University of Ljubljana
Faculty of Pharmacy

Preparation of furosemide loaded microcapsules with self-microemulsifying core

Alenka Zvonar and Mirjana Gašperlin

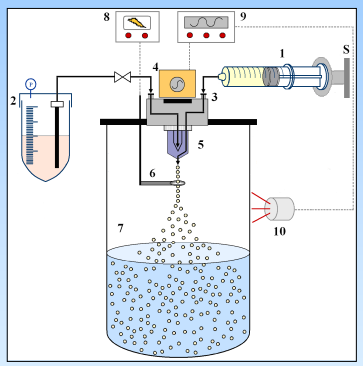
University of Ljubljana, Faculty of Pharmacy, Aškerčeva 7, 1000 Ljubljana, Slovenia

Introduction

A large majority of the newly discovered active pharmaceutical ingredients are poorly water soluble. Since in many cases the dissolution step is the rate limiting step, formulation design can be a usefull approach to improve absorption and thus the oral bioavailability of such drugs (1).

Among methots used self-microemulsifying systems (SMES), composed of a mixture of oil, surfactant and hydrophilic co-surfactant, are of special interest as they are capable of forming fine o/w (micro)emulsion upon gentle agitation provided by the digestive motility of the stomach and intestine (1).

The application of SMES is currently limited to liquid formulations and soft gelatine capsules, but incorporation of these systems into a solid dosage form would offer an important advantage form the viewpoint of patient compliance as well as dosage form preparation (2). The aim of our work was therefore to produce and characterize furosemide loaded microcapsules with SMES in the core by a vibrating nozzle method (Fig. 1).



Legend:
1 *Syringe with shell phase*
2 *Product delivery bottle with core phase*
3 *Pulsation chamber*
4 *Vibration system*
5 *Concentric nozzle*
6 *Electrode*
7 *Reaction vessel with hardening solution*
8 *Electrostatic charge generator*
9 *Frequency generator*
10 *Stroboscope*
P *pressure control system*
S *syringe pump*

Figure 1. *A schematic drawing of the microcapsules production process.*

Results

SMES with different oil phase/surfactants ratios were tested to obtain composition with hightest furosemide loading capacity (Fig.2).

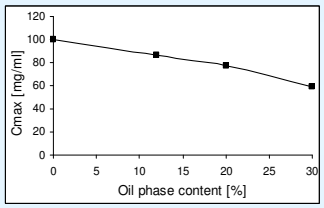


Figure 2. *Furosemide loading capacity of SMES (c_{max}) as a function of oil phase content in SMES. .*

SMES compostion with optimal loading capacity was then optimized, with respect to furosemide encapsulation efficiency, for incorporation in microcapsules.

To decrease the mixing of SMES with pectin shell and thus preventing core leaking during microcapsules production and drying processes, different excipients were added to the SMES (Fig.3). $CaCl_2$ was added to core phase to promote shell hardening as soon as the capsules were formed. Mixing between the two phases was also reduced with increased viscosity of core phase by adding aerosil and cera alba in different concentrations.

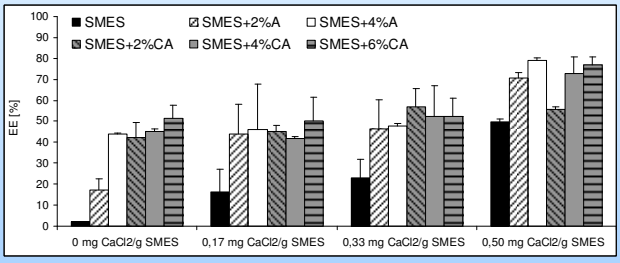


Figure 3. *Influence of concentration of $CaCl_2$ in SMES and thickenning agents used (aerosil (A), cera alba (CA)) on furosemide encapsulation efficiency (EE).*

Microcapsules with optimal core composition were dried according to different procedures (Fig.4) and characterized for furosemide encapsulation efficiency (Fig. 5).

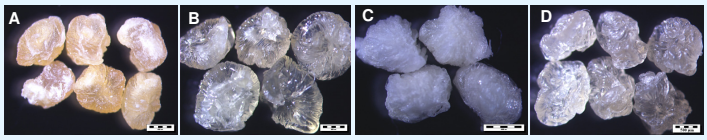


Figure 4. *Microcapsules with SMES core after drying in the air (A), vacuum (B), freeze-drying (C) and drying in the fluid bed system (D).*

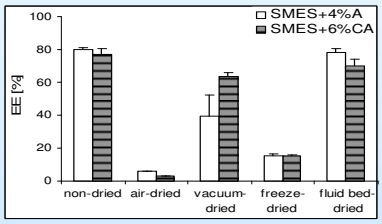


Figure 5. *Influence of applied drying method on furosemide encapsulation efficiency (EE).*

Conclusions

- **Optimal furosemide loadign capacity was obtained by SMES composed of 12 wt.% oil phase and 88 wt.% surfactants mixture (Labrasol/Pl. Oleique = 4/1).**
- **The encapsulation efficiency achieved was the highest for SMES containing 0,5mg $CaCl_2$/g SMES and thickenned with 4-6% aerosil or cera alba.**
- **Drying in the fluid-bed system was found the best for tested microcapsules with SMES core.**

Materials and Methods

SMES composition:

- Lipophilic phase: the medium chain length triglyceride - Mygliol 812® (Hüls, Germany)
- Surfactant: caprylocaproyl macrogolglycerides - Labrasol® (Gattefosse, France)
- Cosurfactant: polyglyceryl-6 dioleate - Plurol oleique® (Gattefosse, France)
- Furosemide (Lek d.d., Slovenia)

Shell forming phase:

Aqueous solution of pectin (Genu® pectin LM, CP Kelco, Denmark) with lactose (5%).

Microcapsules preparation:

Microcapsules were prepared by a vibrating nozzle method as described previously (3) using an Inotech IE-50R encapsulator (Inotech, Switzerland) equipped with a 500µm / 750µm concentric nozzle, a 60 ml syringe and an air-pressure solution delivery system (Fig. 1).

0,5M $CaCl_2$ solution was used as hardening media (15 minutes), additional chitosan-coating was applied by incubating the microcapsules in acetic acid solution of chitosan (1mg/ml) for 5 minutes.

Microcapsules were dried according to different procedures (in the air at room temperature, in the vacuum, freeze-drying, in a fluid bed system (Strea 1, Niro Aeromatic, Switzerland).

References: 1. C.W. Pouton. Eur J Pharm Sci 2000; 11, Suppl. 2: S93-S98.
2. T. Bansal et al. Crit Rev Ther Drug Carrier Syst 2008; 25 *(1):* 63-116.
3. M. Homar et al. J Microencapsulation 2007; 24 *(1):*72-81.