Formulation optimising for aqueous enteric coating systems

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Introduction

Up-to-date galenical investigations deal with the development of aqueous coating systems in order to avoid the disadvantages of organic solvents. There is also an increasing trend to use excipients from natural sources, especially in formulations containing nutritional supplements such as probiotica, since the usual excipients used in the pharmaceutical industry are not allowed in supplementary products (Laicher, A. 1993; Lorck, C. A. 1997; Sultana, Kh. 2000; Chan, E. S. 2005).

Shellac is the purified product of the natural polymer Lac, the resinous secretion of the tiny insect *Kerria Lacca*. Due to its natural origin, shellac is an acceptable coating material for functional food products. The good resistance of shellac to gastric fluid makes it suitable for enteric coating purposes. The major problem is the low solubility of shellac in the intestinal fluid (Penning, M. 1990; Pearnchob, N. 2003 a,b; Pearnchob, N. 2004, Qussi, B. 2005).

The aim of the current study was the investigation of the coating properties of shellac on the one hand and the development of suitable enteric coating formulations containing shellac for food industry on the other hand.

Materials and methods

Materials

Citric acid anhydrous (Jungbunzlauer Ges.m.b.H.,Vienna, Austria), MCC-Pellets (Cellets® 700, Pharmatrans Sanaq AG, Basel, Swizerland), aqueous shellac solution (Marcoat 125®, Syntapharm, Mülheim am Ruhr, Germany), hydroxypropyl methylcellulose (HPMC; Pharmacoat®, ShinEtsu, Tokyo, Japan), glycerin 85% (Sigma-Aldrich, Vienna, Austria), Enterococcus faecium M74 (Medipharm AB, Sweden)

Methods

The coating processes were performed in a laboratory fluid bed equipment (GPCG 1.1, Glatt, Germany) with a bottom spray (Wurster) technique and a modified outlet filter system (Innojet, Lörrach, Germany). For the investigation of coating properties, citric acid anhydrous was used as feed material and was coated with Marcoat 125®. The influence of several process and product parameters, namely the atomising air pressure, the spray rate, the product temperature, the batch size and the amount of coating material on the coating properties were studied. The proportion of uncoated feed material and the dissolution rate of feed material in HCl 0.1N after each coating run, were taken as response variables. The effect of above-mentioned parameters on response variables were studied utilizing response surface methodology. A central composite design with 3 centerpoints developed by the graphic software STATGRAPHICS PLUS®, version 3, was used . To determine the experimental error, the experiment at the centerpoint was performed 3 times on different days (3 centerpoints). The design involved 29 different experimental runs in one block, combining 5 parameters at low and high level for each examined parameter. The ratio of uncoated citric acid after each coating process (n=3, each sample= 3.00 g) was measured by titration using NaOH. 0.5 N After each coating process, a dissolution test (n=3) was performed on a dissolution tester (Pharma-test, Germany). HCl 0.1N was used as the dissolution medium. Samples (5.0g) were assayed from each coated batch and applied using a basket apparatus (EuPh. 5.00). Samples were

taken after 2 hours. The concentration of citric acid anhydrous in medium (g/ml) was measured utilizing a HPLC method (Perkin Elmer ISS 200, USA).
The relative humidities of inlet and outlet air during each coating process were measured using RH Sensors (Vaisala, Finnland). The droplet size of atomised shellac was measured utilizing a spray particle analyser (Spraytec®, Malvern instruments, USA) by different combinations of spray rate and atomising air pressure. The coating surface and thickness were characterized using scanning electron microscopy (Philips XL 30 ESEM).

The best process parameters were taken for the optimisation of an enteric coating formulation with shellac. The formulation should protect the probiotic microorganisms against gastric juice and support their release in the intestine.

Results and discussion

Ratio of uncoated feed material
The analysis of the response surface design for the ratio of uncoated citric acid (R-square=86.5, Lack-of-fit=0.058) showed that the increase of atomising air pressure had the most significant effect on the decrease of the proportion of uncoated feed material in this study. The product bed temperature and the ratio of coating material had also significant effects on this parameter. Too high and too low temperatures in the bed were not suitable for the coating process. The influence of the batch size was significant only in combination with product bed temperature and the spray rate. Higher product temperature in combination with the larger batch size resulted in a lower proportion of uncoated citric acid. However, the effect of this interaction was less significant than the effect of above mentioned factors.

Dissolution rate
The effects of the main factors batch size, atomising air pressure and product temperature on the dissolution rate of citric acid were significant. Increasing the batch size in combination with the increase of atomising air pressure and product bed temperature up to 40°C resulted in the lowest dissolution rate of citric acid (R-square=92.36, Lack-of-fit=0.108).

The investigation of the geometric mean droplet size (d_{50}) and the droplet size distribution of atomised Marcoat 125® by different combinations of spray rate and atomising air pressure showed a significant effect of atomising air pressure on droplet size and droplet size distribution. This confirmed the important role of the atomising air pressure on the coating properties of aqueous systems. At lower atomising air pressure, increasing the spray rate resulted in an increase of the mean droplet size and wider droplet size distribution. At higher atomising air pressure, increasing the spray rate had no significant effect. Table 1 shows the mean droplet size and droplet size distribution by different atomising air pressures and a spray rate of 9g/min.

