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Development of a dosage form for accelerated release

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ABSTRACT

Purpose: It was the aim of this study to develop an oral capsule delivery system capable of rapidly ejecting the incorporated payload in the small intestine.
Methods: The capsule consists of four parts: a reaction mixture comprising of a basic and a corresponding acidic component, a plunger necessary to separate the reaction mixture from the inserted ingredients, capsule cap and body (made out of ethylcellulose (EC)), where at the bottom of the body a semipermeable filter membrane is mounted. As soon as water permeates through the membrane, the reaction mixture dissolves and carbon dioxide (CO_2) is released resulting in a high speed liberation of inserted compounds onto the intestinal mucosa. Several filter membranes were investigated regarding water influx, capillary force and water retention capacity. CO_2 release of sodium hydrogen carbonate ($NaHCO_3$) was examined in presence of several acidic components in different morphological forms (powder, lyophilisate and granule) and the amount of CO_2 liberation out of prepared capsules was determined. Furthermore, release of enteric coated capsules was tested within 0.1 M HCl and 100 mM phosphate buffer pH 6.8.
Results: The rank order regarding membrane permeability was determined to be: cellulose acetate with a pore diameter of 12–15 μm > 4–12 μm cellulose acetate > 8 μm cellulose nitrate > 8–12 μm cellulose acetate. $NaHCO_3$ in combination with tartaric acid in form of a granule could be identified as the most promising reaction mixture with the highest amount of released CO_2 compared to all other reaction mixture combinations. Stability of enteric coated capsules in HCl and a spontaneous release in phosphate puffer could be demonstrated within in vitro release studies.
Conclusion: In light of these results, the developed releasing system seems to be a promising tool for an accelerated delivery of several incorporated excipients.

1. Introduction

As the oral administration exhibits certain disadvantages such as rapid degradation in contact with gastrointestinal fluids and poor absorption through the gastrointestinal epithelium (Hamman et al., 2005), the use of drug carrier systems avoiding these hindrances is preferable. Another possible option to overcome these problems is the use of mucoadhesive dosage forms as oral drug delivery systems (Ahuja et al., 1997). In general, mucoadhesive excipients are able to increase the residence time and therefore the intimate contact with the gastrointestinal (GI) mucosa. On account to the strong connection to the absorption membrane a concentration gradient as steep as possible can be achieved leading to an increased drug concentration at the site of absorption and consequently improved overall bioavailability (Bernkop-Schnürch, 2005). In order to reach an optimal adhesive effect of orally applied mucoadhesive components it is important to administer them in dry form onto the mucosa. Previous in vitro studies for example proved that the application of dosage forms in dry form enables a 2-fold higher mucoadhesion compared to dosage form in their hydrated form (Albrecht et al., 2006). Additionally, Mortazavi and Smart compared dry mucoadhesive materials with their hydrated ones and demonstrated that dry materials exhibit fast swelling and extracting water from the mucus layer (dehydration process), while the hydrated formulations lost water (Mortazavi and Smart, 1993). This in turn generates a strong mucoadhesive effect as the dehydration process of the mucus layer alters its physicochemical properties by making the layer more adhesive (Dünnhaupt et al., 2011). The application of dry mucoadhesive dosage forms to ocular, nasal, vaginal or buccal mucosa was already shown in previous studies (Friedl et al., 2013; Hornof et al., 2003; Salamat-Miller et al., 2005; Ugwoke et al.,

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2005; Valenta et al., 2001), whereas the application of mucoadhesive formulations in dry form to the GI-mucosa was so far not feasible. The use of a drug carrier system in combination with dry mucoadhesive ingredients would therefore be highly beneficial as the hindrances of oral administration can be overcome and a strong mucoadhesive effect can be guaranteed.

It was therefore the aim of this study to develop an oral capsule delivery system capable of rapidly ejecting the incorporated payload in the small intestine. Hence, a capsule was constructed made out of ethylcellulose, containing an acidic and basic part and sealed with a semipermeable membrane before enteric coating. Once the capsule reaches the small intestine, the coating is dissolved and due to the access of water the basic and acidic component react under formation of carbon dioxide (CO_2) which is the driving force for an accelerated release and the ejection of incorporated ingredients. This fast release out of the capsule ensures that the payload remains unhydrated until ejection to the mucosal surface in the small intestine. Within this study, several semipermeable membranes were tested concerning the water penetration into the capsule, their capillary force and their water holding capacity. Furthermore, several alkaline and acidic components as reaction mixtures and various morphological forms thereof were examined regarding their CO_2 releasing capacity, which could be visualized by the use of the model drug methylene blue. Moreover, the ejection power of the capsule system as well as the release kinetic out of capsules is highlighted within this manuscript.

