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Microcapsules with self-microemulsifying core: optimization of shell-forming phase

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Microcapsules with self-microemulsifying core were originated by the vibrating nozzle method. Alginate-pectin (A/P) ratio of the shell forming phase was optimized with regard to core phase retention and drug release kinetics from dried microcapsules. Well shaped microcapsules with high encapsulation efficiency were produced when an A/P composition of 25:75 was used. Microcapsules with higher pectin content exhibited faster drug release, which was additionally enhanced by the addition of sodium chloride to the shell phase.

It is known that between 40% and 70% of all new drug candidates are insufficiently soluble in aqueous media to allow adequate and reproducible absorption from the gastrointestinal tract following oral administration (Haus 2007). Self-(micro)emulsifying systems (S(M)ES) are among the most popular and commercially feasible formulation approaches for obtaining suitable oral bioavailability of such drugs. They are capable of delivering drug in a dissolved state, in small oil droplets, all over its transit through the gastrointestinal tract (Pouton 2000). Given the advantages of solid dosage forms, approaches for transforming conventional liquid S(M)ES into solid S(M)ES have been extensively explored in recent years (Jannin et al. 2007). Inclusion of liquid systems into microcapsules is one of the solidification techniques that allow formulation of solid self-(micro)emulsifying dosage forms (Homar et al. 2007).

The main scope of the current study was to originate microcapsules with SMES in the core by vibrating nozzle technology. The shell forming phase (A/P solution) envelopes the core phase (furosemide-loaded SMES) 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 where polymers are simultaneously cross-linked with Ca-ions. The shell forming phase was optimized to increase encapsulation efficiency of furosemide-loaded SMES (i), and to gain suitable drug release profiles from dried microcapsules (ii).

As shown in Fig. 1, the encapsulation efficiency of furosemide-loaded SMES was not considerably affected by the A/P ratio in the shell forming phase, and was ~70% for all blends tested. Due to the ability of sodium alginate to form gels more rapidly in the presence of Ca-ions as compared to pectin, appreciable improvement in core retention was expected, though. Nevertheless, microcapsules were better shaped when A/P composition of 25:75 was used as shell phase. NaCl was added to the polymer blends to reduce core leakage and to prevent clogging of the nozzle during the production process of microcapsules as reported previously (Homar et al. 2007). However, as shown in Fig. 1, the presence of 1% NaCl resulted in unfavorable effect on the efficiency of SMES encapsulation.

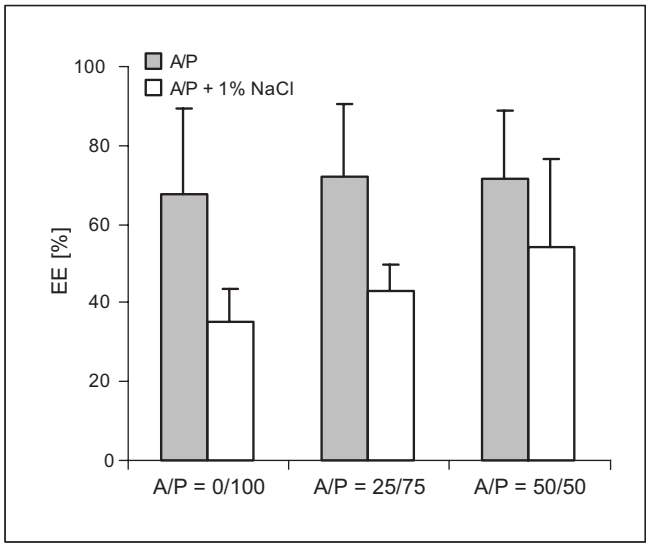

Fig. 1: Dependence of the encapsulation efficiency (EE) of furosemide-loaded SMES on alginate-pectin (A/P) ratio and the presence of NaCl in the shell forming phase

The influence of A/P ratio in the shell of microcapsules on drug release characteristics is shown in Fig. 2. Contrary to our expectations increase in the pectin content resulted in faster drug release, but the differences were not significant. However, addition of 1% NaCl resulted in significant differences in drug release profiles as well as in overall faster drug release. Furosemide was released most rapidly from microcapsules made solely of pectin that were also the most susceptible to the influence of added NaCl. Ca-ions that were used for polymers cross-linking began to undergo exchange with Na-ions when NaCl was present in the shell phase. This caused a decrease in the ionic cross-linking of polymers resulting in faster uptake of water by microcapsules and consequently faster drug release.

