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Production of inert cushioning beads: effect of excipients on the physicomechanical properties of freeze-dried beads containing microcrystalline cellulose produced by extrusion–spheronization

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Abstract

Conventional highly compactible fillers such as microcrystalline cellulose (MCC) can be mixed with drug-loaded membrane-coated beads and compressed to form a tablet. However, due to particle size differences, there is substantial risk of segregation leading to weight variation and content uniformity problems. Furthermore, whenever modified release beads are included in a tablet matrix, care must be taken to assure the integrity of the coated beads. This paper describes the development of placebo beads containing MCC whose properties make them uniquely suitable for tableting modified release beads. These placebo beads have high compactibility and the ability to rapidly disintegrate. They deform readily and may provide a high degree of protection to drug-loaded membrane-coated beads during compression ('cushioning effect'). They can be produced in size ranges that provide minimal segregation propensity. Beads containing different MCC/lactose ratios and different types and levels of superdisintegrants were produced by extrusion–spheronization followed by freeze drying. The presence of high levels of MCC and different superdisintegrants, especially croscarmellose sodium, increased the granulation liquid requirement, thus producing freeze-dried beads with higher porosities and compactibility. Athy–Heckel analysis studies revealed that beads rich in MCC exhibited lower mean yield pressures than those containing high levels of lactose. The freeze-dried beads exhibited both plastic deformation and brittle fracture characteristics. © 2002 Published by Elsevier Science B.V.

Keywords: Microcrystalline cellulose; Croscarmellose sodium; Freeze-drying; Cushioning beads; Extrusion; Spheronization

1. Introduction

Gelatin capsules are frequently used to dispense modified release beads because the beads can be filled into capsules without a compression step, thereby avoiding damage to the release con-

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trolling coating. Interest in the tableting of coated drug beads gained impetus when hard gelatin capsules of Tylenol® were tampered with for criminal reasons. However, the compaction of such beads poses difficult problems in both protecting the integrity of the modified release coating and avoiding segregation in the running mix.

Conventional, highly compactible fillers such as microcrystalline cellulose (MCC) can be mixed with drug-loaded beads and compressed to form tablets. However, due to particle size differences, segregation may be encountered resulting in weight variation and content uniformity problems. Granules produced by dry or wet granulation techniques having a similar size as the drug-loaded beads are able to minimize the segregation due to size similarities. However, the dry or wet granulation of MCC-containing mixtures decreases their compactibility (Millili and Schwartz, 1990; Aulton et al., 1994).

MCC is an important component in the production of beads by extrusion–spheronization (Conine and Hadley, 1970; Reynolds, 1970; Miyake et al., 1973). Though MCC is a highly compactible material, studies show conclusively that beads made from MCC, alone or in combination with predominantly brittle materials such as dicalcium phosphate or lactose, are very hard and not easily deformed or broken (Millili and Schwartz, 1990; Aulton et al., 1994).

The production of softer inert cushioning beads containing MCC was not successful when water was used as the granulating agent. Replacement of part or all of the granulating solution with alcohol to produce softer beads which fragment at lower pressure during tableting improved the compactibility of those beads to some extent (Millili and Schwartz, 1990; Aulton et al., 1994), but the improvement was not sufficient to prevent the fracture of drug-loaded membrane-coated beads.

2. Objectives

The objective of this paper is to investigate the possibility of producing beads, containing MCC, by extrusion–spheronization followed by freeze drying, that act as cushioning beads. The research tests the hypothesis that the freeze drying process can enhance the porosity of MCC-based placebo beads sufficiently to make them suitable for 'cushioning' modified release beads during tableting. The research examines the effects of different formulation variables (MCC/lactose ratio and type and level of disintegrating agents) on the water requirement, moisture content of the fresh undried beads, porosity, compactibility, compressibility, and disintegration of tablets produced from freeze-dried beads.

