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EFFECT OF THE DRYING METHOD ON THE MECHANICAL AND DRUG RELEASE PROPERTIES OF PELLETS PREPARED BY EXTRUSION-SPHERONIZATION

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ABSTRACT

Many pelletization processing variables are capable of influencing the fundamental properties of pellets. This study was designed to elucidate the effect of the drying technique on the mechanical and skeletal properties of spheronized particles. Although much has been reported on the effect of the formulation and processing variables associated with extrusion and spheronization, little attention has been paid to the nature and length of the subsequent drying process. Pellets were prepared containing either 80%w/w ibuprofen or 80%w/w lactose with 20%w/w microcrystalline cellulose. The resulting spherical pellets were dried either by tray drying or fluidized-bed drying. This work has revealed that the drying technique has a quantifiable effect on the diametral crushing strength and elasticity of the pellets, their *in-vitro* drug release and a qualitative effect on the surface characteristics of ibuprofen pellets.

INTRODUCTION

Extrusion-spheronization is a technique which enables the formation of spherical particles with advantages of regularity of shape and size, and smooth surface characteristics which are ideal for the application of a release retarding membrane.

These spheres generally have low friability and have few fines.

The process of pellet formation leads to a greater densification of materials compared with other granulation techniques. This factor, together with the high concentrations of drug which may be incorporated render spherical particles an ideal preparation for presenting a high-dose or low potency drug in the form of a multiparticulate solid oral sustained drug delivery system.

Satisfactory pellet formation by extrusion-spheronization occurs as a consequence of several carefully optimised processing stages. These stages are summarised in Figure 1.

The penultimate stage in pelletization involves the drying of the spheres. The wet pellets may be dried by any conventional method. Conine and Hadley (1970) and Reynolds (1970) stated that fluidised-bed drying will result in a product of greater bulk density than by using the other methods. Many authors, including Jalal et al. (1972) and Zhang et al. (1990), report the use of the hot air oven for drying spheres. This present work illustrates that the drying method is of paramount importance in influencing the mechanical properties of uncoated spheres i.e. their diametral crushing strength, elasticity, skeletal/pore structure and pellet surface quality.

The influence of the drying technique on the drug release from uncoated pellets was evaluated using *in-vitro* dissolution testing. Qualitative evaluation of pellet surface characteristics was made using scanning electron microscopy (SEM).

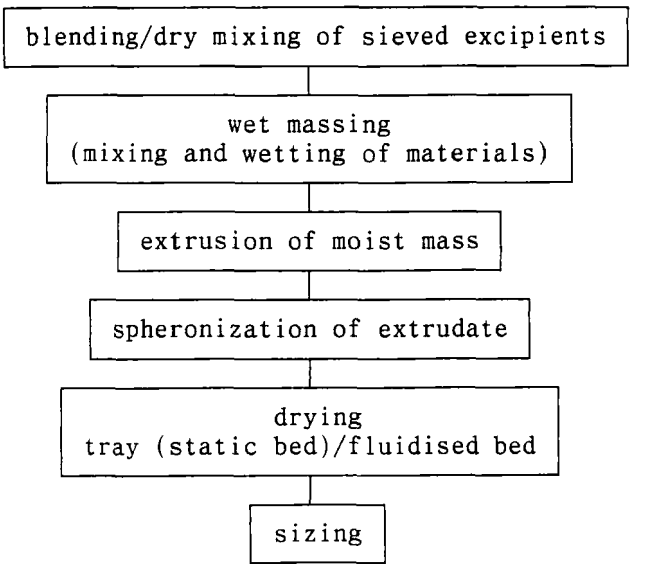

FIGURE 1.
Summary of the stages involved in pelletization.

The mechanical properties of pellets dried by either tray or fluidised-bed drying, were studied using a Single Particle Crushing Assembly. Particular importance was placed on elucidating the relative elasticities of the pellet formulations and their diametral strengths. The fundamental bonding forces resulting as a consequence of the overall pelletization process which determine the strength of pellets are discussed.

MATERIALS

Ibuprofen (Boots Pharmaceuticals, U.K.); microcrystalline cellulose (Avicel PH101) (FMC Corporation, U.S.A.); lactose NF Fast Flo (Wisconsin Dairies, Foremost Ingredient Group, U.S.A.)

and Purified Water BP were used in the pellet formulations described in this work.