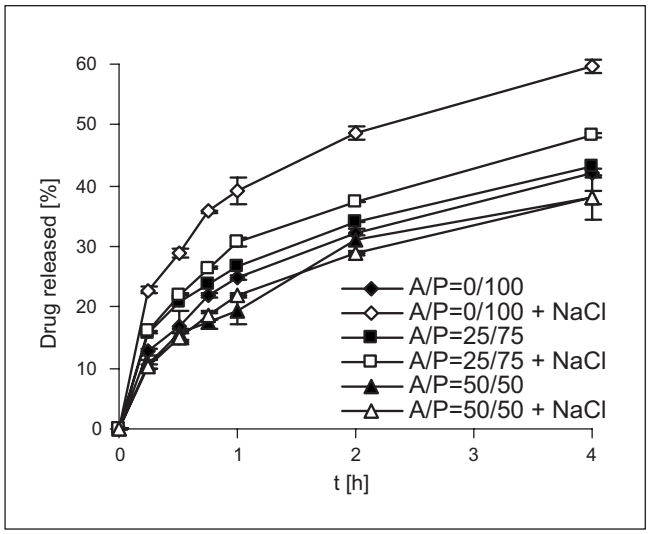

Fig. 2: Percentage of furosemide released from microcapsules with SMES in the core in aqueous HCl at pH 3. The shell of microcapsules was composed of alginate-pectin blends (A/P) with or without NaCl; n = 3

It may be concluded that the shell forming phase with the A/P ratio of 25:75 resulted in best shaped microcapsules with high encapsulation efficiency. Drug release profile of microcapsules can be modified by variation of the A/P ratio and addition of NaCl. The presented results constitute a step closer to a stable and repeatable production of microcapsules with SMES in the core by vibrating nozzle method.

1. Experimental

1.1. Preparation of microcapsules with SMES in the core

SMES was prepared by blending 88% of the Labrasol® and Plurol oleique® (4:1) mixture (both from Gattefosse, France) with 12% of Mygliol 812® (Condea Chemie GmbH, Germany). Afterwards 0.5% of $CaCl_2$ was added to promote shell hardening from the inside out as soon as the capsules are formed. Finally, SMES was loaded with 5% furosemide and thickened with 4% of colloidal silica (Aerosil 200, Degussa, Düsseldorf, Germany).

The shell forming phase was prepared by mixing 2% Na-alginate solution (Low viscosity Na-alginate, Sigma, Germany) with 2% pectin solution (Genu® pectin type LM-104 AS-Z, CP Kelco, Denmark) in 0:100, 50:50, 75:25, and 0:100 ratios. Afterwards 5% of lactose (and 1% of NaCl) was/were added to the homogeneous blends of polymers.

SMES was microencapsulated within the polymeric shell by a vibrating nozzle method using an Inotech IE-50R encapsulator (Inotech, Switzerland) equipped with a concentric nozzle (500 μm/750 μm), a syringe containing the shell forming phase, and an air-pressure solution delivery system containing SMES. Following subsequent incubation in 0.5 M $CaCl_2$ and 1 mg/ml chitosan solution (Fluka, Germany), microcapsules were dried in a fluid bed system. Reference microspheres were prepared from the shell phase loaded with furosemide, following the same procedure.

1.2. Encapsulation efficiency

Freshly produced microcapsules with SMES in the core were crushed and soaked in 50% ethanol. After filtering through the 0.45 μm membrane filter samples were analyzed by HPLC. The encapsulation efficiency of furosemide was expressed as a percentage of the total amount of furosemide used for microcapsule preparation.

1.3. In vitro dissolution test

Drug release was studied using the USP apparatus 2 (VK7000, VanKel, USA). The dissolution medium was 900 ml of pH 3 hydrochloric acid aqueous solution, at $37 \pm 0.5\,^{\circ}C$ and stirred at 75 rpm. Withdrawn samples were filtered through a 0.45 μm membrane filter prior HPLC analysis.

References

Haus DJ (Eds.) (2007) Oral Lipid-Based Formulaitons, Informa Healthcare Inc., New York, USA.

Homar M, Šuligoj D, Gašperlin M (2007) Preparation of microcapsules with self microemulsifying core by a vibrating nozzle method. J Microencapsul 24: 72–81.

Jannin V, Musakhanian J, Marchaud D (2007) Approaches for the development of solid and semi-solid lipid-based formulations. Adv Drug Del Rev 60: 734–746.

Pouton CW (2000) Lipid formulations for oral administration of drugs: non-emulsifying, and 'self-microemulsifying' drug delivery systems. Eur J Pharm Sci 11: S93–S98.