3. Materials and methods

The filler materials used include MCC N.F. (Avicel® PH101) and anhydrous lactose N.F. (Sheffield D.T.). Three different superdisintegrants were studied, croscarmellose sodium N.F. (Ac-Di-Sol®), crospovidone N.F. (Polyplasdone-XL®), and sodium starch glycolate N.F. (Explotab CLV®-low viscosity grade).

3.1. Experimental design

A full-factorial design covering the effect of croscarmellose concentration at three levels (0, 4, and 8%) and the MCC/lactose ratio at three levels (100/0, 62.5/37.5, and 25/75) with a triplicate run of the center point was implemented. Four additional formulations containing 4 and 8% each of crospovidone and sodium starch glycolate in MCC were also prepared.

3.2. Determination of the optimal granulating fluid by image analysis

The optimum level of granulating fluid is that level which results in maximum bead roundness in the targeted particle size range. This point will be further discussed in Section 4.1.

Particle size measurement of the fresh undried beads was performed using an optical microscope (Leitz Wetzlar, Germany) fitted with a video camera (MTI 65, Dage-MTI Inc.) interfaced to a microcomputer (Apple® IIe, Apple computer). The microscopic field was displayed on the com-

puter monitor and particle size measurements were made using a microcomputer image analysis system (Bioquant® II Microcomputer System, R&M Biometrics) which consists of a digital pad and an electronic mouse (Hipad® Digitizer, Houston Instruments). The system was calibrated against a micrometer with 10 μm graduations. The fresh beads were placed onto a 25 × 50 mm glass slide as soon as they were discharged from the spheronizer, and the perimeter and area of 100 different spheres were determined. The mean roundness (4Π*area/perimeter^2) and the mean projected area diameter of the beads were calculated.

3.3. Preparation of beads

In preliminary work, each formulation was granulated using a series of water levels. The optimum level was identified as that level that produced nearly round particles (roundness values close to 1.0) whose average size is similar to the aperture of the extrusion screen.

The different formulations were prepared by first dry blending the powder mass of each (500 g) in an Erweka® planetary mixer (Model PRS, Erweka Instruments Inc) for 5 min. This was followed by adding of the optimal amount of the granulating liquid, as determined by image analysis, over a period of 20 s. Wet mixing was continued for 10 additional minutes with occasional interruptions to scrape the sides of the mixing bowl. Extrusion was carried out using a LUWA® single-screw extruder fitted with a 1 mm screen (Model EXKS-1, LCI Corporation) at a speed equivalent to 48 rpm. The extrudate was immediately spheronized using a G.B. Caleva® spheronizer (G.B. Caleva Ltd) for 5 min at a dial reading of 12.

The initial moisture content (IMC) of the beads was determined immediately after spheronization by means of a Computrac® system (Model Max 50, CT Instruments) and after freeze drying. The moisture content of the freeze-dried beads was determined after the drying cycle was complete (final moisture content) and the dried product was stored in double plastic bags for later evaluation.

Beads were freeze-dried using a Dura-Top® FTS system (FTS Systems, Inc) in three phases. The first phase was the freezing phase in which the product was frozen at −20 °C for 2 h. In the second phase (primary drying), the product was dried at −20 °C and 10 mTorr vacuum for 700 min. The third phase (secondary drying) took lace in three stages, (I) 0 °C and 10 mTorr vacuum for 600 min; (II) 25 °C and 10 mTorr vacuum for 500 min; and (III) 25 °C at atmospheric pressure until the end of the run.

3.4. Porosity determination of the freeze-dried beads

The porosity (ε) of the dried beads (18–20 mesh cut) was calculated using the following equation:

$$\varepsilon = 100\left(1 - \frac{\rho_a}{\rho_t}\right)$$

where (ρ_t) is the true density and (ρ_a) is the granular (apparent particle) density.

