Drug Development and Industrial Pharmacy, 32:585–593, 2006

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040600599814

Taylor & Francis

The Influence of Drug Solubility and Particle Size on the Pellet Formulation in a Rotoprocessor

Kateřina Krejčová, Miloslava Rabišková, David Vetchý and Ermin Polášek
Department of Pharmaceutics, Faculty of Pharmacy, University of Veterinary and Pharmaceutical Sciences, Brno, Czech Republic

Václav Tomášek and Alena Prokopová
Pharmaceutical Development, ZENTIVA a.s., Prague, Czech Republic

ABSTRACT Pellets containing drugs of different properties were prepared in a Rotoprocessor in order to study changes in the formulation process and resulting pellet characteristics. Diltiazem hydrochloride, diclofenac sodium, and theophylline were chosen as model drugs. Pellet size distribution, sphericity, density, hardness, friability, and repose angle were determined using standard methods. The amount of water as a wetting agent necessary for successful pellet formulation was observed for each sample and changed depending on drug solubility, concentration, and particle size. The pelletization of freely soluble diltiazem hydrochloride required 24.8–23.1% of the wetting agent and its amount decreased as the drug concentration increased. The demand for water in the formulation of theophylline pellets was 31.0–34.4% and it increased with increasing drug concentration. The pellet samples containing both drugs were easy to prepare. However, the cohesion of micronized diclofenac sodium particles negatively influenced both the pellet size distribution and the formulation process itself. When the drug concentration exceeded 40%, it was not possible to produce pellets of an appropriate size and the process was not reproducible.

KEYWORDS Rotoagglomeration, Drug solubility, Particle size, Pellet characteristics, Drug cohesion

INTRODUCTION

Drug-loaded pellets are important for the design of some controlled-release dosage forms intended for oral administration. They owe their popularity to the limited risk of overdosing, improved flow properties, and flexibility in formulation, development and manufacture. They are suitable for drug combinations when incompatibility problems exist or when drugs are to be released at different rates from the same dosage form. For these purposes, pellets can be either filled into hard gelatin capsules or compressed into tablets (Ghebre–Sellassie, 1989).

Pelletization is the process of converting powders into spherical particles of desired size and mechanical properties. In industrial pellet production, spherical pellets are traditionally manufactured using drug layering technology or extrusion

Address correspondence to Miloslava Rabišková, Department of Pharmaceutics, Faculty of Pharmacy, University of Veterinary and Pharmaceutical Science Brno, Palackého 1-3, 61242, BRNO, Czech Republic; Tel: ++42 5 41562860; Fax: ++42 5 49240589; E-mail: rabiskovam@vfu.cz

and spheronization, a method that involves several steps and different types of equipment (Rabišková, 2001).

Rotoagglomeration by wetting a powder mixture containing microcrystalline cellulose with water or an aqueous binder liquid is a valuable alternative when used in order to achieve a single-step process (Kristensen et al., 2000). Using a rotary processor, it is possible to produce, to dry and, if desired, to coat pellets in the same equipment. In this way, dust problems and contamination risks can be avoided, and time, equipment, energy, space, and machine operators can be saved (Vertommen & Kinget, 1997).

The rotoagglomeration technique is, however, very sensitive and includes numerous formulation and process variables that have to be optimized for the successful result–spherical pellets of desired properties (Liew et al., 2000, Vetchy & Rabišková, 2002, Heng et al., 2002). Differences in particle size, shape, powder flowability, or other physical properties of raw materials, such as their solubility, plasticity, formulation ratio, degree of liquid saturation, and viscosity of the liquid phase might have significant effects on the agglomeration process and pellet quality (Sienkiewicz et al., 1997).

The aim of this research work was to describe the influence of differences between active ingredients (different water solubility and/or particle size) used for the formulation of active pellets and to investigate the effects of increasing drug loading on the quality of pellets produced in a rotary processor. Diltiazem hydrochloride (a calcium channel blocker), diclofenac sodium (a non-steroidal anti-inflammatory drug), and theophylline (a drug used in the therapy of asthma bronchiale) were chosen as model drugs for the preparation of drug-loaded pellets containing up to 50% (w/w) of the active substance. Microcrystalline cellulose, thanks to its unique pelletizaton properties, was used as a spheronization enhancer and α-lactose monohydrate as a diluent. Properties of drugs and excipients were evaluated before pelletization. Process conditions and the amount of wetting agent (purified water) necessary for successful agglomeration were optimized for each formulation. Pellet properties were determined and compared.

