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COMMUNICATIONS

Correlation of extrusion forces, raw materials and sphere characteristics

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Abstract—This communication reports on the correlation between extrusion forces and sphere characteristics. Dicalcium phosphate dihydrate, α-lactose monohydrate and anhydrous β-lactose were models for respectively an insoluble, a medium soluble and a highly soluble drug and were used to produce spheres. Phase diagrams for ternary mixtures consisting of microcrystalline cellulose, water and a third excipient were constructed. The region where good spheres were obtained correlated well with the area of extrusion forces between 630 and 1260 N. This correlation was seen for the insoluble, the medium and the highly soluble products.

Spheronization was first reported by Nakahara (1964) to produce spheres. The production of spheres consists of different steps. In the first stage the different powders are dry blended and wet granulated. In the second stage the plastic mass is extruded and shaped into cylinders. In the last step the cylinders are cut into pieces and rounded to spheres (cutting and rounding stage). The last step takes place on a friction plate in the spheronizer.

In a previous paper we reported on the instrumentation of a gravity feed extruder, on the influence of particle size of insoluble materials and of product solubility on the extrusion forces (Baert et al 1991). This communication reports on the correlation between the forces recorded during extrusion and the characteristics of the spheres.

Materials and methods

Materials. Two different types of lactose were used: α-lactose monohydrate (Pharmatose 200 M) and anhydrous β-lactose (DCL 21) as models for medium and highly soluble drugs, respectively. Lactose samples were supplied by De Melkindustrie Veghel, Veghel, The Netherlands. Dicalcium phosphate dihydrate (C.N. Schmidt B.V., Amsterdam, The Netherlands) was used as a model for an insoluble drug.

Microcrystalline cellulose (Avicel PH 101—FMC Wallingstown, Little Island, Cork, Ireland) with an average particle size of 50 μm was used as filler and demineralized water was used as the granulating fluid.

Composition of the mixtures and granulation procedure. Different mixtures consisting of lactose or dicalcium phosphate and microcrystalline cellulose were dry mixed for 10 min in a planetary mixer (Kenwood Chef, Hampshire, UK) at 60 rev min^{-1} using a K-shaped mixing arm and were granulated with water for 2 min at 60 rev min^{-1}.

Extrusion procedure. After granulation the mixtures were extruded in an instrumented gravity feed extruder (Extruder 40, GB Caleva Ltd, Butts Pond Industrial Estate, Sturminster Newton, Dorset, UK) (Baert et al 1991). The rotational speed of the axes was 30 rev min^{-1}. Mixtures were considered to be not extrudable if the extrusion forces were higher than 2500 N.

Spheronization. Two hundred grams of the extrudate were spheronized on a friction plate with cross-hatch-geometry in a spheronizer (Spheroniser Model 15, Caleva Ltd, Sturminster Newton, Dorset, UK) for 10 min at 750 rev min^{-1}. Next the spheres were dried in a fluidized bed (Aeromatic AG, Aeromatic Ltd, Basel, Switzerland) for 20 min at 50°C.

Evaluation of spheres. The spheres were evaluated using three criteria: sieve analysis, friability and roundness of the spheres.

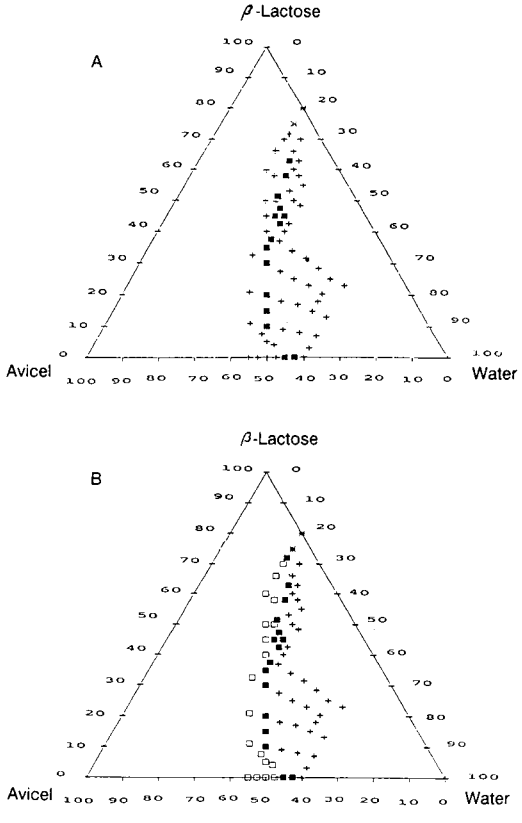

FIG. 1. Ternary diagrams for mixtures of microcrystalline cellulose, β-lactose and water. A. Mixtures producing pellets of good quality (■), not acceptable quality (+) and nonpelletable mixtures (*) are indicated. B. The extrusion forces lower than 630 N (+), between 630 and 1260 N (■) and higher than 1260 N (□) are indicated. Mixtures for which no pellets were obtained (*) are indicated.