METHODS

Uncoated pellet formulation

Pellets containing high percentages of ibuprofen (poorly water soluble) or lactose (highly water soluble) with microcrystalline cellulose were formulated and manufactured. For any dosage form containing high percentages of a given component, the characteristics of that component will significantly influence the success of the manufacturing process and consequently the characteristics of the end product. Active and placebo pellet formulations were prepared in order to ascertain how the aqueous solubility of the pellet components affected the drying and mechanical properties of pellets. The extrusion and spheronization technique was successfully applied here to pellet formulations containing up to 80%w/w ibuprofen and 80%w/w lactose.

Critical processing variables were found to include the total volume of granulating fluid added, the length and severity of the wet massing process, the rate of extrusion and the rate and extent of spheronization. These need to be optimised carefully for each pellet formulation; details are shown in Tables 1 and 2.

Granulation/wet massing

Solid excipients were sieved and passed into a Diosna P25 granulator, dry mixed and then the required volume of water added

TABLE 1.
Formulation and processing variables for fluidised-bed dried and tray-dried pellets containing 80%w/w ibuprofen.

ingredients (%w/w) ibuprofen Avicel PH101	80.0 20.0	
Purified water BP (kg)	0.84	
batch size (solids) kg	1.5	
spheronization details plate weight (g) rotation speed (rpm) residence time (mins)	75 1450 4	
drying method	fluidised bed	tray
drying time (hours)	2	24
moisture content (%w/w)	0.36	0.30

TABLE 2.
Formulation and processing variables for fluidised-bed dried and tray-dried pellets containing 80%w/w lactose.

ingredients (%w/w) lactose NF Fast Flo Avicel PH101	80.0 20.0	
Purified water BP (kg)	1.5	
batch size (solids) kg	4.0	
spheronization details plate weight (kg) rotation speed (rpm) residence time (mins)	4.9 603 7	
drying method	fluidised bed	tray
drying time (hours)	1	24
moisture content (%w/w)	0.63	0.60

slowly. The mass was worked until a uniform distribution of water was achieved which resulted in granulated mass which was free-flowing but cohesive under slight compression.

Extrusion-spheronization

Granulated material was passed through an Alexanderwerk GA65 extruder fitted with a perforated (1mm diameter) cylinder and pressure cylinder rotating at 98 and 134rpm respectively. Sphere formation was facilitated using a Caleva Model 15 spheronizer; both operations were performed using optimised processing conditions (Tables 1 and 2).

Drying

Pellets were dried using either a fluidised-bed apparatus (Aeromatic AG, 10kg capacity) with an inlet temperature of 58 to 60°C, or by tray drying in a hot air oven using a drying temperature of 45 to 50°C. Pellets containing either ibuprofen or lactose with microcrystalline cellulose were prepared in order that the effect of aqueous solubility of the main excipient on pellet physical properties could be evaluated, as a consequence of these two very different drying techniques. A fundamental difference in the two processes is the rate and length of the process.

Quantitative consideration of the effect of the drying methodology on the mechanical and release properties of pellets is discussed subsequently.

In-vitro dissolution

In-vitro dissolution testing was performed using standard USP XXII, type II (paddle) apparatus containing 900ml of pH 6.8 phosphate buffer BP (37°C) with a paddle rotation speed of 100rpm. Sink conditions were maintained throughout. Samples were analysed for ibuprofen using a Hewlett Packard 8450A Diode Array Spectrophotometer (wavelength range 245-300nm).

Mechanical properties

The mechanical strength of a pellet is related to the nature of the excipients from which it is composed, its cross-sectional area, its shape (the degree of sphericity) and any physical parameters influenced by the manufacturing process (these may include massing, extrusion and spheronization variables) and the drying method employed. These parameters all contribute to the elastic, plastic and fragmentary properties of the pellets. Pellet porosity and density are also affected by variables associated with the manufacturing technique.

Single Particle Crushing Assembly

A study of the tensile properties of pellets was facilitated by determining the force required to cause pellet fracture using a Single Particle Crushing Assembly (Wong et al., 1988). The use of this technique yielded quantitative information relating to crushing strength, pellet displacement under applied stress, percentage strain and the elastic modulus of pellets. These

parameters were investigated in order to study those formulation factors influencing the mechanical properties of uncoated pellets, the manufacturing technique and the effect of film coating of pellets on the resultant mechanical properties (Dyer, 1992).