MATERIALS AND METHODS

Materials

As starting materials, microcrystalline cellulose Avicel® type PH 101 (Mingtai Chemical, Taipei, Taiwan), α-lactose monohydrate (Cerapharm, Vienna, Austria), theophylline anhydrous (Lehmann and Voss, Hamburg, Germany), diltiazem hydrochloride and diclofenac sodium (kindly donated by Zentiva, Prague, Czech Republic) were used. Purified water was the wetting agent. All materials were of Ph. Eur. resp. Ph.B. quality.

Material Characterization

The size distribution of diltiazem hydrochloride, theophylline, and coarse diclofenac sodium was determined by sieving with a set of sieves with 45, 90, 180, and 355 μm apertures. The results were expressed as the percentage of weight retained on each sieve size. Mean particle diameter was calculated from the results of sieve analysis by applying the following formula (Haznos et al., 1992):

$$d = \frac{\sum x_i n_i}{100} \quad (1)$$

where x_i is the mean of the upper and lower limits of the sieve fraction and n_i is the percentage of the i fraction.

As the sieving of fine powders in a dry state may be a problem owing to the cohesive nature of these powders, the particle size of fine diclofenac sodium was determined by light microscopy and liquid paraffin was used to make a dispersion (microscope, TH4, Lambda, Czech Republic). Five hundred particles were measured for the computation of particle mean diameter. This method was also used to characterize particle size distribution and mean diameter of used excipients.

For each substance, pycnometric density was measured according to Ph. Eur. 4 using a helium pycnometer (Pycnomatic–ATC, Porotec GmbH., Hofheim, Germany). The test is intended to determine the volume occupied by a known mass of powder (7.5–10.5 g depending on the volume; the cell No. 30) by measuring the volume of gas displaced under defined conditions. The sample volume is determined after degassing the examined powder mass and its pressurization using the following formula:

$$V_s = V_c - \frac{V_r}{\frac{P_i - P_r}{P_f - P_r} - 1} \quad (2)$$

where V_s is the sample volume, V_c is the cell volume, V_r is the reference volume, P_i is the initial pressure, P_r is the reference pressure, and P_f is the final pressure. The density of the powder mass (ρ) is given by the equation:

$$\rho = \frac{m}{V_s} \tag{3}$$

The test was repeated three times.

For dissolution rate studies (Martin et al., 1983), the drug (its amount was sufficient to give a saturated solution at 25°C: for diltiazem hydrochloride 150.0 g, for diclofenac sodium 10.8 g, and for theophylline 2.5 g) was placed with 300.0 mL of distilled water in a vessel linked to a temperature controlled water bath held at 25.0°C ± 0.5°C (Sotax AT 7 Smart, Sotax, Switzerland). Solutions were agitated constantly by paddles at 50 rpm. At 1, 3, 5, and 10 min, two samples (5 mL each) were withdrawn, filtered through a 0.23 μm filter (Pragopor type 8, Pragochema, s.r.o., Prague, Czech Republic), diluted appropriately, and assayed for drug content at 237 nm for diltiazem hydrochloride, 276 nm for diclofenac sodium, and 273 nm for theophylline (spectrophotometer Lambda 25, Perkin Elmer Instruments, Wellesley, MA, USA). Dissolution rate studies were carried out in triplicate, i.e., the values are the mean of six measurements.

The rate constant k expressed in s^{-1} was calculated from the slope of the straight line obtained from a linear regression of the measured values (Martin et al., 1983):

$$\log c_A = -\frac{kt}{2.303} + \log a \tag{4}$$

where c_A is the concentration of the undissolved drug (mol/mL), a is the initial concentration of the drug (mol/mL) at time $t = 0$, t is the time when solution samples were withdrawn, and k is the drug dissolution rate constant.

Preparation of Pellet Samples

Microcrystalline cellulose (MCC), lactose monohydrate, and the drug were mixed for 5 min in a Stephan mixer (type UMC 5, Stephan und Söhne GmbH and Co., Hameln, Germany) to homogenize the powder mixture. Table 1 shows the composition of powder mixtures. A minimum content of 35% of MCC has been experimentally determined to be appropriate for preparing spherical pellets (Vetchý & Rabišková, 2002).

