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Research paper

Mucoadhesive microparticles for local treatment of gastrointestinal diseases

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ABSTRACT

Mucoadhesive microparticles formulated in a capsule and delivered to the gastrointestinal tract might be useful for local drug delivery. However, swelling and agglomeration of hydrophilic polymers in the gastrointestinal milieu can have a negative influence on particle retention of mucoadhesive microparticles. In this work, we investigated the impact of dry-coating with nano-sized hydrophilic fumed silica on dispersibility and particle retention of mucoadhesive microparticles. As a model for local treatment of gastrointestinal diseases, antibiotic therapy of *Clostridium difficile* infections with metronidazole was selected. For particle preparation, we used a two-step fluidized-bed method based on drug loading of porous microcarriers and subsequent outer coating with the mucoadhesive polymer chitosan. The prepared microparticles were analysed for drug content, and further characterized by thermal analysis, X-ray diffraction, and scanning electron microscopy. The optimal molecular weight and content of chitosan were selected by measuring particle retention on porcine colonic mucosa under dynamic flow conditions. Mucoadhesive microparticles coated with 5% (weight of chitosan coating/total weight of particles) of low molecular weight chitosan showed good *in vitro* particle retention, and were used for the investigation of dispersibility enhancement. By increasing the amount of silica, the dissolution rate measured in the USP IV apparatus was increased, which was an indirect indication for improved dispersibility due to increased surface area. Importantly, mucoadhesion was not impaired up to a silica concentration of 5% (w/w). In summary, mucoadhesive microparticles with sustained-release characteristics over several hours were manufactured at pilot scale, and dry-coating with silica nanoparticles has shown to improve the dispersibility, which is essential for better particle distribution along the intestinal mucosa in humans. Therefore, this advanced drug delivery concept bears great potential, in particular for local treatment of gastrointestinal diseases.

1. Introduction

Mucoadhesive drug delivery systems can be beneficial for local treatment of diseases related to mucosal membranes, such as fungal or bacterial infections [1,2]. Since the dosage form can be brought in close contact with the diseased tissue for an extended period of time, the therapeutic efficacy can be increased and lower drug doses may be required, eventually reducing systemic adverse drug effects [3].

Colonic drug delivery is paramount for local treatment of diseases such as ulcerative colitis, Crohn's disease, or pseudomembranous colitis [4,5]. However, these diseases are often characterized by severe diarrhoea episodes [6], making it difficult to reach sufficiently high local drug concentrations for a long enough period of time, particularly in the ascending colon where the volume of fluids is higher [7]. The mucoadhesion approach can be an effective strategy to resist the wash-out of the drug. However, delivery and adhesion to the colonic mucosa still presents a great challenge [8].

In case of hard-gelatine capsules for delivery of a mucoadhesive formulation, there is a lack of strategies to prevent agglomeration after hydration. McGirr et al. [9] have observed an incomplete

Abbreviations: AUC, area under the curve; D50, median particle size; DSC, differential scanning calorimetry; FCC, functionalized calcium carbonate; LMW, low molecular weight; MBZ, metronidazole benzoate; MMW, medium molecular weight; SD, standard deviation; XRPD, X-ray powder diffraction.

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release of mucoadhesive polymers (carbomers) from InteliSite® plastic capsules administered to beagle dogs and opened in the colon by remote control. This was explained by hydration and swelling of the polymer inside the capsule before the polymer could be released.

The gastrointestinal transit of multiparticulate formulations is less variable than single-units, and transit through the colon is slower than monolithic dosage forms due to a sieving effect of multiparticulates [10,11]. Therefore, a drug delivery platform combining mucoadhesive features in multiparticulates can contribute to an overall increased gastrointestinal residence time. Procedures describing the preparation of mucoadhesive multiparticulates, nanoparticles [12–14], microparticles [15–18], and pellets in the millimetre range [19,20] have been reported.

The particle size of mucoadhesive drug carriers plays an important role in terms of mucoadhesion and manufacturability. Schmidt et al. have carried out a first *in vivo* study investigating the size-dependency of carrier uptake to inflamed rectal mucosa [21]. The most striking finding was the significantly enhanced accumulation of microparticles (3 μm) in ulcerous lesions. The authors concluded that size-tuning of drug carriers in the micrometre range offers a possibility for passive targeting of the inflamed regions in the gastrointestinal tract. Moreover, the results of *ex vivo* transport experiments let suggest that nanoparticles are not suitable for local treatment of inflammatory bowel diseases, since translocation towards the serosal compartment could enhance systemic drug absorption leading to higher risk of adverse drug effects [21].

In general, manufacturability of microcarriers is easier compared to nanocarriers due to the improved flowability of larger particles and the possibility of using standardized processes suitable for scale-up. Mucoadhesive microparticles were prepared by spray drying [22], dry powder coating [20], suspension polymerization [15], ionic gelation [23], emulsion-solvent evaporation [24], and supercritical fluid technique [25]. Our group has developed a precipitation method to coat drug-loaded microparticles with the mucoadhesive polymer chitosan [26]. These model particles showed significant retention on porcine colonic mucosa, and they have been used for the implementation and validation of a new particle-retention assay based on marker-ion analysis. However, manufacture of mucoadhesive microparticles by chitosan precipitation was done at small scale, and therefore, a method suitable for large scale is essential.