The Single Particle Crushing Assembly (Figure 2) consists of a fixed horizontal platen which supported the sphere and a moving platen which moved downwards at a constant strain rate to apply force to the sphere. The force was measured with a highly sensitive load cell (U-4000, Maywood Instruments Ltd. Basingstoke U.K.) which was sensitive to $\pm$ 0.025N up to a maximum load of 50N and capable of a high dynamic response as a result of low deflection under load. This particular load cell used transducer strain gauges in a full bridge configuration bonded to a transduction element. A motorised unit, to which an LVDT was connected, was set to approach the pellet mounted on a lower platen at a given rate. The load applied to the pellet and the distance moved by the upper platen were converted to millivolts and recorded on a calibrated X-Y chart recorder.

The chart recorder was calibrated so that displacement of the pellet under applied load was reflected on the x-axis; a 1mm displacement being equivalent to 100mm on the chart recorder. Similarly the load applied to each pellet was recorded on the y-axis; a force of 5N was represented by a distance of 100mm on the chart recorder.

The mean diameter of each randomly selected pellet was determined by measuring pellet diametral dimensions in the X and

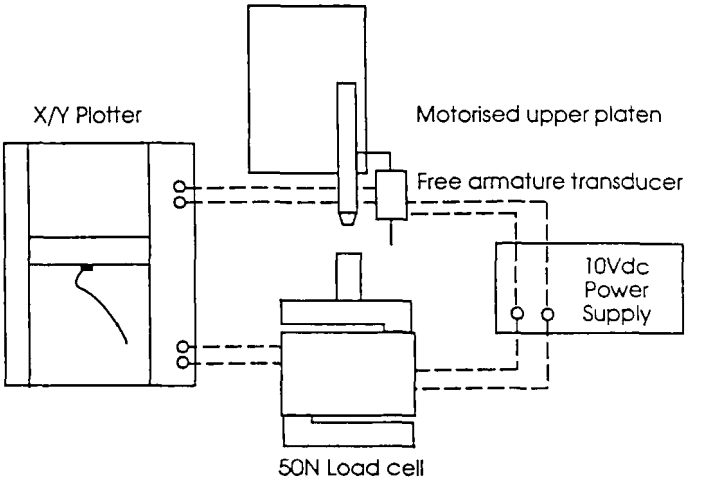

FIGURE 2.
Schematic illustration of the Single Particle Crushing Assembly.

the Y plane of the sphere using a digital micrometer (Mitustoyo, Japan).

Determination of pellet dimensions, together with quantitative information in respect of the applied load and as a consequence particle displacement, enabled calculation of pellet cross-sectional area, applied stress and strain, work done in causing particle fracture and the relative elasticity of the test formulations.

That force causing pellet fracture is represented on the X-Y chart recording by a maximum peak just prior to the major fracture. For a pellet fracturing into many progeny particles, the break will manifest itself as a sharp peak on the chart. For a pellet showing very little fragmentation after crushing resulting in fewer larger particles, the peak representing the

fracture may not necessarily be the highest point on the chart, since further application of force to the fractured material will result in further fragmentation of the progeny particles.

Determination of the mechanical properties of pellets as a consequence of fracture under applied load.

On application of a force (F) to a pellet of diameter (D), the particle will exhibit a degree of deformation or displacement (d), in the direction of that force. The work done (Nm) in causing particle fracture may therefore be defined as the product of that force (N) causing fracture and displacement (m) in the direction of the applied force

$$\text{work done} = \text{force} \times \text{displacement} = F \times d \qquad \text{(Equation 1)}$$

With this technique the work done in causing pellet fracture is represented by the area under the force-displacement peak on the X-Y chart recording.

The force per unit area (F/A) producing the deformation of a solid particle is termed the tensile stress (σ). For a spherical particle or pellet therefore, lowest tensile stress may be defined as follows:

$$\text{stress} = \text{force/cross-sectional area} = 4F/\pi D^2 \qquad \text{(Equation 2)}$$

The linear strain (or relative displacement) ϵ, exhibited by a sphere on the application of load is therefore defined as the

change in diameter in the direction of the applied force divided by the original diameter (Equation 3).

$$\text{strain } \epsilon = \text{displacement/diameter} = d/D \qquad \text{(Equation 3)}$$

The dimensions of displacement and diameter are both length and strain is a dimensionless parameter.

The elastic modulus of a material may be defined as the ratio of tensile stress to linear strain, since for elastic material there is a linear relationship between these two parameters

$$\sigma = E\,\epsilon \qquad \text{(Equation 4)}$$

where E is the elastic modulus of the material.
Substituting Equation 2 into Equation 4, therefore we obtain

$$F/A = 4F/\pi D^2 = E\,d/D \qquad \text{(Equation 5)}$$

Qualitative assessment of pellet surface characteristics was made using the technique of scanning electron microscopy (SEM). Samples were mounted onto aluminium stubs, coated with a conducting layer of gold measuring approximately 1-4nm and were then individually examined using SEM.