One kilogram of the powder mixture was placed into the inner container of the Rotoprocessor insert (Aeromatic MP-1, Aeromatic-Fielder AG, Bubendorf, Switzerland). Water was sprayed into the process chamber by a tangentially situated binary spray nozzle with a diameter of 1.0 mm at the indicated rate of 30 g/min using 80 kPa of atomization pressure. The product temperature was held at approximately 25°C and the disc speed was maintained between 680–1360 rpm to keep the spiral rope-like movement of the material for optimal pelletization. Once all the formulation water was sprayed, spheronization was performed at the specified rotor speed of 1800 rpm for 2 min. After completion of the pellet formulation, the pellets were dried at 50°C by lifting the inner container of Rotoprocessor. Three batches of all samples were prepared.

Determination of Pellet Properties

The size distribution of prepared pellets was determined by sieve analysis, using standard sieves with apertures in the range of 125–2000 μm. Particles smaller than 125 μm were considered as irregular pellets or dust and particles bigger than 2000 μm as oversized agglomerates and were excluded. The pellet mean diameter was calculated from the results of sieve analysis (Eq. 1). Pellets of size from 0.5 mm to 0.8 mm were used for further characterization. The mean values are the average of three determinations.

The sphericity of pellets (S), as a parameter of particle shape, was calculated from the area and the perimeter determined by image analysis (Leco IA 32, Leco Instruments, St. Joseph, MI, USA) of 500 pellets according to the following formula (Sienkiewicz et al., 1997):

$$S = \frac{4\pi \times \text{area}}{\text{perimeter}^2} \tag{5}$$

The pellet hardness was tested on the C 50 Tablet Hardness & Compression Tester (Engineering Systems, Nottingham, England) fitted with a C 5 load cell for pellet evaluation. The average hardness of 10 single pellets was calculated.

The pellet friability was measured in an adapted Roche friabilator (type TAR 10, Erweka GmbH, Ensenstam, Germany). Ten grams of pellets were rotated in a stainless

TABLE 1 Composition of the Powder Mixtures, Their Densities, and the Formulation Water Amount

			Model drug [%]					
Sample	MCC[a] [%]	LM[a] [%]	DH[a]	DS[a] (fine)	DS[a] (coarse)	TA[a]	Powder density [g · cm^{-3}]	FWA[b] [g]
1	35	65	—	—	—	—	1.539 ± 0.001	440
2	35	55	10	—	—	—	1.498 ± 0.003	330
3	35	45	20	—	—	—	1.480 ± 0.001	320
4	35	35	30	—	—	—	1.467 ± 0.001	310
5	35	25	40	—	—	—	1.441 ± 0.001	300
6	35	15	50	—	—	—	1.419 ± 0.003	300
7	35	55	—	10	—	—	1.533 ± 0.002	440
8	35	45	—	20	—	—	1.530 ± 0.002	455
9	35	35	—	30	—	—	1.528 ± 0.001	490
10	35	25	—	40	—	—	1.524 ± 0.000	530
11[c]	35	15	—	50	—	—	—	—
12	35	55	—	—	10	—	1.541 ± 0.003	460
13	35	45	—	—	20	—	1.533 ± 0.001	475
14	35	35	—	—	30	—	1.528 ± 0.001	510
15	35	25	—	—	40	—	1.525 ± 0.002	550
16	35	15	—	—	50	—	1.524 ± 0.003	580
17	35	55	—	—	—	10	1.535 ± 0.001	450
18	35	45	—	—	—	20	1.529 ± 0.002	450
19	35	35	—	—	—	30	1.524 ± 0.002	460
20	35	25	—	—	—	40	1.523 ± 0.002	470
21	35	15	—	—	—	50	1.518 ± 0.002	525

[a]Microcrystalline cellulose (MCC), lactose monohydrate (LM), diltiazem hydrochloride (DH), diclofenac sodium (DS), and theophylline anhydrous (TA).
[b]Formulation water amount (FWA).
[c]Impossible to prepare pellets.

steel abrasion drum along with 200 pieces of 4-mm glass beads for 10 min at 20 rpm. The dust was thereafter removed and pellets were reweighed. The friability, i.e., the weight loss after agitation, was expressed as a percentage.

For each sample of pellets, pycnometric density was determined by the gas displacement technique using a helium pycnometer and helium as the intrusive gas (Ph. Eur. 4).