The true densities (ρ_t) of the dried beads were determined by helium displacement (Multivolume Pycnometer 1305, Micromeretics Instrument Corp). The true volume of the sample (an average of five runs) was calculated by determining the volume of helium displaced by the sample during the test. The true density was then calculated by dividing the weight of the sample by the average true volume. For some formulations true density was measured in duplicate or triplicate to check reproducibility.

The granular density (ρ_a) of the dried beads was determined using a mercury intrusion porosimeter at a low pressure of 20 psi (Pore Sizer Model 9305, Micromeretics Instrument Corp). For some formulations granular density was measured in duplicate or triplicate to check reproducibility.

3.5. Compaction of inert cushioning beads

The freeze-dried beads were compressed on a single station of an Manesty D3B tablet press (Thomas Engineering Inc.) instrumented (Specialty Measurement Inc.) to monitor the upper

punch compression force. The tablet press was run at 25 rpm using 1/2 in. flat-faced beveled edged tooling. The target weight was 430 mg. Approximately 20 tablets were collected at each of 40, 60, 80, 100, 120, 140, and 160 MPa compression pressure. After 24 h of storage, the thickness of five individual tablets at each compression pressure was determined using a digital micrometer. The breaking force (F) of the tablets was determined by diametral loading in a standard motorized tester (Key Tablet Hardness Tester, Model NT-300, Key International Inc.). The breaking force (mean of five determinations at each compression pressure) was used to calculate the tablet tensile strength (σ) in MPa using Eq. (1) (Fell and Newton 1970):

$$\sigma = \frac{2}{\Pi}\frac{F}{Dt} \tag{1}$$

where F is the breaking force of the tablet (N), D is the tablet diameter (mm), t is the tablet thickness (mm). The compactibility of the beads, defined as the ability of the beads to be transformed into a compact of a certain mechanical strength, was determined from the calculated tensile strengths of the compacts as a function of compression pressure.

3.6. Disintegration testing

The disintegration times for three tablets produced at compression pressures of 60 and 80 MPa were evaluated for each formulation according to a modified USP disintegration test in which distilled water at room temperature was used as the medium.

3.7. Studies to monitor changes in bed density

Compression studies to monitor changes in bed density were carried out using an upgraded Mand compaction simulator (Mand Testing Machines Ltd, Stourbridge, UK) located at Glaxo Smith Kline (King of Prussia, PA 19406). The compaction simulator was interfaced to a digital oscilloscope (Nicolet Digital Oscilloscope Model 440) and an IBM PS/2 running EXCEL® software. A saw tooth displacement profile was used to control the upper punch while the lower punch was kept stationary. Flat-faced 10 mm punches were used. The tablet weight for each material (18–20 mesh cut) was adjusted to obtain a tablet thickness of 3.0 mm at zero porosity based on the true density of the beads as determined previously via helium pycnometry. Three tablets were produced for each formulation at a compression speed of 100 mm/s. From the upper and lower punch force and displacement values, it was possible to calculate the thickness of the compact during a single compression event as a function of the punch pressure. From the compact weight and true density data, the relative density of the tablet during compression was calculated.

The Athy–Heckel Eq. (2) was used to analyze the relationship between relative density during compression and the applied pressure. The Athy–Heckel equation (Heckel, 1961a,b) is based on the void spaces decreasing as a first order process.

$$\ln\frac{1}{1-D} = KP + A \tag{2}$$

where D is the relative density of the compact at pressure P, K is a material constant and is the slope of the straight line portion of the plot. The reciprocal of K is the mean yield pressure of the material (P_y). The term A is a function of the original compact volume and can be related to the densification that occurs during die filling plus that which occurs by particle rearrangement before any appreciable interparticle bonding starts.

Regression analyses were carried out on the Athy–Heckel plots over the range of 50–150 MPa. These results were then used to determine the mean yield pressures of the different freeze-dried formulations (18–20 mesh sieve cut).

Two approaches were undertaken to study the mechanism of compaction of the freeze dried beads.