The fluidized-bed technology is an efficient and established pharmaceutical process often used for drug layering of non-porous pellets, particularly for low drug dosages, with several products in the pharmaceutical market [27,28]. The suitability for drug loading of porous microcarriers has also been demonstrated [29]. Additionally, this technology can be used to stabilize the drug as a solid dispersion leading to increased dissolution rate and bioavailability of poorly water-soluble drugs [30–32]. Scarce literature is available on the preparation of mucoadhesive microparticles using a fluidized-bed process, being a publication from Möschwitzer and Müller [17] one of the few examples. However, no mucoadhesion studies with these chitosan-layered pellets have been carried out.

In the present work, we describe a two-step fluidized-bed method for preparation of mucoadhesive microparticles with optimized drug-loading and chitosan-coating process to address local drug delivery to the colon. Metronidazole benzoate (MBZ, prodrug of metronidazole) was used as a model drug for poor aqueous solubility and local treatment of gastrointestinal diseases (*Clostridium difficile* infections). Further objectives of this work were to evaluate the feasibility of hydrophilic fumed silica to improve the dispersibility of the mucoadhesive microparticles, and to investigate its impact on the mucoadhesivity.

2. Materials and methods

2.1. Materials

Functionalized calcium carbonate (FCC, Omyapharm 500-OG) was kindly provided by Omya, Switzerland. Metronidazole benzoate (MBZ) was purchased from Farchemia, Italy. Ammonium formate, formic acid (98%), HCl, methanol (all HPLC-grade), and chitosan with low and medium molecular weight (LMW and MMW, respectively) and 75–85% of deacetylation were purchased from Sigma-Aldrich, Switzerland. Ethocel® Std. 10 cp was received from Colorcon, UK. Aerosil 300 was obtained from Evonik Industries AG, Germany. Acetone, acetic acid (99%), sodium dihydrogen phosphate dihydrate ($NaH_2PO_4 \cdot 2H_2O$), and NaOH pellets were purchased from Hänseler AG, Switzerland.

2.2. Particle preparation

For preparation of mucoadhesive microparticles, we used a laboratory-scale fluidized-bed equipment (Strea-1, Aeromatic Fielder, Switzerland) with top-spray configuration. A spray nozzle with an orifice diameter of either 0.5 or 0.8 mm was used (Schlick, Germany). The spray rate was controlled using a peristaltic pump and a balance. The mucoadhesive microparticles were prepared in two steps: (1) drug loading of the porous microcarrier FCC with the model drug MBZ dissolved in a mixture of ethanol and acetone co-loaded with a binder polymer, and (2) spray coating of the drug-loaded carrier particles with a chitosan solution.

After preliminary experiments, three different mucoadhesive formulations, and one non-mucoadhesive control formulation were prepared in this study. MMW-5 and MMW-10 particles containing 5% and 10% (w/w) MMW chitosan, respectively, were prepared to evaluate the optimal chitosan content in terms of mucoadhesivity. LMW-5 particles containing 5% (w/w) LMW chitosan were the optimized formulation in terms of higher drug load and easier manufacturability. The viscosity of the spray solution is lower for LMW chitosan than for MMW chitosan (20–300 cps vs. 200–800 cps, 1% (w/w) in 1% acetic acid [33,34]), which should result in decreased droplet size and reduced risk of nozzle blocking, leading to an overall improved coating quality. The fluidized-bed process parameters of the drug-loading and chitosan-coating batches are summarized in Tables 1 and 2, respectively.

2.2.1. Drug loading

After a preliminary screening, two drug-loading batches were prepared according to Table 1. For preparation of PEG-MBZ-FCC particles, PEG 3000, MBZ, and FCC were used at a ratio of 28.6:28.6:42.8 (w/w). PVP-MBZ-FCC particles were prepared at a higher drug load using PVP K-25, MBZ, and FCC at a ratio of 37.5:37.5:25 (w/w). The drug solution consisted of 10% MBZ (w/w), and 10% polymer (w/w) dissolved in a mixture of acetone

Table 1
Fluidized-bed process parameters used for the two drug loading batches PEG-MBZ-FCC and PVP-MBZ-FCC.

	PEG-MBZ-FCC	PVP-MBZ-FCC
FCC (g)	180	96
MBZ (g)	120	144
Polymer (g)	120	144
Co-loaded polymer	PEG 3000	PVP K-25
Theoretical drug load (%, w/w)	28.6	37.5
Inlet temperature (°C)	50	50
Air volume (level)	2–3	2–3
Atomization pressure (bar)	0.8	0.8
Spray rate (g/min)	5	5
Spray nozzle orifice diameter (mm)	0.8	0.8
Process time (h)	4	5