Pellet intraparticular porosity was calculated from the pellet density values and the true density of responding powder mixtures according to the following formula (El Saleh & Kleinebudde, 1998):

$$\varepsilon = \frac{\rho_t - \rho_p}{\rho_t} = 1 - \frac{\rho_p}{\rho_t} \tag{6}$$

where ε is porosity, ρ_t is the true density, and ρ_p is the pellet density. The porosity is expressed as a percentage ($\varepsilon \times 100$).

The repose angle represented the flowability of produced spheres. Fifty grams of pellet sample was placed in a glass funnel with a stem. The funnel was maintained upright so that the stem terminated 10 cm above a flat solid underlay protected from vibrations. Pellets flowed out of the funnel and formed a cone. Its height h and base diameter d were measured. The repose angle value α was calculated using the following equation:

$$\alpha = \text{arc tg}\,(2\,h/d) \tag{7}$$

The friability and pycnometric density, as well as repose angle of pellet samples, were carried out in triplicate and the results were expressed as an arithmetic mean ± standard deviation (Table 2).

RESULTS AND DISCUSSION

Material Characterization

Drug and excipient particle size, density, solubility, and the drug dissolution rate were determined before pelletization. Results are represented in Table 3 and

TABLE 2 **Properties of the Pellet Samples**

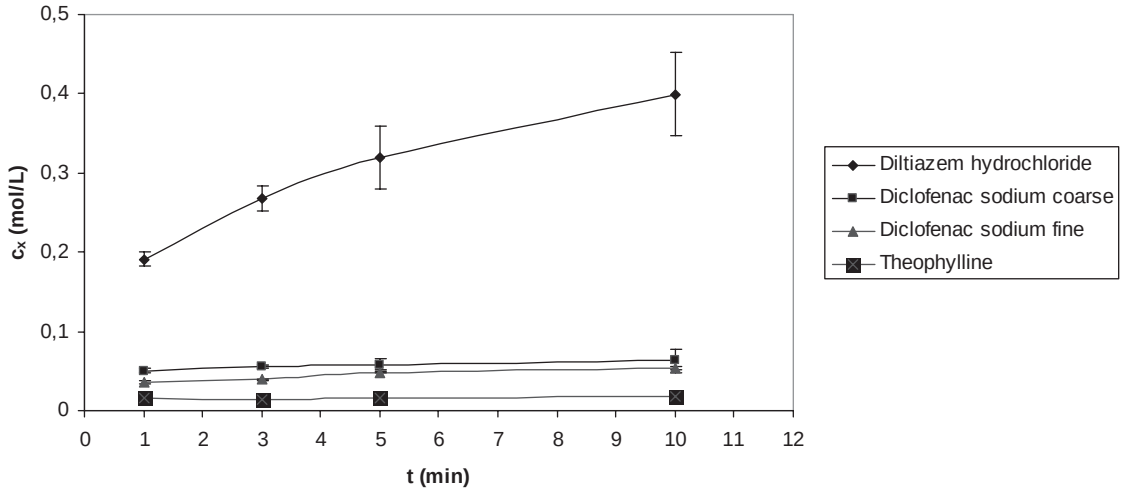
Sample	Pellet mean diameter [mm]	Sphericity	Pycnometric density [g·cm^{-3}]	Porosity [%]	Hardness [N]	Friability [%]	Repose angle [°]
1	0.75	0.956	1.534 ± 0.001	0.33 ± 0.07	3.54 ± 0.65	0.20 ± 0.05	21.4 ± 0.7
2	0.74	0.880	1.497 ± 0.001	0.13 ± 0.01	2.76 ± 0.84	0.23 ± 0.10	22.1 ± 0.6
3	0.82	0.858	1.458 ± 0.001	1.49 ± 0.01	2.20 ± 0.89	0.17 ± 0.04	22.5 ± 0.6
4	0.66	0.818	1.428 ± 0.002	2.52 ± 0.01	1.17 ± 0.03	0.90 ± 0.12	23.2 ± 0.3
5	0.60	0.807	1.419 ± 0.001	1.54 ± 0.01	1.37 ± 0.38	0.98 ± 0.08	23.6 ± 0.7
6	0.63	0.804	1.384 ± 0.001	2.46 ± 0.05	1.29 ± 0.27	0.96 ± 0.06	24.1 ± 0.6
7	0.65	0.889	1.499 ± 0.011	2.31 ± 0.56	2.93 ± 0.82	0.59 ± 0.32	22.6 ± 0.2
8	0.82	0.887	1.486 ± 0.001	2.83 ± 0.08	2.31 ± 0.55	0.64 ± 0.09	21.1 ± 0.5
9	0.75	0.887	1.468 ± 0.007	3.93 ± 0.46	1.92 ± 0.60	0.86 ± 0.15	19.8 ± 0.6
10	1.01	0.865	1.429 ± 0.005	6.21 ± 0.31	1.62 ± 0.19	0.82 ± 0.25	18.6 ± 1.0
12	0.67	0.880	1.520 ± 0.002	1.36 ± 0.10	2.47 ± 0.14	0.37 ± 0.12	18.1 ± 0.2
13	0.68	0.882	1.503 ± 0.004	1.98 ± 0.27	1.97 ± 0.17	0.43 ± 0.18	18.8 ± 0.8
14	0.69	0.864	1.469 ± 0.005	3.94 ± 0.38	1.83 ± 0.06	0.64 ± 0.16	19.1 ± 0.2
15	0.78	0.821	1.472 ± 0.004	3.56 ± 0.25	1.73 ± 0.04	0.82 ± 0.03	19.6 ± 0.4
16	0.89	0.871	1.477 ± 0.001	3.13 ± 0.08	1.66 ± 0.05	1.68 ± 0.50	20.2 ± 0.5
17	0.91	0.864	1.518 ± 0.001	1.13 ± 0.01	4.83 ± 0.70	0.29 ± 0.05	19.4 ± 1.7
18	0.69	0.869	1.512 ± 0.001	1.12 ± 0.04	4.57 ± 1.50	0.26 ± 0.07	22.6 ± 0.4
19	0.72	0.883	1.505 ± 0.002	1.23 ± 0.13	3.83 ± 1.69	0.39 ± 0.13	23.9 ± 0.7
20	0.66	0.804	1.493 ± 0.001	1.97 ± 0.03	3.54 ± 1.16	0.55 ± 0.15	22.6 ± 0.3
21	0.87	0.882	1.470 ± 0.001	3.20 ± 0.08	3.53 ± 0.81	0.27 ± 0.08	21.7 ± 0.5