RESULTS AND DISCUSSION

Consequence of drying method on the mechanical and drug release properties of pellets containing ibuprofen and lactose

The main differentiating factor between the two drying methods is the rate of water removal from the product. Those pellets dried by fluidised-bed technique achieve the desired moisture content much more quickly due to the rapid evaporation of water as a result of the turbulent motion of the fluidised particles. Water removal from tray-dried material is slow due to the static nature of the bed.

The free movement of individual fluidised particles leads to rapid water removal and also minimises the migration of solute particles within the spheres. The tray-dried entities are more likely to exhibit solute migration during the lengthy drying process. For pellets in which the main excipient is lactose, which is freely soluble in the granulating fluid, solute migration is inevitable and is exacerbated by the slow drying associated with static bed dryers.

Effect of drying method on *in-vitro* drug release from uncoated pellets containing 80%w/w ibuprofen

Dissolution testing was performed on uncoated pellets containing 80%w/w ibuprofen with 20%w/w microcrystalline cellulose (Avicel PH101) which had been dried by fluidised-bed drying and by tray drying in a hot air oven. Figure 3 shows the effect of the drying method on the *in-vitro* release profiles of uncoated ibuprofen pellets.

It is apparent that drug release from tray-dried pellets is slightly faster than from fluidised-bed dried material. It is

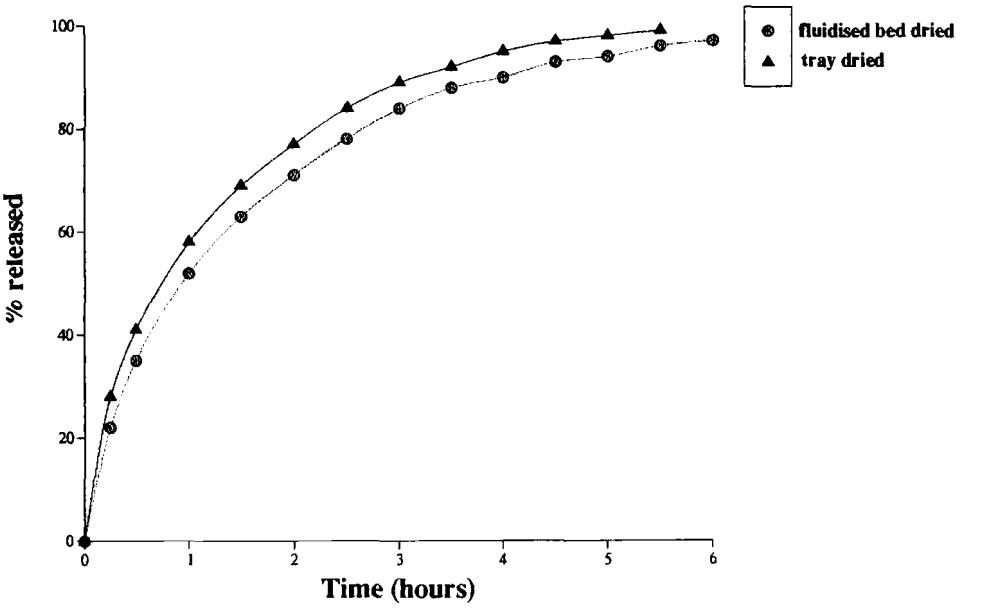

FIGURE 3.
Effect of drying method on the *in-vitro* release from uncoated pellets containing 80%w/w ibuprofen.

postulated that the slower water removal from the static bed leads to a degree of solute migration. It would appear that drug in solution migrates to the pellet surface as the water is slowly driven off during the lengthy drying necessary with static bed drying. Fluidised material however dries much more quickly and therefore this technique enables the use of a slightly higher drying temperature; the possibility of causing thermal damage to the product is reduced due to the continuous motion of fluidised particles.

Ibuprofen exhibits poor aqueous solubility and although one might expect little dissolution of drug within the uncoated cores during

pelletization, there is evidence of some dissolution of drug and some solute migration. This phenomena is apparently minimised by the rapid drying of fluidised product (Figure 3).

