Calcium carbonate microparticles as carriers for intranasal drug delivery system to the brain

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INTRODUCTION

Mental and neurological disorders such as epilepsy, headache, Alzheimer's and Parkinson's disease, multiple sclerosis, stroke are widely effuse all over the world. The medical treatment of these diseases is complicated since there are many obstacles on the way of medicine to the delivery target. One of the common methods to provide a systemic action of the medicine is an oral administration, but this way has low efficiency on account of over 95 % of the present medication cannot pass the blood-brain barrier. Nasal administration is an alternative way to the brain drug delivery that attracted much of attention by many research groups (Furubayashi 2007).

In presented work, we propose new microcontainers based on porous calcium carbonate (CC) microparticles for the delivery to the central nervous system by intranasal administration. The aim of this work is to develop a new delivery system and show that CC microparticles can be used as an effective drug carrier system for intranasal delivery. The central anesthetic loperamide was used as a model drug.

MATERIALS AND METHODS

Calcium chloride dehydrate ($CaCl_2$*$2H_2O$), sodium carbonate (Na_2CO_3), ethanol, loperamide hydrochloride, hyaluronic acid sodium salt (Mw 1000 kDa), fluorescein isothiocyanate-labeled poly-L-lysine hydrobromide (FITC-PLL) were purchased from Sigma-Aldrich.

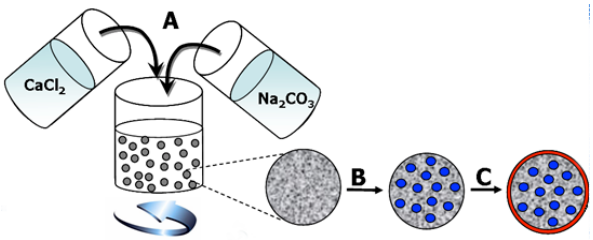

Figure 1 : The scheme of the microcontainer fabrication: A. formation of $CaCO_3$ microparticles; B. Loperamide absorption; C. modification of the particle surface

Spherical CC microparticles were prepared by mixing 0.33M $CaCl_2$ and 0.33M Na_2CO_3 aqueous solution according to (Antipov 2003). Loperamide was absorbed on calcium carbonate particles from an aqueous/ethanol solution. The amount of encapsulated loperamide was determined by spectrophometry at 259 nm (spectrophotometer Lambda-650, Perkin Elmer). The loperamide-loaded particles were modified with a hyaluronic acid (HA) or poly-L-lysine (PLL) by exposure to their solutions (5 mg/ml in 0.2M NaCl aqueous solution) under stirring on a shaker for 15 min. Figure 1 reveals the container preparation process. The particles were stored in a dried form.

The structure of the particles and containers was investigated by scanning electron microscopy (SEM) using Jeol 7401F microscope. The study of loperamide release was performed in ethanol solution in an incubator shaker at 500 rpm (IKA MS 3 basic, USA). The drug content was determined using a standard curve of loperamide. Confocal observations were obtained using a Leica TCS SP confocal scanning system (Leica, Germany) equipped with a 100×oil immersion objective (numerical aperture 1.4).

RESULTS AND DISCUSSION

The synthesized particles reveal a quite narrow size distribution (3-5 μm) and mesoporous structure. The SEM-investigations were carried out to illustrate the surface morphology of the microparticles. Figure 2 displays the initial carbonate particles (Fig. 2A, B) and the particles modified with HA (Fig. 2C, D).

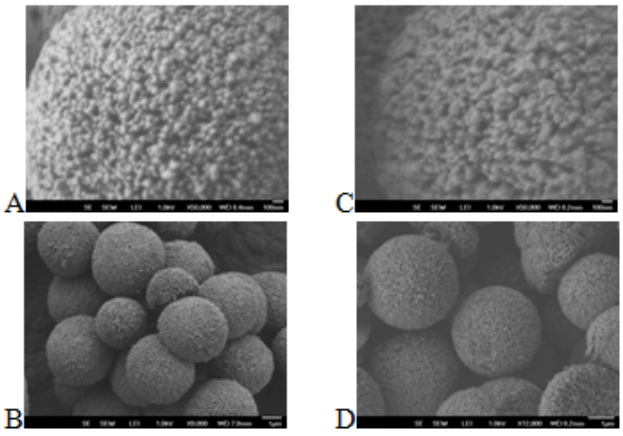

Figure 2 : SEM images of the pristine CC-particles (A, B) and coated with HA (C, D) under different magnifications

The images demonstrate that the microcontainer surface is smoother than to the pristine microparticles (Fig.1A, C). The porosity is slightly decreased after the polymer adsorption showing the success of the coating process (Fig. 1B, D).

