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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-

ond for 15 s after drop formation. The circle fitting method was used for CA determination. For the calculations we used the mean CA values for the 3rd second of at least five continuous measurements. SFE values, and polar and disperse surface tension (SFT) values were calculated from the contact angles determined with water (for the polar component of SFT) and diiodomethane (for the disperse component of SFT).

According to Wu, SFT is 72.80 mN/m for water and 50.80 mN/m for diiodomethane: The polar part of SFT is 50.20 mN/m and 1.80 mN/m and the disperse part of SFT is 22.60 mN/m and 49.00 mN/m.

2.7. Dissolution study

For the dissolution tests, we used a dissolution tester with paddle accessory. The dissolution medium was 50 ml PBS solution with a pH of 7.00 ± 0.05. The temperature and rate of agitation were kept at a constant value—37 ± 0.5 °C and 100 ± 0.1 rpm. Four parallel measurements were performed in case of each various samples. The volumes of manually taken samples were 1.0 ml.

API concentration of filtrated samples was measured spectrophotometrically (Helios α, Thermo Spectronic, Cambridge, UK) at a wavelength of 258 nm. For filtration filter paper was used (S&S, Dassel, Germany). Measured absorbance values were adjusted extracting the absorbance values of blind samples (in case of Sample 1, Sample 3 was used for correction while in case of lactose containing Sample2, Sample 4 was used).

Dissolution profiles were compared by using similarity factor f_2 (Costa & Lobo, 2001). For two similar preparations, the values of this factor must be between 50 and 100. If the value is lower, the dissolutions from the tested preparation (T) and from the reference preparation (R) are not significantly similar:

$$f_2 = 50 \times \log\left[\left(1 + (1/n)\sum_{t=1}^{n}|R_t - T_t|^2\right)^{-0.5} \times 100\right]$$

2.8. Differential scanning calorymetry (DSC) study

The crystallinity of the components was also examined since the better solubility of amorphous materials is well known (Blagden et al., 2007; Leuner & Dressman, 2000). A Mettler-Toledo DSC 821e (Mettler–Toledo GmbH, Switzerland) instrument with was used for this test. A dynamic method in the interval 25–300 °C (heating rate of 5 °C/min) was applied. Argon and nitrogen were used as purge gases.

3. Results

The SEM pictures revealed needle and columnar shape of the original trandolapril crystals (Fig. 1). The coating of these crystals and the co-spray-drying can be observed in Figs 2 and 3. The morphological study of the products demonstrated that not only the covering of the particles occurred. Several addition products (spray-dried particles and small agglomerates) can be seen. The proportion of the spray-dried coating materials must be minimized.

If the cohesion between the discrete coating particles is not adequately high during the process, then the possibility of coalescence is lower and the film formation is less effective (Cole et al., 1995). Without the coalescence the drying is quicker and thus the appearance of the spray-dried product is more inhomogenous (in certain cases, the droplets dry without film formation and small spray-dried polymer particles form.) For evaluation of the cohesivity of the coating particles during the process, samples were produced without trandolapril (Samples 3 and 4). It can be seen that the par-

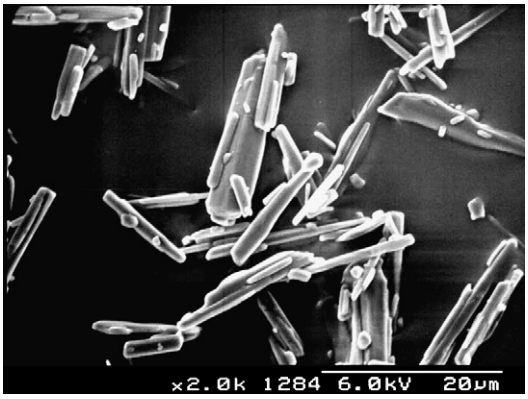

Fig. 1. SEM picture of trandolapril.

Fig. 2. SEM picture of Sample 1.

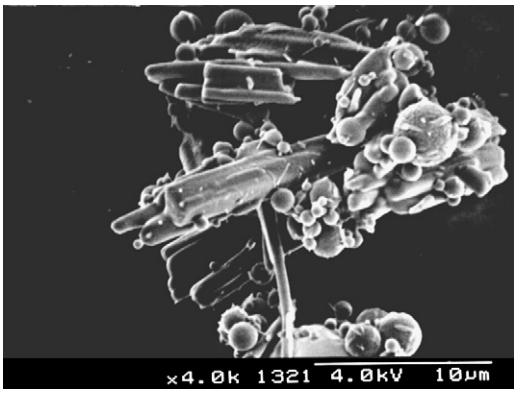

Fig. 3. SEM picture of Sample 2.

