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Physical properties of pellets manufactured in the high shear mixer after optimizing the process parameters

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The high shear mixer was used for the production of pellets. The steps of mixing, wetting, aggregation and spheronization could be carried out in one apparatus simplifying the steps of the technological process and reducing time compared to other methods (extrusion and spheronization). In the present study the authors examined the effect of the production parameters – rotating number, feeding rate – on the physical and mechanical properties of the produced pellets in the case of different compositions, which can be of decisive impact on the further technological steps. In order to evaluate the pellets, crushing strength, real density, deformity factor, particle size distribution and friability of the particles were determined. It could be concluded that the feeding rate is connected with particle size distribution of the pellets. The Avicel content of the particles seems to affect their crushing strength.

1. Introduction

Pellets as multiple-unit dosage forms show several advantages in therapeutical, physiological and technological aspects. It is generally verifiable that this dosage form can be characterized by better gastrointestinal distribution and absorption of the active ingredient than the single-unit dosage form. Dose dumping and local irritation are avoidable, too. To ensure controlled release of the active ingredient and steady blood levels without fluctuation it is possible to use coated pellets or to form multiple-unit time-controlled release systems (SRS) [1–5].

Several properties (coating, pressing, flowability, wetting or the liberation and absorption of active ingredient) are highly influenced by the proportion of minimal surface/volume of the pellets or matrix pellets, sphericity, particle size distribution and uniform particle size, as well as particle size and crystal form of the active ingredient [6, 7]. According to Sherrington et al. four processes (mixing, compressing, layering and globulation) are known to be suitable to the applied technological methods (spheronization, spray-drying or lyophilization, extruder/spheronization) [8].

The aim of our study was to work out such a pellet-building process which makes it possible to form pellets with adequate physical parameters in one apparatus. The optimal quantity of the granulating fluid in the case of different compositions was determined because it has a decisive impact on the physical characteristics and production of pellets. The effect of several manufacturing parameters on particle size and particle size distribution were examined and the shaping properties of the mixing intensity, feeding rate and Avicel content of the particles was studied. The shape of the particles as well as the mechanic behaviour characterizing parameters were defined. This is important information for the further pharmaceutical technological steps, i.e. coating or pressing.

2. Investigations, results and discussion

2.1. Optimization of the production parameters

The spheronization method was used for the preparation of pellets of different compositions and the manufacturing was carried out with the high shear mixer, in one apparatus. The different compositions of the prepared pellets are shown in Table 1. Creating the compositions we have taken into consideration the well-known capability of Avicel PH101 for shaping of spherical particles and the high crushing strength of the comprimate as well as the elastic character of the starch and rigidity of the lactose crystalls.

In the first step the effect of changing the revolution number for the particle size distribution was examined applying a 2-factor, 3-level face-centered central composite design. The effect of formulation factors (i.e. revolution number and Avicel PH101 content) on the pellet characteristics was described by a second-order polynomial model [9]. The greatest quantity of the particles were 800–1250 μm in size and their sphericity was also adequate (sphericity factor 0.95–0.96). That is why they were chosen for the optimal revolution number for the further experiments.

Further on the effect of the feeding rate for the particle size distribution as well as for the characteristics of the particles was studied. It follows from these premises that having selected the optimal 900 rpm, the feeding rate of the granulating liquid was changed from 100 ml/min to 200 ml/min. In the initial stage of the moistening period atomization water had been used to achieve the even wetting by keeping of 3 min intervals and continuous atomization. In the period of wetting and kneading or spheronization different choppers were applied to shape particles. In the case of compositions 1, 2 and 5 the feeding rate seemed not to cause significant deviation in the particle size distribution as it can be seen in Figs. 1 and 2. At the same time particles of smaller sizes are formed in the case of compositions 3 and 4. On a low feeding rate of 125 ml/min, pellets of 800–1250 μm can be observed to be ideal in the aspect of coating.

2.2. Physical characteristics of the pellets

Having examined the crushing strength of pellets which is an important property from compressibility aspects and regarding the resistance to abrasion, it can be observed

Table 1: Composition of the pellets

Composition	Model substance	Avicel PH 101	Lactose	Amylum solani	Amylum tritici	Amylum maydis
1	20%	80%	–	–	–	–
2	20%	40%	20%	20%	–	–
3	20%	40%	20%	–	20%	–
4	20%	40%	20%	–	–	20%
5	20%	60%	20%	–	–	–

