furosemide from microcapsules with S(M)ES in the core was considerably faster than from microspheres. Together with increased solubility this is drug delivery advantage that could improve oral delivery of drugs with poor biopharmaceutical properties.

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