Effect of drying method on pellet surface characteristics

The pore structure of pellets can affect the capillary action of the dissolved drug and consequently influence the rate of release of drugs from pellets (Ghebre-Sellassie, 1989). The pore structure and the pellet surface characteristics also affect film deposition and formation. Figures 4 and 5 show scanning electron micrographs (SEM's) of the surfaces of the same batch of uncoated ibuprofen pellets dried using fluidised-bed and static-bed drying techniques.

It is clear that there is a significant difference in the nature and quality of these pellets and that slower water removal appears to cause some solute migration during drying and impaired surface quality (smoothness).

Effect of drying method on diametral crushing strength and elasticity of uncoated pellets

The resistance of individual particles to crushing is related to the cohesive and adhesive properties of the excipients from which they are composed, their geometric size and shape and any physical parameters incorporated as a result of the manufacturing process (Dyer, 1992). The physical properties of pellets are influenced by many factors including the volume of the granulating

FIGURE 4a.
SEM of an uncoated pellet surface dried by fluidised-bed methodology; magnification x400.

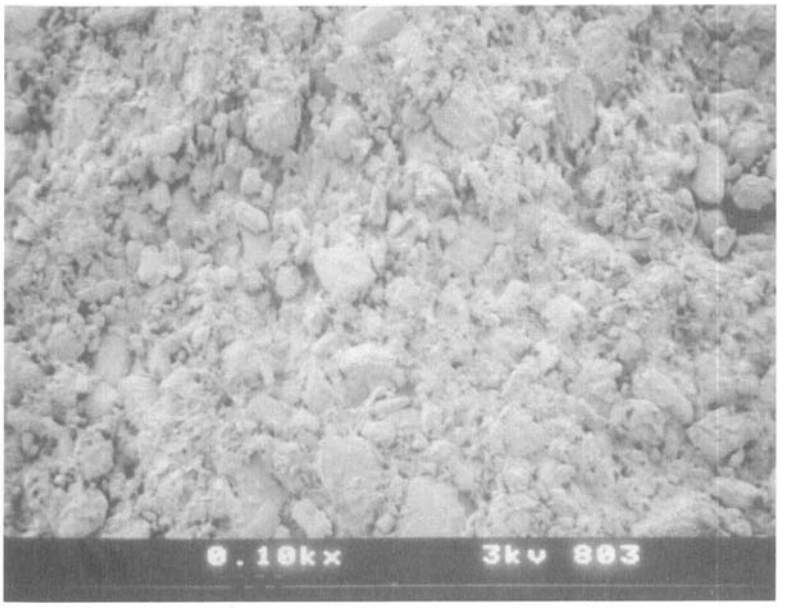

FIGURE 4b.
SEM of an uncoated pellet surface dried by tray drying; magnification x400.

FIGURE 5a.
SEM of an uncoated pellet surface dried by fluidised-bed methodology; magnification x800.

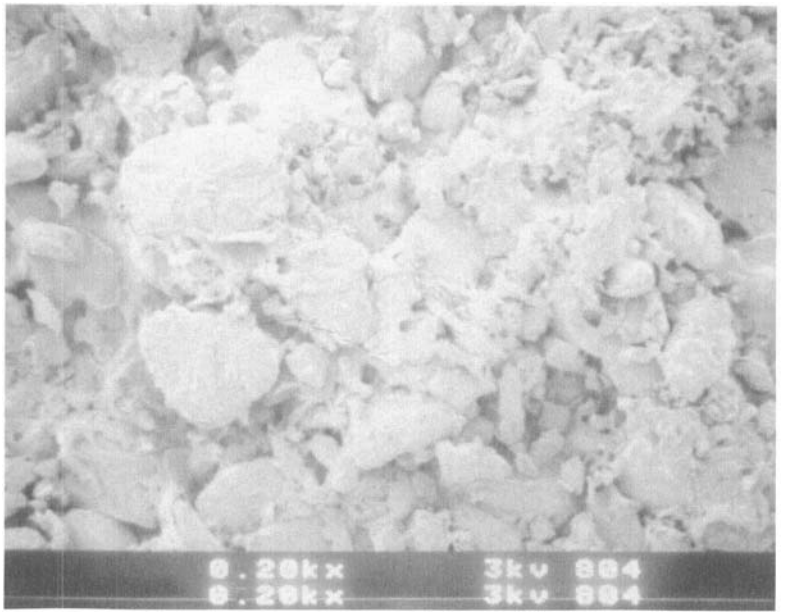

FIGURE 5b.
SEM of an uncoated pellet surface dried by tray drying; magnification x800.

fluid; variables associated with the mixing/massing procedure; the size of the holes of the perforated screen during extrusion and the rate of extrusion of granulate; the amount of material being spheronized, spheonization residence time and rotation speed; the drying technique and associated with this the rate and length of the drying process. Whichever combination of these parameters exists for any given pellet formulation, there will be an influence on the matrix structure and the elastic, plastic and fragmentary properties of the resultant product (Dyer, 1992).