	Atomising air pressure (bar)			
	0.6	0.8	1.0	1.2
d_{50} (µm)	178.9	158.2	40.17	23.3
Span (µm)	1.60	1.78	1.60	4.18

Table 1. Geometric mean droplet size and droplet size distribution of atomised Marcoat 125® by different atomising air pressures and 9 g/min spray rate

Investigation of different runs, processing under constant product and process parameters and varying only the atomising air pressure showed the effect of this parameter on the relative humidity of inlet and outlet air during the process and the coating properties (Table 2).

	Atomising air pressure (bar)		
	0.6	1.0	1.4
Relative humidity of outlet air after 10 min. (%)	27.8±2	28.3±2	18.3±2
Relative humidity of inlet air after 10 min. (%)	9.5±2	8.4±2	4.7±2
Proportion of uncoated feed material (%;w/w)	60.04	11.45	6.81
Particle size distribution before coating process	1.23±0.02	1.23±0.02	1.23±0.02
Particle size distribution after coating process	1.32±0.02	1.27±0.02	1.24±0.02

Table 2. Relative humidity during coating process and coating properties by variation of the atomising air pressure

Figures 1 to 4 show the surfaces and the sections of coatings prepared at atomising air pressures of 1.4 and 0.6 bar.

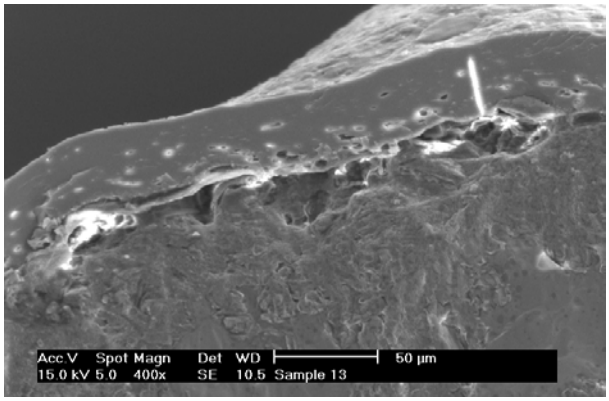

Figure 1. SEM photography showing the section of coating prepared at 1.4 bar atomizing air pressure at 400 magn.

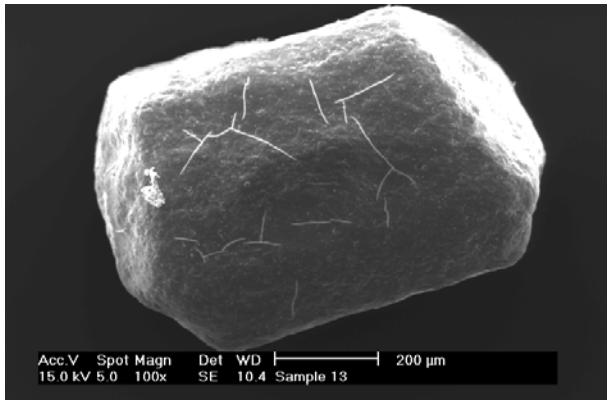

Figure 2. SEM photography showing the coating prepared at 1.4 bar atomising air pressure at 100 magn.

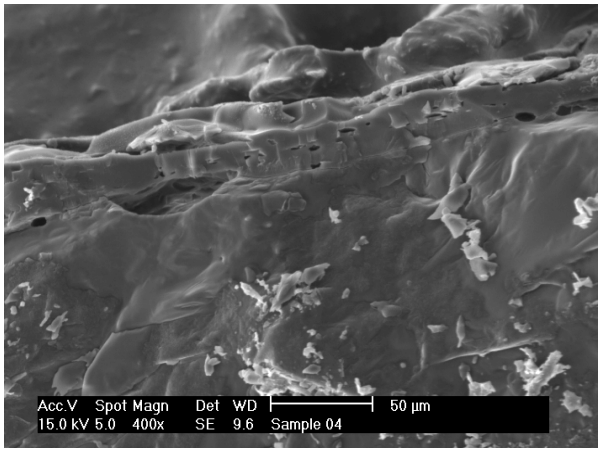

Figure 3. SEM photography showing the section of coating prepared at 0.6 bar atomizing air pressure at 400 magn.

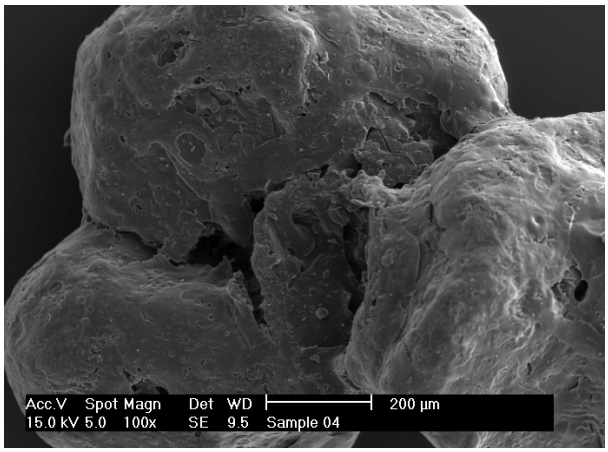

Figure 4. SEM photography showing the coating prepared at 0.6 bar atomising air pressure at 100 magn.

Conclusions

Optimisation of product and process parameters for aqueous coating systems showed the important role of the atomising air pressure and the product bed temperature on the moisture content in the product container and their influence on the coating properties.

Investigation of the coating properties confirmed the suitability of shellac for coating purposes. After investigation of coating processes, the best product and process parameters were taken and adapted for development of enteric coating formulations containing shellac.

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