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Evaluation of the effects of lactose on the surface properties of alginate coated trandolapril particles prepared by a spray-drying method

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ABSTRACT

This preliminary work involved a comparison of untreated microcrystals, alginate-based spray-dried microparticles, and alginate-based lactose containing spray-dried of the antihypertensive drug, trandolapril. Physicochemical properties, such as surface free energy, the polarity and the dissolution profiles of the untreated drug and the spray-dried particles were investigated. The main objective was the separation of crystals suitable for the production of intermediates for high-speed tablet-making from materials with low melting point. The aim was to modify the surface properties of trandolapril without changing the dissolution profile of the active agent; this was achieved by the application of spray-drying technology for the production of coated particles with a hydrophilic surface in order to attain better wetting properties, and better processibility. The aggregation of the spray-dried coated particles and their subsequent coalescence is very favourable for the liquid containing lactose. The kinetics of dissolution of the active ingredient was not changed appreciably by the surface modification obtained by spray-drying, regardless of whether alginate or alginate and lactose was used. Slightly quicker dissolution was observed for the sample containing lactose. The spray-drying with alginate increased the polarity of the surface of the particles. The application of lactose caused a more marked increase in this property; and this can be a very useful way to produce a powder mixture containing polar components (e.g. lactose). Thus, the spray-drying method is a very suitable procedure for the preparation of coated crystals as intermediates for tablet-making. The evaluation of the surface properties of these particles can promote an understanding of the production process and optimization of the composition.

1. Introduction

A knowledge of the process of direct compression is very important in the technology of tablet-making. The behaviour of powders during such processes may be followed well with instrumented tablet machines, or other indirect methods (Ritschel & Bauer-Brandl, 2002). The understanding of a process leads to the ability to identify the critical points of tablet-making coating control. This information is necessary for the application of Process analytical technology, which cannot only lead to a better manufacturing process, but also speed up the research and development (Davies & Ellis, 2005). The parameters that must be considered are the precompression and main compression forces on the upper and lower punches, the punch displacements, the ejection force, the die wall hoop stress, the die and punch temperatures, etc. (Ridgway Watt, 1988). The temperature is an important parameter, because the energy expenditure of compression is the sum of the useful energy, the energy of reversible elastic strain and the energy dissipated as heat (Lieberman & Lachman, 1981). The crystal rearrangement in the die can influence the heat genesis. It is well known, that if crystals are arranged side to side with a high thermal conductivity edge, then this promotes the attainment of a higher temperature in a very small volume. This increased temperature (it is known that 140 °C can be reach in the tablet during tablet-making (Pintye-Hódi, Szabó-Révész, Miseta, & Selemczi, 1984) can be higher than the melting point of the material and the crystals melt. Since melted materials recrystallize after compression, the particles lose their individuality. Such sites in the texture are called hot spots (Bogs & Lenhardt, 1971; Fuhrer & Parmentier, 1977; Kedvessy & Garamvölgyi-Horvát, 1973). A particular difficulty in the processing of these materials is known from industrial experience: A crust of the material is formed on the punches and table of a high-speed tablet machine during direct compression.

Various methods may be used, which separate the crystals and so help to avoid the formation of hot spots. One such process is the film-coating of crystals. We have studied the application of a gastric soluble film to increase the processibility of dimenhydrinate (Bajdik et al., 2001, 2000, 2002a, 2002b, 2004). The film-coating method applied in fluidized bed apparatus was not appropriate for small particles. The formulation of irregularities and extensive aggregation in this case is inevitable. Some other surface treating

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method must therefore be used for very small particles. The spray-drying of a dispersion containing a soluble film-former and insoluble active agent can be applied to prepare a surface-coated product. This method was used in the present study to evaluate the change in the surface properties of the crystals. The formulation of these products has been very well studied, but the main field of application is to change the dissolution profile (Ozeki et al., 2005; Takeuchi et al., 2005; Wong et al., 2006).

In this study, the main objective was the separation of the crystals to produce intermediates for high-speed tablet-making from materials with low melting points; change of the dissolution kinetic was not the primary aim. Before the formulation of a solid dosage form, aspects such as wetting, surface free energy, polarity, etc. must be studied for a better understanding of this process. These parameters are very informative, because they can also determine the processibility (e.g. mixing) (Buckton, 1995; Podczeck, 1998).

Trandolapril (practically insoluble in water) was chosen as a model active pharmaceutical ingredient. The melting point of this material is 130 °C. The rheological properties of different alginates were previously studied and the most suitable one was chosen. Alginates are well studied, water-soluble linear polysaccharide extracted from brown seaweed (Rioux et al., 2007), and is composed of alternating blocks of 1–4 linked α-L-guluronic and β-D-mannuronic acid residues. They are often used in pharmaceutical technology (Babu et al., 2007; Chan et al., 2006; Wang et al., 2007). The applied film-former was sodium alginate.