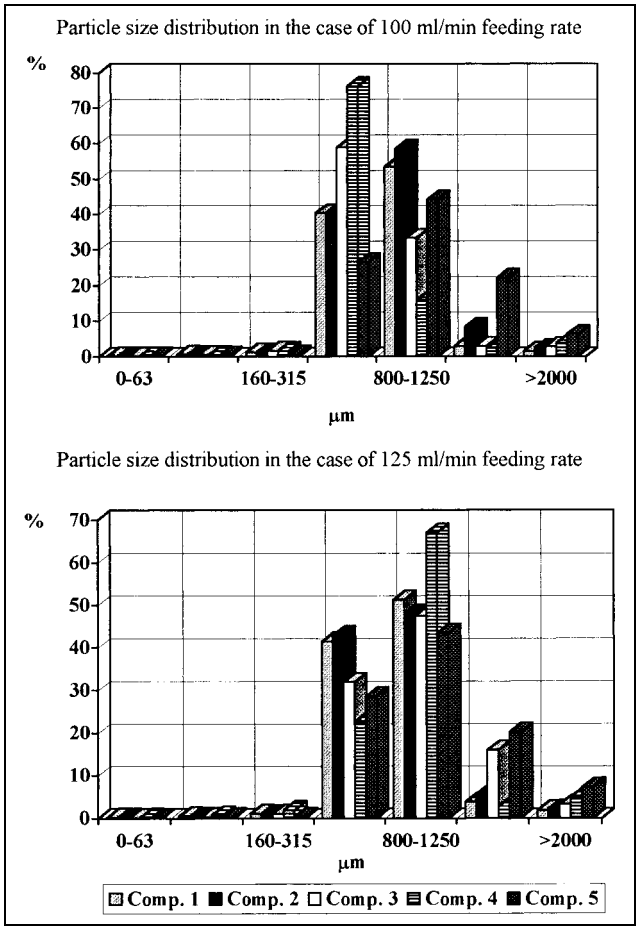

Fig. 1: Particle size distribution in the case of first and second conditions

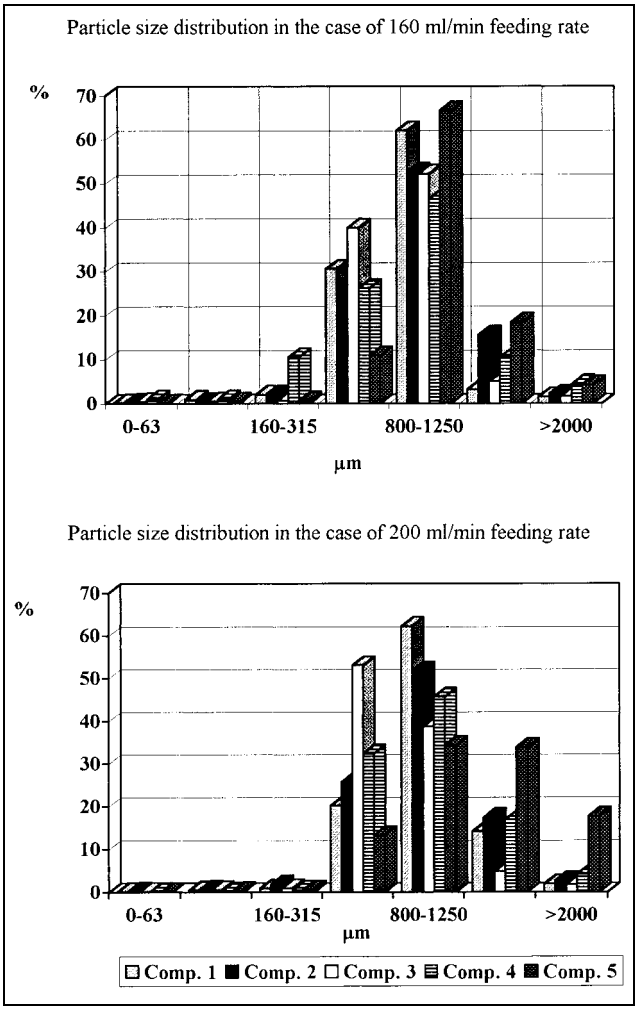

Fig. 2: Particle size distribution in the case of third and fourth conditions

that the compositions 3 and 5 had a higher strength value in each particle size than the other two compositions (Table 2). This difference may be explained by the different types of starch used and by the variant Avicel content of the particles. In the case of composition 1 the particles showed plastic deformation caused by the applied pressing force and did not break in smaller pieces within the measuring range. Since a higher amount of water was used during kneading, the water could be built into the swellable polymer system containing the active ingredient. It was also promoted by the applied drying method because in the case of heat-transmitting drying, an thermodiffusional liquid stream from the outside warmer surface of the pellets to their inner colder liquid space could be observed. As a result the surface of particles was closed and the granulating liquid remained entrapped inside the pellets which leads to their plastic behaviour. In the case of the other three compositions this plastic character could not be observed directly because they also contained lactose. The plastic character of cellulose-derivatives experienced during the pressing is known from the literature [10].

Table 2: Relation between the crushing strength and the particle size of the different compositions

Mesh (µm)	Crushing strength (N)			
	Comp. 2	Comp. 3	Comp. 4	Comp. 5
315–500	8.20	8.50	7.70	9.20
630–800	12.17	16.00	12.08	16.55
800–1000	13.56	18.15	13.20	19.90
1000–1250	16.75	20.50	15.75	22.95

The fractions of 800–1250 µm particle size were selected for the determination of the pellet-characteristics on a feeding rate of 160 ml/min (Table 3). In the case of compositions 1–3 or compositions 4 and 5 the real density values differed only slightly from each other, while the compacting factors (i.e. Carr's index) showed significant differencies. The sphericity of particles was acceptable in all cases as indicated by a deformity factor of approximately 1.0. Having examined the effect of other three feeding rates on the pellets it can be seen that the values of the deformity factor altered from 0.78 to 0.96 and we generally got greater differences among Carr's indexes (4%–8%–12%), too.
Thus we can consider that 160 ml/min is an ideal feeding rate because the amount of pellets of 800–1250 µm in size is the greatest.
This particle size is ideal from the point of coating, and the physical properties of the particles were the best with smaller differences (see Table 3) in this case, too.