TABLE 3 **Physical Properties of the Materials**

Drug	Particle mean diameter [μm]	Pycnometric density [g/cm^3]	Solubility in water[d] [g]
Diltiazem hydrochloride	156.0	1.297 ± 0.002	520.0[e]
Diclofenac sodium (fine)	5.2	1.503 ± 0.002	36.0[f]
Diclofenac sodium (coarse)	92.0	1.501 ± 0.001	36.0[f]
Theophylline	277.5	1.468 ± 0.001	8.3[g]
Lactose	29.0	1.534 ± 0.001	216.0[h]
Microcrystalline cellulose	76.2	1.547 ± 0.001	insoluble[h]

[d]Solubility in 1.0 L of water at 25°C.
[e]Experimentaly determined.
[f]Ho et al., 1997.
[g]Kim & Fassihi, 1997.
[h]Rowe, 2003.

Fig. 1. The largest particles were determined with theophylline ($d = 277.5$ μm) having the lowest solubility and the slowest dissolution rate ($k = 1.38 \times 10^{-4}$ s^{-1}); smaller particles were observed for diltiazem hydrochloride ($\bar{d} = 156.0$ μm) with the highest solubility, a fast dissolution rate ($k = 6.41 \times 10^{-4}$ s^{-1}), and the lowest density; and the smallest ones were measured for diclofenac sodium ($\bar{d}_{coarse} = 92.0$ μm and $\bar{d}_{fine} = 5.2$ μm) with the highest density among the model drugs, moderate solubility, and a dissolution rate that is different for the micronized ($k = 4.84 \times 10^{-4}$ s^{-1}) and the coarse drug ($k = 5.45 \times 10^{-4}$ s^{-1}). The dissolution rates of the drugs in general corresponded to their solubilities: the faster the dissolution rate, the more soluble the drug. Micronized diclofenac sodium was expected to dissolve faster due to its significantly smaller particles (and thus larger surface area) than the coarse substance. The results indicate however the opposite tendency. This situation can be explained by the formation of cohesive agglomerates of micronized