Figure 3 illustrates the typical confocal images of the microparticles modified with FITC-labeled PLL. The

presence of fluorescence on the particle surface shows the spatial distribution of the polymer and additionally proves the polyelectrolyte adsorption during the microcontainer fabrication.

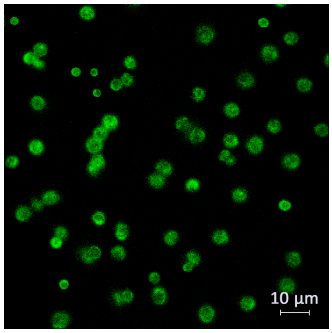

Figure 3 : CLSM image of the microcontainers modified with FITC-labeled PLL

Since loperamide has known to be very slightly soluble in water, it's adsorption process was studied from ethanol and the aqueous/ethanol solutions. It was found that an addition of water to the ethanol solution activates the adsorption process (Roldugin 2008).

Figure 4 demonstrates an amount of encapsulated loperamide as a dependence of this ratio at different concentration of the drug in the solution. The data shows enhance of the encapsulation efficacy when using more concentrated solution of the drug. The most effective adsorption of loperamide was observed at the ethanol:water ratio of 1:3 with all used loperamide concentrations (the process saturated). In the following experiments the solution of this ration was used.

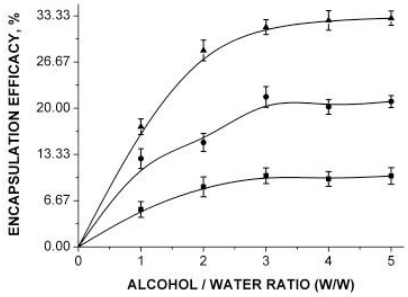

Figure 4 : Drug load efficiency depending on the alcohol-water ratio. The ▲ curve corresponds to a drug concentration of 10 mg/ml, ●- 6.6 mg/ml, ■ - 3.3mg/ml

Cumulative release of loperamide as a function of time presents in Figure 5 for the uncoated particles and HA-coated microcontainers. The initial burst release was shown for the control particles, where almost 80% of loperamide was found in a supernatant. The initial burst effect was slightly decreased in the case of the microcontainers followed by a slow release (60% at the same time).

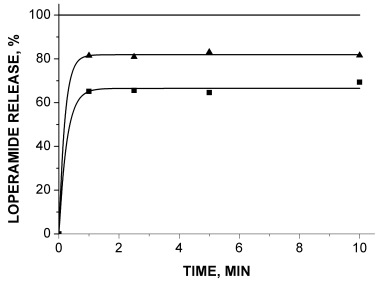

Figure 5 : Drug-release profiles from loaded calcium carbonate particles without coating - ▲ and with HA-coating - ■

The further release kinetics was not significantly different in the absence or presence of the polymer coating. It is clear that the one polymer layer is not enough to prolong notably the release of the encapsulated component. On the other hand, the obtained extension together with the mucoadhesive properties of the microcontainers is well enough to increase the residence time of the drug in the nasal cavity, prolonging and improving its absorption.

CONCLUSIONS

Calcium carbonate microparticles owing to its porous structure and good adhesive feature can be successfully used as drug carriers to intranasal delivery of the loperamide. The most effective adsorption of loperamide was observed at the ethanol:water ratio of 1:3 for all concentrations of loperamide. It was shown that HA-coating of the microcontainers prolong slightly the drug release. Proposed system could be found to be promising for medical application.

REFERENCES

- Antipov R.N. et al. (2003) *Carbonate microparticles for hollow polyelectrolyte capsules fabrication*. Colloids and Surfaces A: Physicochem. Eng. Aspects, 224 (1-3) 325.
- Roldugin V.I. (2008) *Intellect*. Physico-chemistry of the surface, 568.
- Furubayashi T. et al. (2007) *Evaluation of the Contribution of the Nasal Cavity and Gastrointestinal Tract to Drug Absorption Following Nasal Application to Rats*. Biological & Pharmaceutical Bulletin 30 (1007-1010).

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