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Preparation of gastroresistant mesalazine lipidic microcapsules

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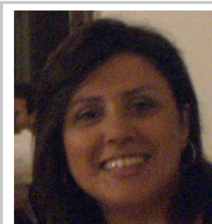

INTRODUCTION AND OBJECTIVES

Mesalazine or 5-aminosalicylic (5-ASA), a typical anti-inflammatory drug, is customarily used to maintain remission in inflammatory bowel disease (Carter, 2004). Mesalazine acts topically on the colonic mucosa; current 5-ASA delivery systems have been developed to avoid absorption of mesalazine in the small intestine, thereby delivering maximal amounts of the drug to colonic mucosa (Van den Mooter 2006). The aim of this work was to develop and characterize gastro-resistant multiparticulate system for mesalazine colon delivery in paediatric administration.

MATERIAL AND METHODS

Mesalazine was kindly supplied by Doppel (Cortemaggiore, Italy) and stearic acid was purchased by ACEF (Fiorenzuola, Italy). Carnauba wax (Produits Roche S.A. France) and Eudragit®L (Rhom Pharma, Germany) were also used. All other chemicals were of analytical grade.
The 5-ASA microcapsules were manufactured in two steps through the spray-congealing technique. In the first step, the mesalazine was dispersed in a solution of Eudragit®L in isopropyl alcohol prepared under stirring at the temperature of 70°C. The carnauba wax was added to the dispersion and the temperature was raised up until 95°C to evaporate the isopropyl alcohol and to melt the lipid. The melted mass was sprayed through the WPN nozzle at 3.0 bar. In the second step the microcapsules were obtained by disperding the 5-ASA cores in a low melting point lipid as stearic acid at the temperature around 70°C. At this temperature the microsphere did not melt and remained well dispersed in the liquid mass. The dispersion was sprayed with the WPN nozzle at 1.2 bar and the microcapsules were obtained.
The drug loading was determined by adding the samples to a simulated intestinal fluid (SIF) at pH 7.4 and heating up to 70°C or to 85°C to melt the lipophilic carrier as stearic acid or carnauba wax, respectively. The process was carried out under magnetic stirring for 5 hours to extract completely the 5-ASA. The solution was filtered with microcellulose filter and then assayed by UV at 330 nm. The analysis was performed in triplicate.
The lipid microcapsules were examined both under an optical stereomicroscope (Citoval 2, Jena, Germany) connected to a video camera (JVC, Tokyo, Japan) and Scanning Electron Microscopy (SEM, JSM 6400, Jeol Ltd., Tokyo, Japan).
Physical changes in microcapsules during heating were monitored by Hot Stage Microscopy (HSM). A hot plate (FP 52 Mettler, Grefensee, Switzerland) connected to a temperature controller (FP 5 Mettler) was used.
Temperature and enthalpy measurements of the raw materials and of the lipidic microparticles were performed by means of Differential Scanning Calorimetry (Mettler DSC 821e STARe, Mettler Toledo, Switzerland). Samples of about 5–10 mg in pierced aluminum crucibles were subjected to a thermal program from 30 to 300°C, at a scan rate of 10°C/min under a dynamic nitrogen atmosphere (100 ml min^{-1}).
The powder diffraction data were obtained with a Miniflex X-ray Diffractometer (Rigaku, Tokyo, Japan) with a graphite monochromator in the diffracted beam-path. A system of diverging, receiving, and anti-scatter slits of 0.58, 0.58, and 0.2 mm, respectively, was used. The patterns were collected with 30 kV of tube voltage and 15 mA of tube current in the angular range $2 \leq 2\theta \leq 50°$ in a step scan mode (step width, 0.05°; counting time, 2 s/step).
Dissolution tests were performed using the USP XXXI apparatus rotating at 100 rpm at the temperature of 37°C at variable pH. A weighted amount of the 5-ASA formulation was put in 300 mL of simulates gastric fluid (SGF) at pH 1.2 for 1 h. After this period, 600 mL of aqueous solution containing 2.6 g of NaOH and 6.12 g of KH_2PO_4, were added into the medium in order to reach pH 7.4. A 0.01% of Sodium Lauryl Solphate (SLS) was added in the aqueous medium to improve the wettability of the formulation. The samples were collected at predetermined time intervals from 0 to 480 min and filtered with 0.42 µm filter. 5-ASA concentration was determined by UV at 301 nm and 330 nm in acid and basic medium, respectively.

RESULTS AND DISCUSSION

The manufacture of the microcapsules was divided in two steps. In the first step, the cores were obtained according to the formulation reported in Table I. In the second step the cores were dispersed into the melted stearic acid and sprayed again (Table I). The drug loading in the cores and in the microcapsules was 31% (± 0.02) and 17% (± 0.16), respectively.
The cores and the microcapsules were characterized in term of optical stereomicroscopy and scanning electron microscopy (SEM).
From the image 1a it is possible to observe that the cores had round shape with a homogeneous distribution size around 50 - 75 µm. The surface was smooth and without irregularity (Figure 1b). The microcapsules, as shown in Figure 1c, had less round shape, due to the incorporation

of the cores inside the lipophilic matrix. It is important to notice that the cores inside the matrix of the microcapsule are visible, as reported in the Figure 1d. The surface of the lipid microcapsules was smooth and needles of 5-ASA raw material were not observed (Figure 2a). Some rifts were present on the surface of the lipid microcapsules (Figure 2b) due to the spray congealing process, but they did not affect the gastroresistant characteristics of the lipid microcapsules (Passerini 2003).