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Sieve analysis. A 100 g sample was sieved using 2000, 1400, 1000, 710, 500 and 250 μm sieves. The sieves were placed on a vibrating sieve shaker (Retostat, Germany) for 5 min at the maximum speed (position 270). The amount of spheres remaining on each sieve was calculated and expressed as percentage of the total weight.

Friability. Sphere friability was determined by subjecting 10 g of spheres (710–1000 μm fraction) together with 200 glass beads (average diam. 4 mm) to falling shocks for 10 min in an Erweka Friabiliator (Erweka, Frankfurt, Germany) fitted with an abrasion wheel.

Roundness. Photographs were taken of a 710–1000 μm fraction and the largest (R1) and the smallest diameter (R2) of 10 individual spheres were determined. For each sphere the E value (R1/R2) was calculated.

Spheres were considered of acceptable quality if 90% of the spheres showed a particle size between 710 and 1400 μm, a friability lower than 0·2% and an E value between 1 and 1·20.

Results and discussion

Several authors have reported on the influence of different processing parameters on sphere quality. Spheronization speed (Woodruff & Nuessle 1972; O'Connor et al 1984; Chariot et al 1987; Hasznos et al 1990), spheronization load (Chariot et al 1987; Hasznos et al 1990), moisture content of the extrudate (Elbers et al 1990; Hasznos et al 1990) and composition of the granulating fluid (Millili & Schwartz 1990) have been reported to be important parameters for sphere quality. This communication reports on a correlation study between extrusion forces recorded on an instrumented gravity feed extruder and sphere characteristics. In this study sphere quality was defined in terms of particle size distribution (90% between 710 and 1400 μm), friability (less than 0·2%) and sphericity (E value between 1 and 1·20).

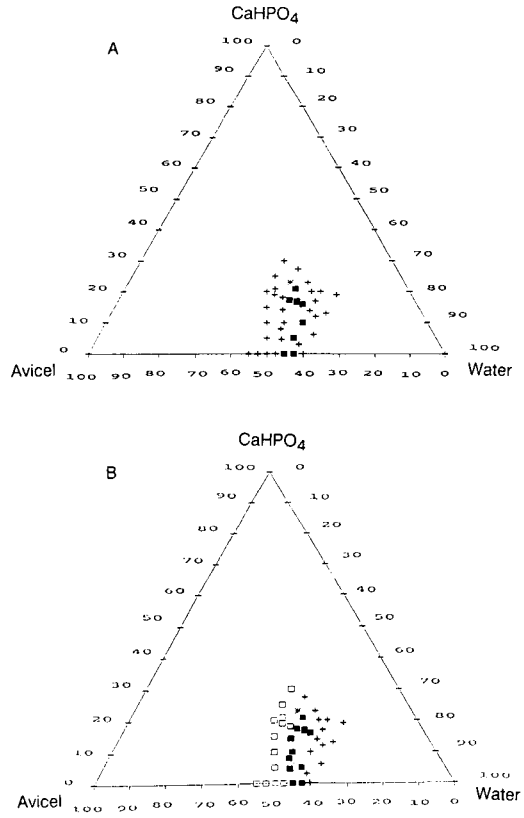

FIG. 3. Ternary diagrams for mixtures of microcrystalline cellulose, dicalcium phosphate dihydrate and water. A. Mixtures producing pellets of good quality (■), not acceptable quality (+) and nonpelletable mixtures (*) are indicated. B. The extrusion forces lower than 630 N (+), between 630 and 1260 N (■) and higher than 1260 N (□) are indicated. Mixtures for which no pellets were obtained (*) are indicated.

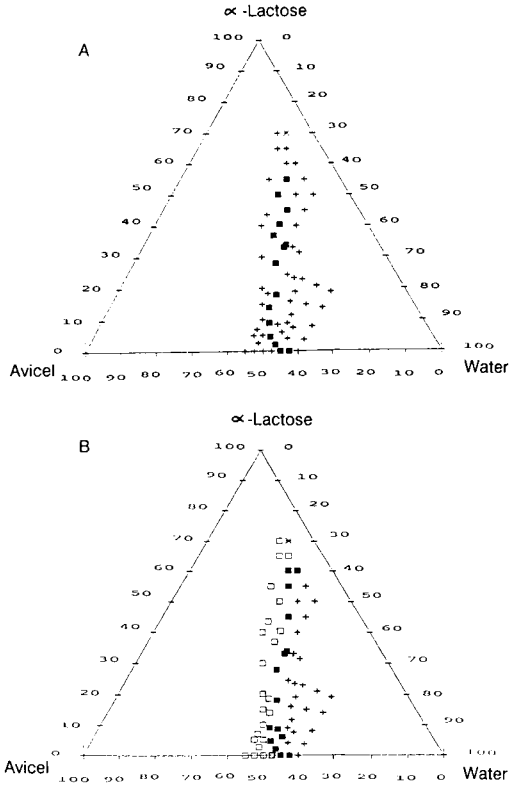

FIG. 2. Ternary diagrams for mixtures of microcrystalline cellulose, α-lactose monohydrate and water. A. Mixtures producing pellets of good quality (■), not acceptable quality (+) and nonpelletable mixtures (*) are indicated. B. The extrusion forces lower than 630 N (+), between 630 and 1260 N (■) and higher than 1260 N (□) are indicated. Mixtures for which no pellets were obtained (*) are indicated.