Linear regression of the experimental data log $c_A = f(t)$ gived straight lines with

the correlation coeficients: Diltiazem hydrochloride: r = 0.9568
Diclofenac sodium (coarse): r = 0.9358
Diclofenac sodium (fine): r = 0.9617
Theophylline: r = 0.9668

and the dissolution rate constants: Diltiazem hydrochloride: $k = 6.41 \times 10^{-4}$
Diclofenac sodium (coarse): $k = 5.45 \times 10^{-4}$
Diclofenac sodium (fine): $k = 4.84 \times 10^{-4}$
Theophylline: $k = 1.38 \times 10^{-4}$

FIGURE 1 **Dissolution of the Model Drugs.**

drug in the dry state and also during dissolution (Fig. 2a). These agglomerates are bigger than individual particles of the coarse drug (Fig. 2b) and can result in a slower dissolution rate.

The particle mean diameters of used excipients were evaluated: $\bar{d} = 29.0$ μm for lactose and $\bar{d} = 76.2$ μm for MCC.

Pelletization and Pellet Properties

Drug free pellets and pellet samples containing 10, 20, 30, 40, and 50% of the drug were prepared using rotoagglomeration. For each sample, the formulation water amount and rotating disc rate during the wetting phase were optimized to reach the characteristic movement of particles for successful pelletization. The properties of pellets: pellet size distribution, their mean diameter, sphericity, density, porosity, hardness, friability, and repose angle were determined.

Formulation Water Amount

In any pelletization process, the moisture content is very important in deciding the outcome of the process (Harris & Ghebre-Sellassie, 1989). Table 1 demonstrates that the water amount neccessary for pellet formulation changed when lactose was replaced with the drug. The optimal value of water used for the production of plain, drug-free, microcrystalline cellulose/lactose pellets (sample 1) was 440 g (i.e., 30.6% of wetted mass). To manufacture spheres containing freely soluble diltiazem hydrochloride, the smallest water amount was used. This amount was significantly lower (samples 2–6, 330–300 g, i.e., 24.8–23.1%) than in the case of inactive pellets (sample 1) and it decreased as drug concentration increased. These results were expected as the solubility of diltiazem hydrochloride is higher than that one of lactose (Table 3), drug dissolution is faster, and thus, a smaller amount of water is necessary for sufficient wetting of the powder mixture and to formulate pellets. If