2. Materials and methods

2.1. Materials

Ethylcellulose, tartaric acid, citric acid, oxalic acid, polyethylene, triethyl citrate, polyvinylpyrrolidone (PVP) and fluoresceine isothiocyanate dextrane (FD 20) were obtained from Sigma–Aldrich, Austria. Gelatine capsules, sodium hydrogen carbonate ($NaHCO_3$), ethanol, liquid paraffin and petrolatum were purchased from Herba Chemosan, Austria. Filter papers (1288, 1289, 50N and Type $597^1/_2$) were received from Sartorius, Germany and from Schleicher and Schuell, Germany. Eudragit® L 100 was purchased from Röhm, Germany and hard paraffin from Gatt-Koller, Austria. All other chemicals were of analytical grade.

2.2. Construction of the releasing system

The releasing system in form of a capsule was constructed as shown in Fig. 1. For the preparation, all parts of the capsule were generated out of ethylcellulose (EC). Therefore, conventional gelatine capsules with a size of 00 for the bottom part (capsule body) and size 0 for the upper part (capsule cap) and plunger were coated. In brief, gelatine capsule shells were dipped for six times into the coating solution (16.5% ethylcellulose in 81% ethanol containing 4.0% triethyl citrate as plasticizer), let drain well under rotation to ensure an equal distribution and thickness of each layer over the capsule and subsequently dried at 55 °C for 15 min after each dip. After terminal drying, the capsules were added into water of 45 °C in order to dissolve gelatine and to obtain the ethylcellulose capsules. Afterwards, the bottom of ethylcellulose capsules was cut off and different filter papers (cellulose nitrate (CN) filter with a pore diameter of 8 μm and cellulose acetate (CA) filters with pore diameters of 4–7 μm, 8–12 μm and 12–15 μm, respectively) were fixed on the bottom by using ethylcellulose solution as described above. To ensure release in the intestine filter membranes were coated with Eudragit® L 100. Therefore, Eudragit® L 100 was dissolved in a concentration of 20% in a solution of ethanol and triethyl citrate (24:1). Eudragit® solution was applied on the filter membrane with a brush to ensure a very thin layer. Each capsule was

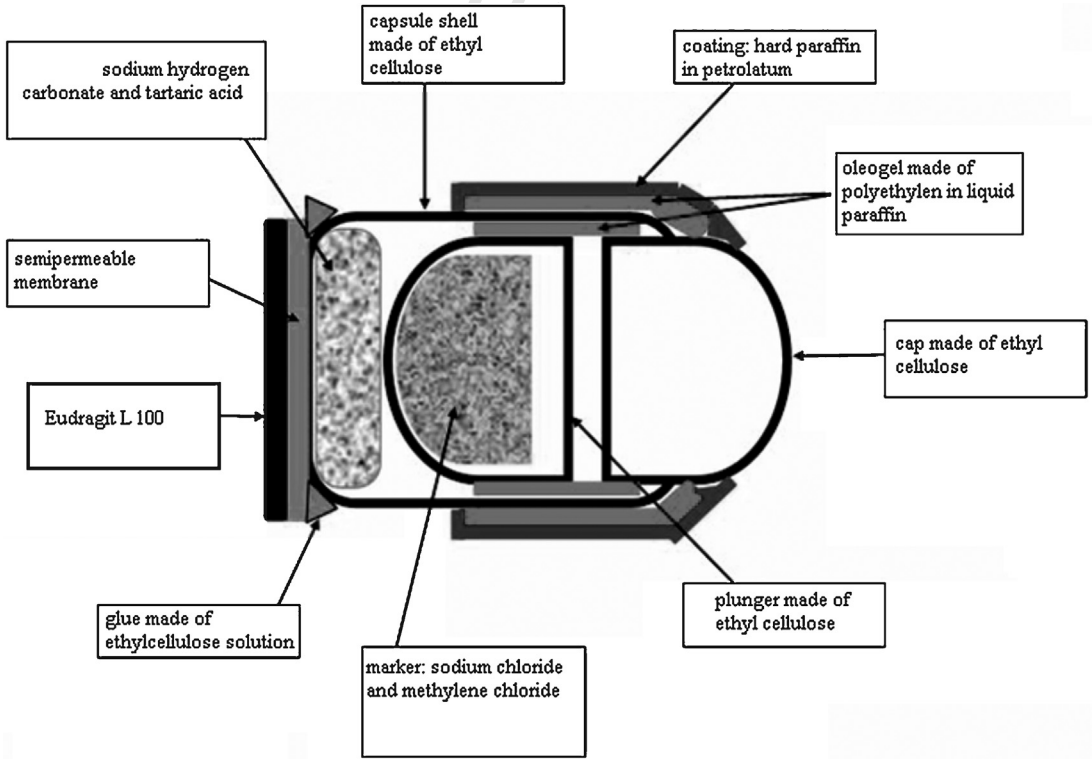

Fig. 1. Schematic construction of the capsule.

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