1. For selected batches the yield pressure values were determined at two different punch speeds to estimate the strain-rate sensitivity index (SRS) according to Eq. (3) (Roberts and Rowe 1985):

$$\mathrm{SRS} = \frac{P_{y2} - P_{y1}}{P_{y2}} \times 100 \tag{3}$$

where, P_{y1} and P_{y2} are yield pressures at fast and slow punch velocities, respectively. The two punch speeds tested were 100 and 20 mm/s.

2. For selected batches, the Athy–Heckel analysis was conducted on 14–18,18–20, and 20–25 mesh sieve cuts at an upper punch speed of 100 mm/s.

3.8. Scanning electron microscopy

Selected batches of the freeze dried beads and their cross-sections were examined by scanning electron microscopy (Model, JSM-T200, Jeol Ltd). The tablets produced by compacting the freeze dried beads and their cross-sections were also examined. The samples were placed on aluminum mounts using double sided Scotch® tape. The samples were stored overnight at 0% relative humidity in tightly sealed plastic containers and then sputter coated (Hummer VI Sputtering System, Technics East Inc) with a gold–palladium mixture. Settings used on the sputtering system were as follows, vacuum, 75 mTorr; voltage, 9 V; sputtering time, 5 min. The samples were observed at a working distance of 20 mm and an excitation voltage of 25 kV.

4. Results and discussion

The ideal properties of placebo 'cushioning' beads intended to be used as diluent with drug-loaded beads were previously reported (Aulton et al., 1994). These properties should include the following:

1. Fragment initially into primary powder particles followed by plastic deformation. This is important because during the compaction of the cushioning beads with the drug-loaded membrane-coated beads it is important not only to fill the voids between the drug-loaded beads but also to surround them so that the tablet is held together by excipient–excipient contact.
2. Minimize segregation propensity by means of similar size and density.
3. Deform much more readily than the drug-loaded beads.
4. Produce tablets that rapidly disintegrate and release the drug-loaded beads.
5. Have no effect on the drug release kinetics.

In this work, MCC-containing beads which deform at low pressures during tableting were produced by freeze-drying. These beads can potentially be used as cushioning beads to prevent the fracture of membrane-coated drug-loaded beads and to minimize the segregation propensity due to size differences. The effects of different formulation variables (MCC/lactose ratio and type and level of disintegrating agents) on the water requirement, moisture content of the fresh undried beads, porosity, compactibility, compressibility, and disintegration of tablets produced from freeze-dried beads were investigated.

4.1. Effect of formulation variables on the granulating fluid requirement and initial moisture content (IMC) of the cushioning beads produced by extrusion–spheronization

The amount of granulating fluid, which is usually affected by the composition of the formulation (Elber et al., 1992), has a major influence on the properties of beads. These properties include drug release (Beart and Remon, 1993), shape, size distribution (Pinto et al., 1992), internal porosity, and mechanical strength (Otsuka et al., 1994). Thus, changing the moisture content of the wet granulated mass prior to extrusion–spheronization has a major impact on the size and size distribution of beads together with other physico-mechanical properties (Millili and Schwartz, 1990; Hasznos et al., 1992).

Therefore, in order to investigate the effect of different formulation variables on the properties of beads produced by extrusion–spheronization it is essential to identify the optimal fluid level required by each formulation. Different techniques to characterize the optimal liquid level suitable for extrusion–spheronization have been reported in the literature (Harrison et al., 1985; Alleva and Schwartz, 1986; Elber et al., 1992; Shah et al., 1994). However, if a more critical evaluation of the product is required, it is necessary to consider

the shape, size and size distribution of the product of the process. A preparation that is too dry is difficult to extrude and results in anisomeric particles, whereas one that is too wet results in gross agglomeration on the spheronizer plate leading to greatly enlarged agglomerates. At an optimum water level, nearly spherical particles are usually obtained. Thus, image analysis of the freshly produced pellets can be used to determine the optimum water level (Kleinebudde, 1993, 1994a,b).