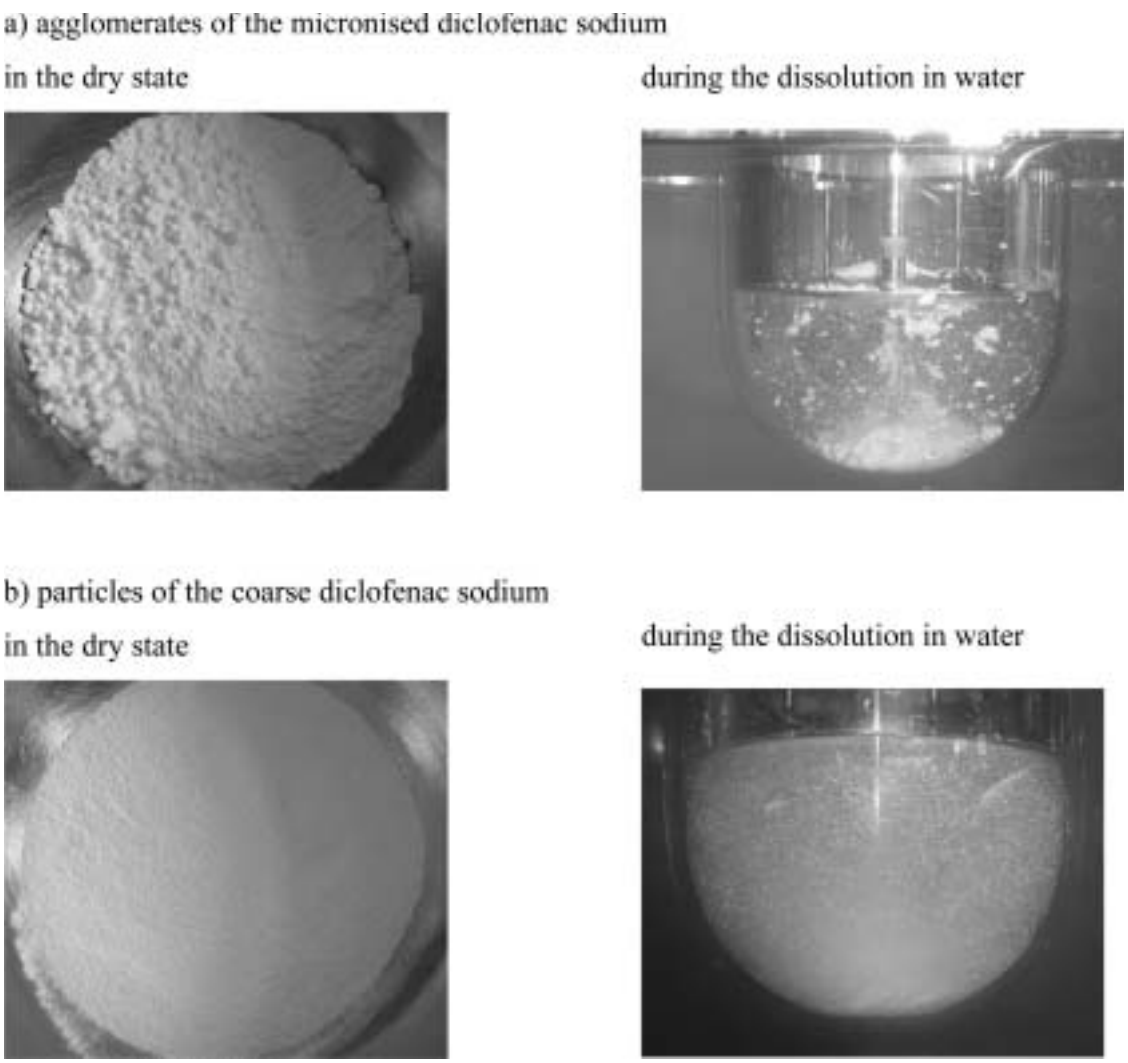


FIGURE 2 **Photos of Diclofenac Sodium.**

we only considered drug solubility, a higher formulation water amount would be appropriate to produce pellets containing diclofenac sodium and the highest amount would be demanded for theophylline pellets. In practice, however, the results showed that the formulation of theophylline pellets required, in general, a lower amount of wetting agent (samples 17–21, 31.0–34.4%, Table 1) than that of diclofenac sodium pellets (samples 8–16, 31.3–38.1%, Table 1). As rotoagglomeration is a rather fast process (pellet formulation was completed in 12 to 20 min), the probability of the dissolution of drugs slightly or less soluble in water is low, and thus, the particle size of these drugs (and their surface area) could play a more important role in the wetting phase and following agglomeration.

This hypothesis is confirmed by the results obtained: theophylline particles (d = 277.5 μm) are several times bigger than diclofenac sodium particles (d = 5.2 μm for fine diclofenac sodium, or d = 92.0 μm for coarse diclophenac sodium, Table 3). The surface area of the same weight of theophylline particles is smaller than that one of diclofenac sodium particles and, thus, the water amount for sufficient particle wetting would be lower. Sample 7 (Table 1) is an exception as the wetting liquid amount is identical to sample 1 (lactose/MCC pellets). This can be explained by the majority of lactose in the formulation (55 resp. 65%) and its influence on the formulation process. Furthermore, when we compare diclofenac sodium pellets from the drug particle size point of view, the water amount required for pellet formulation

containing coarse particles (samples 12–16) should be lower than for pellets consisting of fine diclofenac sodium. The opposite tendency was, however, observed. We suppose that the reason is the formation of secondary drug agglomerates due to the cohesive forces of fine particles in the dry state that are insufficiently wetted as we observed (Fig. 2a). Such behavior of micronized particles has been recently reported (Stewart & Zhao, 2005). These particles are likely to be tightly packed within the agglomerates. The packing arrangement in these agglomerates is unknown, however it contains some void space. These cohesive agglomerates of fine diclofenac sodium are, after all, bigger and thus provide a smaller surface area than individual particles of the coarse substance. This might be the explanation why rotoagglomeration of fine diclofenac sodium pellets requires less water amount than pellets containing coarse diclofenac sodium. In addition these secondary agglomerates cause difficulties in the process itself: when the drug concentration exceeds 40% it is not possible to produce pellets of appropriate size and the process is not reproducible. Difficulties in the processing of pellets containing fine particles have been reported by other authors (Sienkiewicz et al., 1997).