Table I. Composition (%) of 5 ASA cores and microcapsules

	5-ASA	Carnauba Wax	Eudragit®L	Stearic Acid
Core	31	68	1	-
Microcapsule	17	37.4	0.55	45

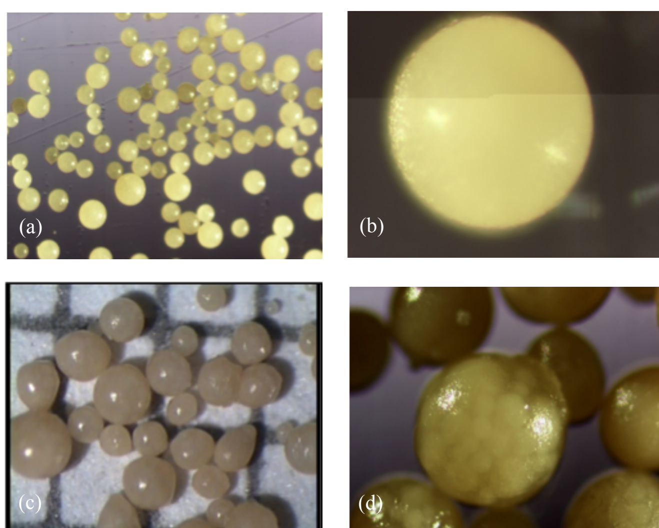

Figure 1. Optical images of the cores ((a) 4X and (b) 20X) and of microcapsules ((c) 4X and (d) 20X)

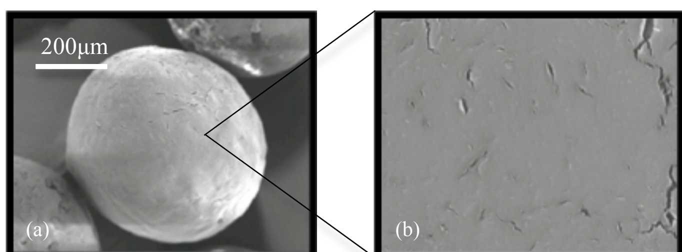

Figure 2. SEM images of the microcapsule (a) and of a detail of the microcapsule surface (b)

The HSM confirmed the encapsulation of 5-ASA cores inside the matrix of stearic acid. The microcapsules were intact until 56°C when the stearic acid started to melt. While heating, the carnauba wax started to melt at about 79°C in correspondence with the endothermal event registered with the DSC analysis (Figure 3). The fusion of the drug was observed at about 288°C.
The PXRD patterns of microcapsules confirmed the DSC and HSM analysis.

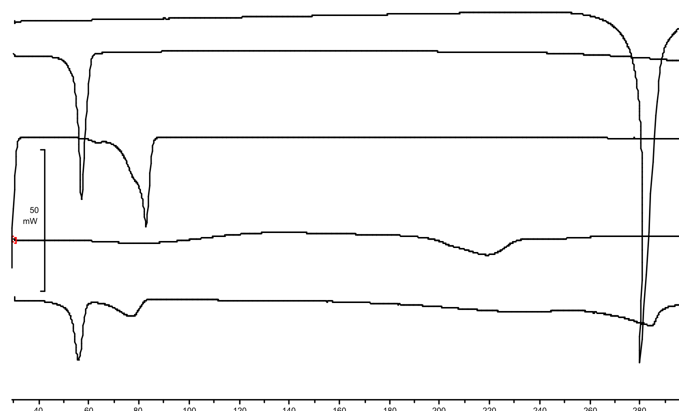

Figure 3. Thermograms (from the top) of 5-ASA raw material, stearic acid, carnauba wax, Eudragit®L and 5-ASA microcapsules

The dissolution test at variable pH shows that in the 5-ASA microcapsules less than 10% of 5-ASA was released in acid medium after 2 hours, while the drug release rose the 80% after 5 hour in pH 7.4 medium (Figure 4).

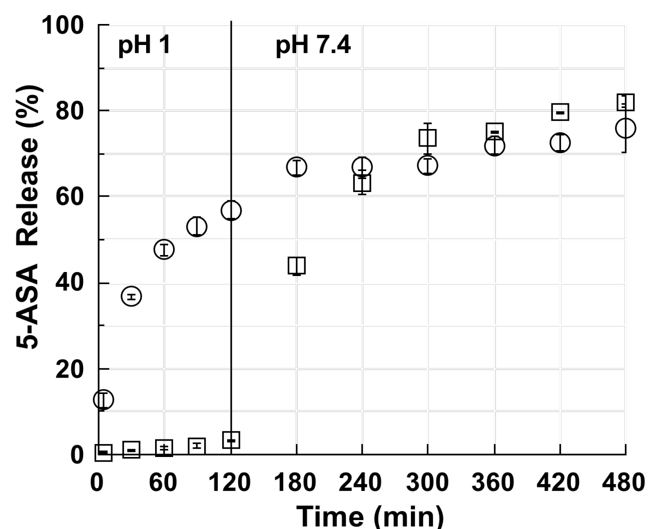

Figure 4. Dissolution profiles of cores (○) and microcapsules (□) in variable pH

CONCLUSIONS

The microcapsules based on lipid excipients were manufactured by spray congealing technique through two steps. The gastroresistant property was guarantee as demonstrated by the in-vitro dissolution profile.

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