Tables 3 and 4 summarise the mechanical properties of active pellets containing a high percentage of a poorly water soluble drug (ibuprofen) and placebo pellets containing lactose, dried by tray drying in a hot air oven and by fluidised-bed methodology. Precise details relating to the drying temperatures and times are given previously.

During the drying process any residual moisture in the product leads to the formation of solid bridges in the granules by fusion at the point of contact. For solute particles (for example lactose, dissolved in the granulating fluid), crystallisation of the dissolved particles will cause a greater degree of bonding and hence a mechanically stronger particle. Placebo pellets are mechanically stronger than drug-containing entities (c.f. Figures 6 and 8) due to the greater aqueous solubility of lactose compared with ibuprofen.

The drying method also has an effect on the elastic modulus of both ibuprofen-containing pellets and placebo pellets (Figures

TABLE 3.
Effect of drying method on the mechanical properties of uncoated pellets containing 80%w/w ibuprofen.

	drying method	
	tray	fluidised-bed
bead diameter (μm)	1093 (*881-1269)	1086 (878-1343)
crushing force (N)	2.81 (0.9-4.25)	1.91 (1.0-3.05)
displacement (μm)	88 (65-170)	67 (40-110)
work done (μJ)	127 (32-298)	67 (23-167)
% strain	8.1 (6.3-15.1)	6.2 (4.0-8.9)
stress (MPa)	3.0 (1.48-4.31)	2.1 (1.14-3.5)
n	48	44

* = range values

TABLE 4.
Effect of drying method on the mechanical properties of placebo pellets containing 80%w/w lactose with Avicel PH101.

	drying method	
	tray	fluidised-bed
bead diameter (μm)	1073 (*915-1235)	1080 (909-1201)
crushing force (N)	14.0 (8.8-18.3)	9.0 (5.1-12.8)
displacement (μm)	168 (110-270)	122 (75-210)
work done (μJ)	1197 (539-2333)	535 (191-903)
% strain	15.7 (10.3-24.1)	11.4 (6.6-21.5)
stress (MPa)	15.5 (10.8-23.2)	9.4 (5.9-13.1)
n	40	44

* = range values

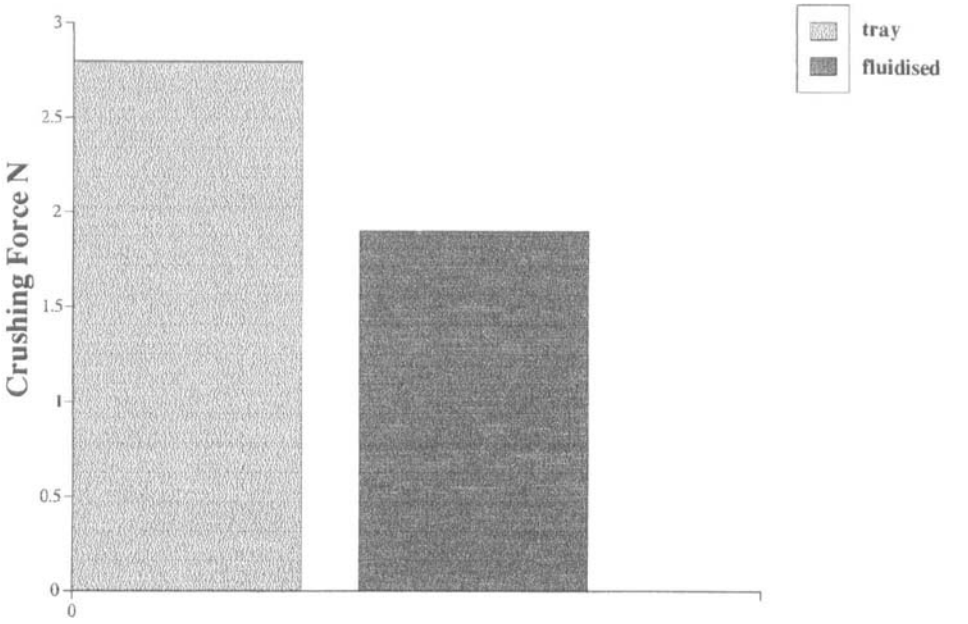

FIGURE 6.
Effect of the drying technique on the mechanical strength of uncoated pellets containing 80%w/w ibuprofen.