Table 3: Physical parameters of the prepared pellets (feeding rate 160 ml/min)

Comp.	Real density (g/cm^3)	Carr's index (%)	Hausner ratio	Outflow time (s)	Deformity factor
1	1.45	8.0	1.09	5.35	0.96
2	1.43	8.0	1.09	5.45	0.96
3	1.42	8.0	1.09	5.58	0.96
4	1.53	12.0	1.14	5.52	0.95
5	1.52	12.0	1.14	5.49	0.96

We experienced that during the applied production circumstances, the Avicel content of each composition had slightly changed the shaping parameter of the particles. So we did not use more than 40% Avicel PH101.
Summarizing our results, it can be established that the described process allows the production of drug containing pellets in one apparatus. The process is considerably influenced by the proper choice of the manufacturing parameters (intensity of mixing and feeding rate of the granulation liquid). Optimization of the process parameters offers the opportunity to prepare reproducible products of adequate physical parameters.

3. Experimental

3.1. Materials

Salicylic acid (Sigma-Aldrich Ltd., Budapest); Avicel® PH101 (Fluka, Germany), α-D-lactose monohydrate (Hungaropharma, Budapest); Amylum solani, Amylum tritici, Amylum maydis (Hungaropharma, Budapest).

3.2. Preparation of pellets

The pelletization was carried out in a Stephan UMC 5 electronic apparatus (Stephan Maschinen GmbH, Wien, Austria) equipped with different choppers. Five various compositions, containing Avicel PH101, lactose, amylum solani, amylum tritici, amylum maydis as well as salicyclic acid were prepared. The granulation liquid, distilled water, was atomized in a rate from 160 ml/min to 200 ml/min.

3.3. Particle size distribution of pellets

The prepared and dried pellets were fractionated using a Retsch AS 200 control type vibrating sieve (Retsch Verder GmbH, Haan, Germany). Sieving was done in 200 g parts, for 5 min with a 2.5 mm amplitude without intervals and sieving aids. The sieve fractions were the following: 1250–2000 μm; 800–1250 μm; 315–800 μm; 160–315 μm; 63–160 μm.

3.4. Friability

The weight loss of the particles by abrasion was controlled with a friabilator (Erweka GmbH, Germany) according to the official method.

3.5. Crushing strength

The crushing strength of 20 pellets from each composition were determined by measuring the collapsing force using a Dr. Schleuniger Pramatron Model 6D tablet tester (England).

3.6. Real density

The density of the solid particles was determined with a pyknometer as usual.

3.7. Flow properties

The outflow time of the particles from an ASTM funnel was determined. In the case of every sample the examined material quantity was 40 g.

3.8. Sphericity factor

The shape of the pellets was examined with a light microscope (Zeiss, Jena Germany) at 16× magnification. Major and minor axes of 12 particles of each composition were measured. The sphericity factor was determined as a mean value of 12 measurements.

3.9. Calculations

We used the equations described for the calculations of parameters qualifying the physical characteristics of the pellets as follows.
Real density (g/cm^3, eq. 1) has a great importance during the characterization of particles or powders.

$$\varrho = \frac{w}{\frac{w_1}{\varrho_1}} = \frac{b-a}{\frac{(d-a)-(c-b)}{\varrho_1}} \quad (1)$$

where w: weight of solid (g); w_1: weight of liquid (g); ϱ_1: density of liquid (g/cm^3); a, b, c, d: weights of various determinations (g).
Calculating the Carr's index (eq. 2) we can obtain information for the compressibility of particles.

$$\text{Carr's index} = 100(D_t - D_f)/D_t\ (\%)\,, \quad (2)$$

where D_t: tapped density (g/cm^3); D_f: fluff density (g/cm^3).
Hausner ratio (eq. 3) leads to an additional simplification from the point of compacting.

$$H = D_t/D_f\,. \quad (3)$$

Deformity factor (eq. 4) defines the shape of particles.

$$F = X_{min}/X_{max}\,, \quad (4)$$

where X_{min}: smallest measured diameter (μm); X_{max}: longest measured diameter (μm).

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Solid state stability of ketoprofen in the presence of different excipients

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Physical mixtures of ketoprofen (KT) were prepared using different excipients, namely, lactose, mannitol, sorbitol, β-cyclodextrin, polyvinylpyrolidone (PVP) K30, polyethyleneglycol (PEG) 20,000 and urea in a ratio of 2:1 (drug/excipient). The prepared samples as well as KT alone were stored at 40, 50 and 60 °C in sealed glass vials for 12 weeks. The fresh and stored samples were subjected to physical examination and instrumental analysis including m.p., IR and dissolution