The application of lactose together with alginate is known to be very useful in the formulation of spray-dried products (Takeuchi et al., 2005). The concentration of this component was chosen in accordance with our previous experiments. It is of interest to evaluate the effects of this component on the surface properties. The surface properties of the intermediate must be very similar to those of lactose since this is the filler mainly applied during tablet-making. The wetting and morphological properties of the products and the dissolution of the active agent were evaluated.

2. Experimental

2.1. Materials

Trandolapril, an antihypertensive drug with angiotensin-converting enzyme inhibitor effect with mainly an apolar character (Guay, 2003; Parfitt, 1999) soluble (>100 mg/ml) in chloroform, dichloromethane and methanol (Dr. Reddy's Laboratories Ltd., India), sodium alginate (Manugel GHB, ISP Co., UK), and α-lactose monohydrate (Ph.Eur.) (Sigma, Hungary) were used for the experiments. Distilled water (Ph.Eur.) and diiodomethane (Merck KGaA, Darmstadt, Germany) were applied for surface free energy (SFE) measurements.

2.2. Preparation of dispersions

Dispersion of sodium alginate was prepared with distilled water at a concentration of 2.0 w/w%. Lactose was dissolved in 100 ml distilled water, and mixed thoroughly with the polymer dispersion. Samples were diluted with distilled water in order to decrease their viscosity. For homogenization, an overhead stirrer (Heidolph RZR2020, Heidolph Instruments, Germany) was used with a propeller stirrer tool at 300 rpm. Trandolapril was suspended by use of a high-speed mixer (Diax900, Heidolph Instruments, Germany) at 2000 rpm, for 30 min.

2.3. Compositions of samples

Table 1 lists the compositions of the various spray-dried samples.

Table 1
Composition of samples

Sample	Dry matter wt%		
	Trandolapril	Lactose	Sodium alginate
TR	100	0	0
Sample 1	50	0	50
Sample 2	50	30	20
Sample 3	0	0	100
Sample 4	0	60	40

2.4. Spray-drying

For the preparation of spray-dried microparticles, a laboratory spray-dryer (Büchi B-191, Büchi Labortechnik AG, Flawil, Switzerland) was used. Spray-drying was carried out on well-homogenized suspensions of trandolapril. After homogenization, slurries were sonificated in a sonification bath, for 10 min in order to eliminate air bubbles. The parameters of the process were as following: Inlet air temperature: 115 °C, compressed air flow rate: 800 l/h, aspirator capacity: 80%, peristaltic pump feed capacity: 7%.

Different products were therefore formulated with and without active agent (Table 1).

2.5. Morphological study

The surfaces of the various samples were analysed with a scanning electron microscope (Hitachi S2400, Hitachi Scientific Instruments Ltd., Tokyo, Japan). A SEM sputter coating unit (Polaron E5100, VG Microtech, UK) was used for charging of the surfaces for the SEM measurements. The air pressure during the analyses was 1.3–13 mPa.

2.6. Contact angle (CA) measurements

The surface free energy (SFE) of a sample can provide very important information (e.g. adhesion, spreading, etc.) concerning the processibility of the solid product. It is therefore desirable to know this parameter before the formulation. The wetting abilities of the materials are also very important from the aspect of the dissolution of the drug from the dosage form.

For these measurements, tablets (0.10 g each) were made by using a hydraulic press (Specac, UK) at a 10 kN of compression force. Prepared samples were dried for 24 h, and then stored for another 24-hour period in a desiccator dish (RH < 20%, at 25 °C) before the tests. Measurements were carried out with a drop-contour analyser (Dataphysics OCA20, Dataphysics Instruments GmbH, Filderstadt, Germany), by a sessile drop method at room temperature (25 ± 1 °C).

The SFE of the solid was calculated according to the method of Wu (1971). This is the sum of the polar (γ_s^p) and dispersion (γ_s^d) components for the solid. The SFE of the solid can be assessed by measurements of the contact angles (CA) of two liquids of known polarity and the solution of two equations (one for both liquids) with two unknowns:

$$(1+\cos\Theta)\times\gamma_l = \frac{4\times(\gamma_s^d\gamma_l^d)}{\gamma_s^d+\gamma_l^d} + \frac{4\times(\gamma_s^p\gamma_l^p)}{\gamma_s^p+\gamma_l^p}$$

where γ_l is the surface tension of the liquid and γ_s is the SFE of the solid, Θ is the solid–liquid surface CA.

The polarity value, as a percentage, can be derived from the SFE. It is the ratio of the polar part and the total SFE.

For the determination of SFE, distilled water and diiodomethane were chosen. Bilateral solid–liquid surface contact angles were measured with both liquids. CA values were registered every sec-