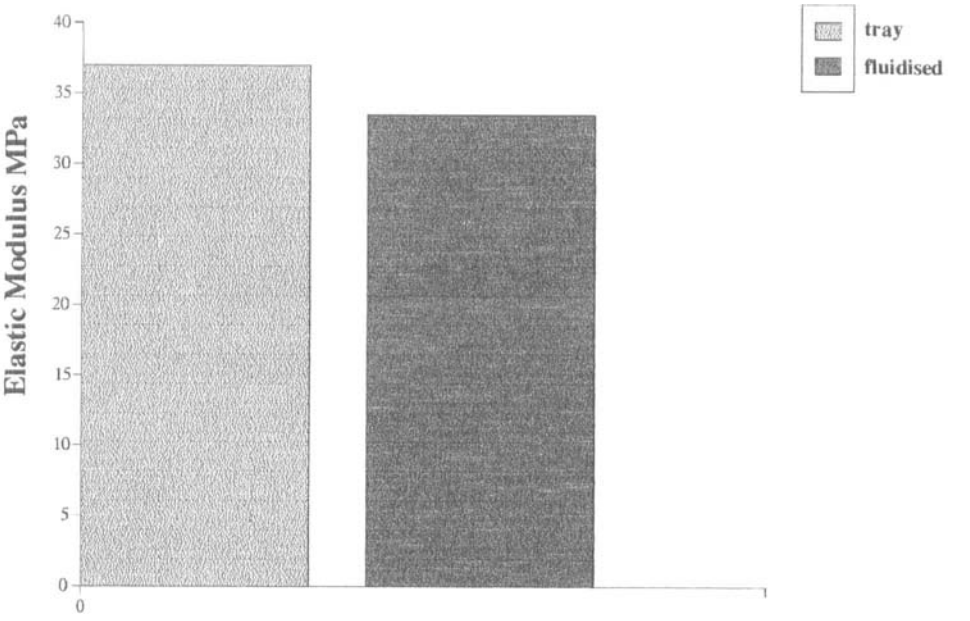

FIGURE 7.
Effect of the drying technique on the elastic modulus (MPa) of uncoated pellets containing 80%w/w ibuprofen.

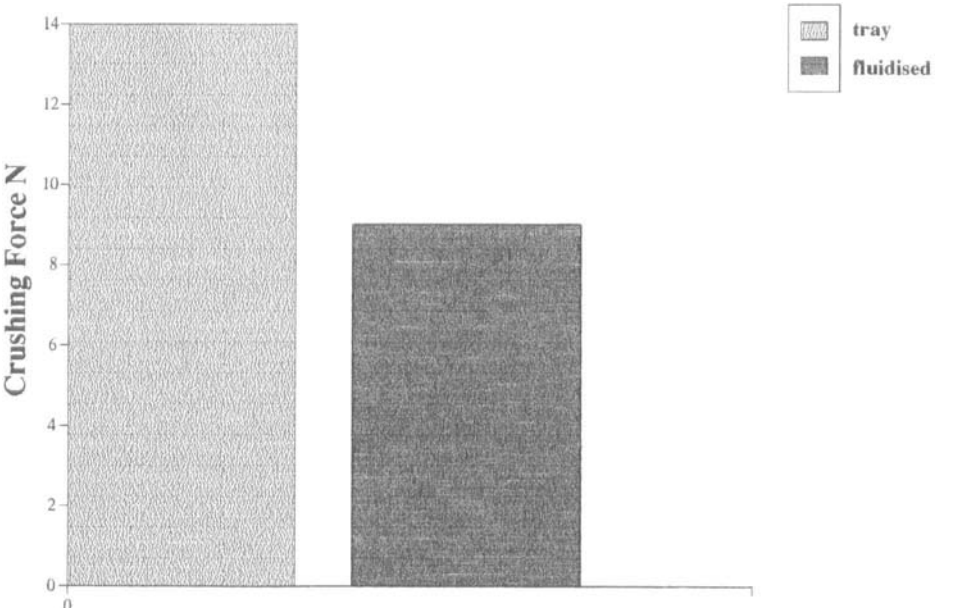

FIGURE 8.
Effect of the drying technique on the mechanical strength of placebo pellets containing 80%w/w lactose with Avicel PH101.

7 and 9). Ibuprofen is virtually insoluble in water and it is reasonable to expect little re-crystallisation of solute particles during the drying process. Conversely lactose is freely soluble; lactose-containing pellets exhibit a high degree of solute migration and crystallisation during the drying process. This leads to mechanically stronger, less elastic, brittle particles (Figures 6 to 9).