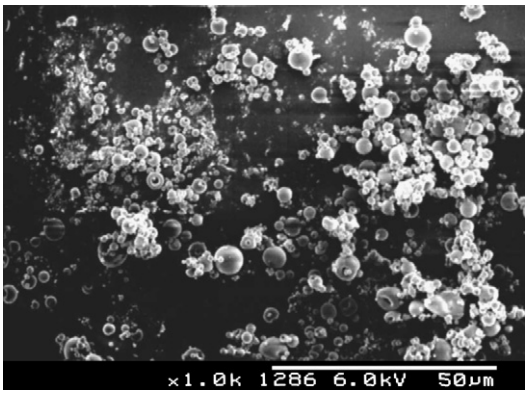

Fig. 4. SEM picture of Sample 3.

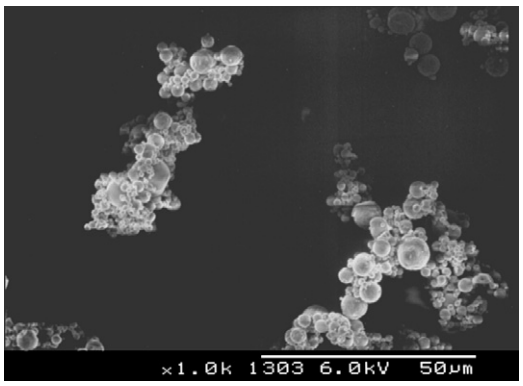

Fig. 5. SEM picture of Sample 4.

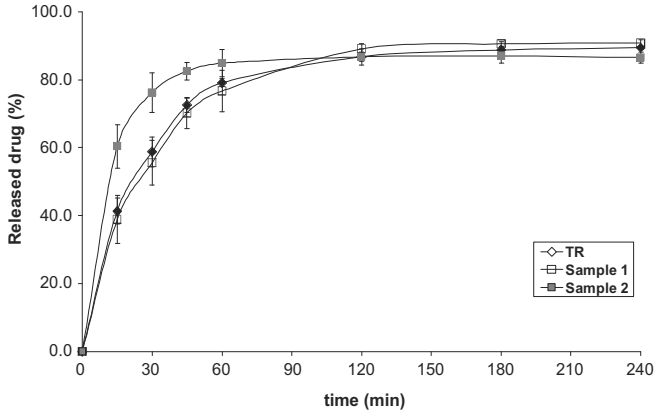

Fig. 6. Dissolution curves of samples.

ticles containing lactose formed agglomerates (Fig. 4). Accordingly the cohesivity of these particles was more preferable than without this additive (Fig. 5). Film formation (coalescence for these drops) was not detected for these two samples because the drying was quicker than during the formulation of the trandolapril samples (in accordance with the higher heat capacity of trandolapril, the heating of the coating material was less intensive).

For the mixing of different components to produce a homogenous powder mixture closely similar polarities are advisable. The polarity of a solid surface is the ratio of the polar part of SFE and the total SFE, expressed as a percentage, and therefore determination of SFE is necessary. The lowest SFE was that of trandolapril, and the highest that of lactose (Table 2).

Samples 1 and 2 exhibited higher polarities than that of untreated trandolapril (~36% higher for Sample 1, and ~49% higher for Sample 2). The cause of this increased polarity is the presence of lactose and alginate in the compositions, because these additives have higher polarities than that of untreated trandolapril.

The sample containing lactose (Sample 2) had a higher polarity than Sample 1, and was closer to the polarity of lactose. This can be very useful for the production of solid dosage forms since lactose is the conventionally used filler for these systems. Thus the application of lactose in the coating fluid can favourably change the surface properties of the spray-dried product.