Pellet Properties

Pellet size distribution (Table 4) was found nearer in diltiazem hydrochloride pellets and theophylline pellets where the majority of particles lay within the interval 0.5–1.0 mm (diltiazem hydrochloride 63.9–71.7%; theophylline 64.1–71.1%) and pellets larger than 1.25 mm occurred less than 15% of the time. In diclofenac sodium, pellets up to 37, resp. 25% of particles larger than 1.25 mm were found (sample 10, resp. sample 16). Their size distribution was broad (samples 8–10 and 15–16), changing negatively with increasing drug concentration. These results indicate the worse reproducibility of the pelletization process with fine diclofenac sodium particles.

Pellet density corresponds in general to the particle density of the model drug. Higher density is observed in pellets containing theophylline and coarse diclofenac sodium: 1.47–1.52 g/cm^3 (Table 2). Lower pellet density was found in pellets with fine diclofenac sodium, which simultaneously had the highest porosity values–up to

TABLE 4 **Size Distribution of the Pellet Samples**

	Particle size [%]					
Sample	2.0–1.25	1.25–1.0	1.0–0.8	0.8–0.5	0.5–0.25	0.25–0.125 [mm]
1	6.05	5.75	20.39	55.64	11.85	0.32
2	1.62	12.37	22.81	48.92	14.08	0.20
3	9.26	11.52	27.80	36.12	15.17	0.13
4	5.18	4.36	7.44	57.13	25.46	0.43
5	0.85	2.48	7.29	58.70	29.02	1.66
6	2.36	3.68	9.37	57.23	26.12	1.24
7	6.13	4.37	8.83	50.03	20.97	9.67
8	18.96	5.50	9.20	42.20	22.77	1.37
9	18.85	4.75	9.65	36.25	29.90	0.62
10	36.98	6.93	7.15	31.28	17.13	0.53
12	2.73	3.73	17.50	52.10	23.82	0.12
13	6.80	2.60	6.90	62.27	20.13	1.30
14	6.27	7.30	9.00	53.13	20.14	4.16
15	17.37	6.17	8.10	38.73	27.00	2.63
16	25.50	8.47	10.67	30.45	23.07	1.84
17	8.12	21.41	39.41	24.65	4.90	1.51
18	4.35	4.32	13.19	57.91	19.00	1.23
19	8.65	2.77	11.10	57.63	19.45	0.40
20	6.12	2.25	7.45	56.95	25.71	1.52
21	14.85	12.75	13.58	50.82	7.85	0.15

6.21% (samples 7–10, Table 2). The lowest density was determined in pellets with diltiazem hydrochloride (samples 2–6, Table 2); among the model drugs used, its pycnometric density also had the lowest value (Table 3). The pellet density decreases with increasing drug content. As lactose densifies easily after liquid addition and its density is higher than that one of the model drugs, this can be due to decreasing lactose content.

Theophylline pellets had the best mechanical properties: the highest values of pellet hardness and the lowest pellet friability (samples 17–21). The hardness of the other pellet samples was almost equal. Pellet friability was under 1.7% which is considered to be appropriate (Vertommen & Kinget, 1997). In general, higher hardness and lower friability have been found in pellets with lower drug contents.

Samples 1 and 2 exhibit very low porosity values 0.33 and 0.13%, respectively. The porosity of the other samples reached values 1–4% (Table 2). Lower porosity was determined in diltiazem hydrochloride pellets. This can be explained by the partial dissolution of the drug during the process. Diltiazem hydrochloride solution then contains probably less air than the undissolved particles of the other drugs. Porosity can also be influenced by drug particle size and secondary agglomerates formation (samples 7–10, Table 2).

All pellet samples containing the drug had a regular spherical shape and good flow properties as indicated by sphericity measurements (0.804 to 0.889) and repose angle values under 25° (Table 2).

CONCLUSION

We can conclude that the formulation of active pellets using the rotoagglomeration technique is a process that is very sensitive to formulation and process variables. The content of a particular drug, its solubility, particle size, density, etc., are involved in the formulation process as well as the appropriate water amount acting as a wetting agent. Formulation of pellets containing freely soluble diltiazem hydrochloride went well. Also, theophylline pellets, when the suitable amount of wetting agent was determined, were easy to prepare. The cohesion of micronized diclofenac sodium caused difficulties in the pelletization process and it negatively influenced size distribution of the resulted pellet samples. Further studies addressing the problem of drug cohesion within rotoagglomeration will be reported.

ACKNOWLEDGEMENT

This experimental work was supported by Czech pharmaceutical company ZENTIVA.

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