In summary, the drying technique for a given uncoated pellet formulation has a significant effect on the mechanical properties of pellets prepared by extrusion-spheronization. Pellets dried by tray drying require a greater crushing force and the work done in

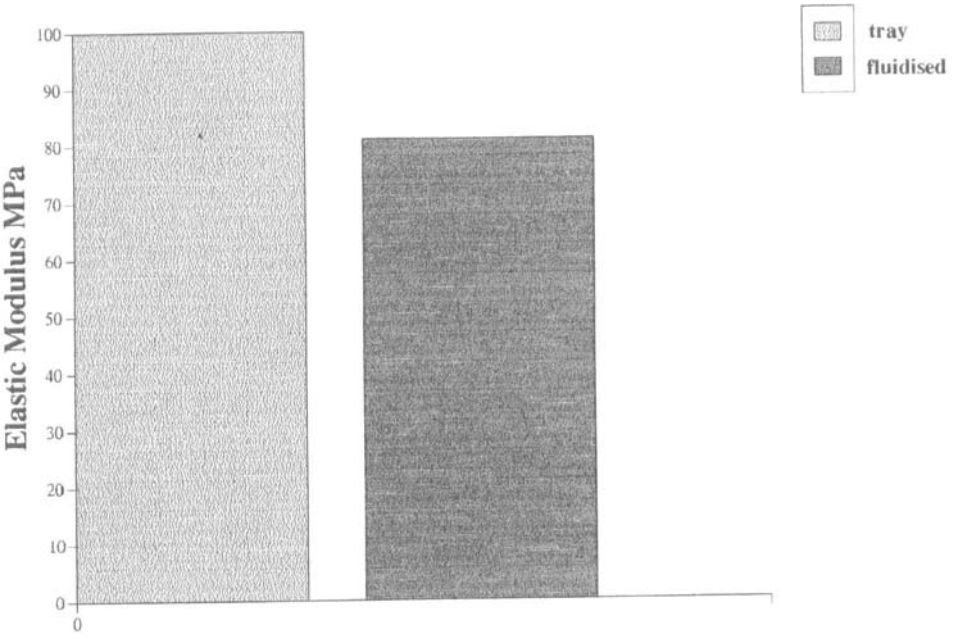

FIGURE 9.
Effect of the drying technique on the elastic modulus (MPa) of placebo pellets containing 80%w/w lactose with Avicel PH101.

causing pellet fracture is therefore greater; tray-dried entities also exhibit greater displacement prior to fracture than the fluidised-bed dried entities. Fluidised-bed dried pellets however demonstrate greater elasticity; this is reflected in the relatively low elastic modulus values obtained.

The solubility of the excipients from which pellets are composed affects the degree of solute migration occurring during the drying process. The drying method, and as a consequence the length of the drying process, also affects the degree of solute migration and is highlighted by the *in-vitro* release profile for ibuprofen pellets dried using these two methodologies.

CONCLUSIONS

This work has revealed that for a given pellet formulation, the drying method employed has a significant effect on the mechanical properties of pellets prepared by extrusion-spheronization.

Pellets dried by tray drying exhibit greater diametral strength and are less elastic than their fluidised-bed dried counterparts.

In-vitro drug release from tray-dried pellets is slightly enhanced when compared with the same batch of pellets dried by fluidised-bed methodology. This is a consequence of the lengthy drying time which is associated with static bed drying. It is therefore postulated that it is the actual speed of the drying process which is the primary cause of any solute migration and that the solubility of the pellet components in the granulating fluid influences the degree of solute migration occurring during drying.

A further consequence of the effect of the drying method and therefore the rate of the drying process on uncoated ibuprofen pellets is on the surface characteristics. Scanning electron micrographs have illustrated the effect of a lengthy drying process and solute migration on the quality of the surface smoothness of uncoated multiparticulates. This has ramifications in respect of the suitability of tray-dried pellets for subsequent application of a polymeric membrane or film coating. Particles prepared using this technique are well documented as possessing

the ideal qualities necessary for the application of a release retarding membrane due to their uniform shape, particle size distribution and smooth surface characteristics.

It should also be noted that in addition to the many processing variables which are capable of significantly influencing the nature and quality of the final product, the drying technique employed as a pelletization process variable will influence the surface characteristics of pellets and this may have consequences in respect of the suitability of such material for film coat application.

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