Ternary mixtures consisting of microcrystalline cellulose, water and a third excipient were extruded and spheronized. Figs 1A, 2A and 3A indicate that there is a defined region where pellets meeting the desired quality were obtained. Figs 1B, 2B and 3B show the extrusion forces for ternary mixtures microcrystalline cellulose, water and a third excipient. The region where pellets of good quality were obtained correlated well with the area where extrusion forces lay between 630 and 1260 N. The solubility of the third excipient seemed to play a key role on the size of the regions where good pellets were obtained. The area is largest in the case of the most soluble product added to a microcrystalline cellulose/water mixture (β-lactose) and smallest in the case of a product with the lowest solubility (dicalcium phosphate dihydrate). Recording the extrusion forces allowed us to predict whether a mixture would yield pellets with a previously defined quality. If extrusion forces were lower than 630 N very large spheres (>2000 μm) were obtained. Spheres became smaller when the extrusion forces were higher than 1260 N, and more dust was produced. The E value, which is an

indication of the roundness of the spheres, increased dramatically if extrusion forces were higher than 1260 N.

The most important parameters influencing the extrusion forces were the solubility of the excipient and the amount of fluid phase used as was shown in previous work (Baert et al 1991). When an excipient was added to the binary mixtures of microcrystalline cellulose, the ratio microcrystalline cellulose/water can vary from 1·22 to 1·63 in the case of dicalcium phosphate, from 1·09 to 2·00 in the case of α-lactose monohydrate and from 1·00 to 2·08 in the case of β-lactose, in order to obtain spheres with the defined quality. The lower limit of microcrystalline cellulose concentration that can be used in order to obtain good spheres depended on the solubility of the third compound. A lower limit of 12, 15 and 31·5% of the mixture was observed in the cases of β-lactose, α-lactose monohydrate and dicalcium phosphate dihydrate, respectively. The largest quantity of excipient that can be used depended also on the solubility of the third excipient and values of 63, 55 and 21% of the mixture for β-lactose, α-lactose monohydrate and dicalcium phosphate, respectively, were recorded, representing an amount of 85, 79 and 40% on dry pellet base, respectively. It should be emphasized that the experiments have been performed on a gravity feed extruder and with fixed parameters during the spheronization process. Nevertheless formulators may apply these observations in the case of sphere formulation development with additives or active ingredients of different solubility.

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Effect of compressional forces on piroxicam polymorphs

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Abstract—The effect of compressional force on the polymorphic transition in piroxicam has been examined, using pure polymorph, by differential scanning calorimetery, powder X-ray diffractometry and by determination of dissolution rates from tablets of the individual polymorphs. The needle shaped polymorph was found to undergo transition to the cubic polymorph during compression.

Mechanical processes such as size reduction and compression have been reported to bring about polymorphic changes in drugs. Nogami et al (1969) reported transitions of metastable forms of barbitone to a stable polymorph during tableting. Summers et al (1976) reported reduction in transition temperature due to dislocations in crystal boundaries during compression. Ibrahim et al (1977) reported transition of metastable polymorphs of phenylbutazone to stable polymorphs by mechanical stress. Similar observations were made by Chan & Doelker (1985), Takahashi et al (1985), Debord et al (1987) and Otsuka et al (1989).

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Piroxicam, a long-acting non-steroidal anti-inflammatory drug (NSAID) is available in monohydric and anhydrous forms. Influence of water of hydration of this drug on its tableting behaviour has been reported by Huettenrausch & Fricke (1989). The existence of the needle shaped and cubic polymorphs has been reported by Mihalic et al (1986).

We have studied the effect of compression force on polymorphic transition of piroxicam. The results obtained from other studies including X-ray diffraction, IR spectroscopy, solid state ^{13}C NMR spectroscopy, and differential scanning calorimetry on pure polymorphs have been extended to this study wherever applicable. IR spectra of the powdered tablets were not recorded since the two polymorphs do not exhibit differences in the IR spectra.

Materials and methods

Materials. Piroxicam USP (Sekhsaria Chem. Pvt. Ltd, Bombay, India), absolute alcohol (Riedel de Haen, India), benzoic acid AR, lactose USP, starch IP, magnesium stearate IP, conc. hydrochloric acid (all from Qualigens, India) were purchased from the companies stated.