Multparticular dosage forms consist of small sub-units containing the drug and having the advantage of more uniform and predictable transit time, better distribution and less local irritation in the gastrointestinal tract, compared to single unit dosage forms [1,2]. Those multiparticulates, when designed as mucoadhesive formulations, can potentially prolong and normalize the residence time in the gastrointestinal tract, and increase oral bioavailability due to their adhesive interactions with the gastrointestinal mucosa [3]. Examples of methods for preparation of mucoadhesive pellets and microspheres are extrusion-spherization [1], spray-drying [4], and emulsion-solvent evaporation [5].

INTRODUCTION

Development of mucoadhesive drug delivery systems by precipitation of chitosan on drug-loaded microparticles

MATERIALS & METHODS

Particle preparation

Drug loading: Metronidazole benzolate (MBZ) was used as model drug for the preparation of mucoadhesive drug loaded microparticles. Drug loading into FCC was performed by solvent evaporation according to Preisig et al. [6]. Theoretical drug load was 40% (w/w).

Precipitation method: The MBZ-loaded FCC particles were used for mucoadhesive coating by precipitation of chitosan (Figure 2). The chitosan solutions were prepared in diluted acetic acid by stirring for 2 h and adjusting to pH 5. The MBZ-loaded FCC particles (10.0 g) were dispersed in 1 L of chitosan solution, and NaOH (0.05M) was slowly added (0.5 mL/min) under magnetic stirring until pH 7 was reached. By varying the chitosan concentration in solution (0.1%, 0.2% and 0.5%, w/v), three batches of microparticles with different chitosan contents were prepared (9.1%, 16.7%, and 33.3%, w/w). Separation of chitosan-coated microparticles from aqueous phase was done by centrifugation at 1000 rpm for 5 min (102 K, Sigma, Germany). After removing the supernatant, the product was washed with ultra-pure water and centrifuged again. This washing and centrifugation step was repeated three times. The product was dried in a vacuum oven and sieved to yield 2 size fractions (<90 µm, and 125-250 µm).

Particle characterization

Coating quality was visually analyzed by scanning electron microscopy (SEM). Drug load quantification was done by a validated HPLC method [6]. FCC content of chitosan-coated microparticles was determined by calcium precipitation using capillary electrophoresis. Chitosan precipitation was performed by a colorimetric assay described by Larionova et al. [10]. Drug release was measured using the USP IV flow-through method in phosphate buffer (pH 6.8). Sample mass was 50 mg, and the flow rate was set to 16 mL/min.

Particle-retention assay

The flow channel for measuring particle retention was adapted from Batchelor et al. [9], and designed and built in-house (Fig. 3). It consisted of three main parts, i.e. a) upper plate, b) fixture plate, and c) support plate. Porous calcium muccosa was spread on the mucus holder (d) of the support plate and immobilized with the fixture plate. After a pre-hydration phase of 5 min with a constant flow of ultra-pure water (37°C, 200 mL of water was evenly distributed over the center area of the mucosa (see Fig. 4). The flow channel was kept in horizontal position for 5 min. Subsequently, the assembly was tilted to 45° and the flow was started. The outlet flow medium was collected in beakers which were changed every 10 min. The duration of the experiment was set to 30 min. The remaining particles were scrapped-off the mucosa for determination of FCC recovery.

RESULTS & DISCUSSIONS

Particle characterization

SEM images of non-mucoadhesive control particles (MBZ-loaded FCC) are shown in Fig. 5 (A: < 90 µm, B: 125 - 250 µm). Fig. 5 also shows MBZ-loaded FCC coated with 33% (w/w) chitosan (C: < 90 µm, D: 125 - 250 µm). The distinct pore structure of FCC was completely covered indicating the formation of micrometer-thick chitosan layers. The particle compositions after chitosan precipitation were consistent with expected values demonstrating a good control of the deposition process (see Fig. 6).

Particle-retention assay

The results in Table 1 show that mucoadhesion strongly depended on the extent of chitosan coating. Mucoadhesive granules (125-250 µm) dispersed in FCC content of 33.3% (w/w) showed strongest retention on colonic mucosa (81.6 ± 6.2%, w/w). Immediate washout of the control particles (<90 µm) was observed after only 2 min. Most values for FCC recoveries were between 84.6% and 96.5% (w/w), indicating a good reliability of the FCC quantification method.

Table 1: Particle retention after 10 min (FCCapp) of mucoadhesive particles with different chitosan contents (%w).

<table>
<thead>
<tr>
<th>Chitosan (%w)</th>
<th>FCCapp (% recovery)</th>
<th>FCCapp (% recovery)</th>
<th>FCCapp (% recovery)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0 - 2.6 ± 4.9</td>
<td>11.5 ± 5.6</td>
<td>62.0 ± 14.9</td>
</tr>
<tr>
<td>9.1</td>
<td>27.6 ± 7.0</td>
<td>98.0 ± 8.8</td>
<td>82.0 ± 14.9</td>
</tr>
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<td>16.7</td>
<td>32.3 ± 7.4</td>
<td>92.1 ± 11.7</td>
<td>69.2 ± 6.5</td>
</tr>
<tr>
<td>33.3</td>
<td>64.4 ± 9.0</td>
<td>91.7 ± 17.6</td>
<td>96.5 ± 8.5</td>
</tr>
</tbody>
</table>

Particle-release and drug-dissolution kinetics for the particles with an expected chitosan content of 33.3% (w/w) are shown in Fig. 7. The retention kinetics of mucoadhesive particles were characterized by an initial burst detachment within the first 10 min, followed by a lower detachment rate for the remaining time of the experiment. The two different dissolution methods (flow-channel and USP IV) showed comparable drug-release kinetics for tested particles.

REFERENCES