Table 3
Differences of dissolution profiles

f_2 values		(T)ested	
		Sample 1	Sample 2
(R)eference	TR	81.07	49.71
	Sample 1	100.00	46.03

The characteristics of the dissolution curves were very similar for all the samples (Fig. 6), but the first phase for Sample 2 was accelerated. The similarity factors were calculated, and indicated no difference between the dissolution profiles of Sample 1 and trandolapril (the value was higher than 50), whereas Sample 2 differed slightly from the other samples (Table 3). The difference can be explained by the more hydrophilic behaviour of this sample, amorphisation of active agent and the presence of lactose. The increasing effect of lactose on the dissolution of poorly soluble materials is well known (Allahham & Stewart, 2007; Vogt et al., 2008). The DSC studies revealed that Sample 2 containing amorphous lactose and crystalline active agent (Fig. 7). The physical mixture with the same composition exhibited crystalline form of both components. Thus it can be concluded that the spray-drying did not caused the total amorphisation of active agent, but it changed the state of lactose. The explanation of quicker dissolution therefore can be the more hydrophilic surface and presence of lactose.

4. Conclusions

It can be concluded that spray-drying is a very good method for the treatment of trandolapril crystals with sodium alginate. Various additional products (e.g. agglomerated crystals, spray-dried pure sodium alginate particles) can also be formed during the process. However, this can be decreased by the incorporation of lactose into the coating fluid. The aggregation of the coating particles and the subsequent coalescence is very favourable for the liquid containing lactose. The kinetics of dissolution of trandolapril did not change appreciably with the surface modification resulting from spray-drying, independently of whether alginate or alginate and lactose was used, but 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. Since very similar polarities of the different materials is necessary for the most effective mixing, the change in this parameter can be very useful for the formulation of a solid dosage form containing lactose as a filler.

The homogeneous distribution of trandolapril not only influences the content uniformity, but can also eliminate the formation of hot spots, which prevent tablet-making due to the sticking to the punches and die wall, and cap formation during tabletting. Thus,

Table 2
Wetting properties and surface free energies of samples

	$\Theta_{diiodomethane}$ (°)	Θ_{water} (°)	γ_d (mN/m)	γ_p (mN/m)	γ_{tot} (mN/m)	Polarity (%)
TR	19.53 ± 0.70	66.15 ± 2.00	43.64	13.53	57.17	23.67
Lactose	18.30 ± 2.50	6.10 ± 1.40	43.49	37.38	80.87	46.22
Sample 1	25.05 ± 1.70	53.89 ± 1.70	41.77	19.91	61.69	32.27
Sample 2	23.09 ± 1.40	47.37 ± 2.40	42.34	23.02	65.36	35.22
Sample 3	26.62 ± 1.30	47.98 ± 2.80	41.22	23.02	64.23	35.84
Sample 4	25.98 ± 1.20	51.05 ± 3.30	41.45	21.40	62.85	34.05

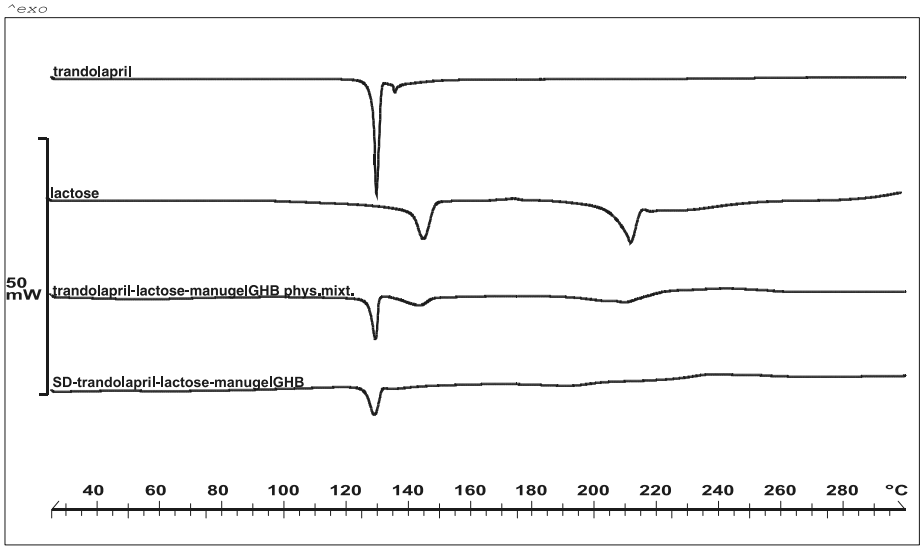

Fig. 7. DSC curves of samples.

the spray-drying method is a very suitable procedure for treatment of the crystal surface and for the preparation of an intermediate for tablet-making. Evaluation of the surface properties of these particles can greatly promote an understanding of the production and optimization of the composition.

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