The optimal fluid level requirement and the IMC of the fresh undried beads after being discharged from the spheronizer can be found in Table 1. Regression analysis revealed a significant effect of the MCC/lactose ratio, croscarmellose sodium and crospovidone level on the IMC. No significant difference in IMC ($P = 0.1$) was associated with the presence of sodium starch glycolate. An increase in the MCC/lactose ratio, croscarmellose sodium level, and crospovidone level resulted in an increase in the IMC.

The regression coefficients for the croscarmellose sodium and the crospovidone levels were 1.392 and 0.2375, respectively. Thus, an increase in the IMC due to the presence of croscarmellose sodium is approximately six times that of crospovidone which can be attributed to the fact that croscarmellose sodium can take up more water than crospovidone without causing gross agglomeration and size enlargement of the beads during spheronization. When higher granulation fluid levels were used, formulations containing sodium starch glycolate agglomerated during spheronization, resulting in massive balling. This is due to the higher viscosity encountered with sodium starch glycolate when used at such levels (4 and 8%), even though a low viscosity grade was used. Although superdisintegrants tend to increase the fluid level requirement and IMC, ideally they should do this without causing massive agglomeration of the beads during spheronization.

An increase in the MCC/lactose ratio was associated with an increase in the fluid level requirement and IMC. This is in accordance with the findings of other investigators that more granulating liquid is required as the level of MCC is increased (Bains et al., 1991; Elber et al., 1992; Pinto et al., 1992).

4.2. Effect of freeze-drying on the size of cushioning beads produced by extrusion–spheronization

The average area diameters of the fresh undried and the freeze-dried beads for all formulations can be found in Table 1. It is clear that shrinking occurring during freeze drying is minimal. This is in accordance to Kleinebudde's finding (Kleinebudde, 1994a,b) that there is a remarkable difference in the physico-mechanical properties of pellets as a result of the drying technique with only a minor shrinking tendency during freeze drying. Kleinebudde suggested that removing the water in the frozen state leaves a skeleton of solid materials with resultant freeze-dried pellets having similar size to the wet pellets, but with high porosities.

4.3. Effect of different formulation variables on the porosity of cushioning beads produced by extrusion–spheronization

The granular density, true density, and the calculated porosity for the various formulations can be found in Table 1.

Measurement of the true densities was performed in triplicate for two formulations to check for reproducibility and variability associated with the helium pycnometer measurements. The relative standard deviation (R.S.D.) for the MCC/lactose (25:75) formulation and the 8% crospovidone in MCC formulation were 0.47 and 0.49%, respectively. The R.S.D. associated with the measurements of the granular density for the plain MCC formulation, the 8% croscarmellose sodium in MCC formulation, and the 8% crospovidone in MCC formulation were 1.99, 0.5, and 4.59%, respectively.

Regression analysis revealed a statistically significant ($P < 0.05$) effect of MCC/lactose ratio as well as the presence of different superdisintegrants on the porosities of the freeze-dried beads. Increasing the MCC/lactose ratio and the different superdisintegrant levels increased the porosity of the freeze dried beads.

The inclusion of sodium starch glycolate or croscarmellose sodium increased the porosity of

Table 1
Effect of formulation variables on the granulating fluid level, IMC, Size, granular density, true density and porosity of beads

Formulation	Optimal water level (mg/500 g)	IMC[b] (%)	Size of undried beads (mm)	Size of freeze dried beads (mm)	Granular density[c] (g/ml)	True density[c] (g/ml)	Porosity (%)
MCC[d]	625	55.7	0.99 (0.16)[a]	0.93 (0.13)[a]	1.02	1.59	35.62
4% Croscarmellose/MCC	725	59.5	0.95 (0.15)	0.93 (0.13)	0.70	1.61	56.35
8% Croscarmellose/MCC	825	62.1	0.89 (0.14)	0.88 (0.14)	0.65	1.62	60.25
MCC:lactose (62.5:37.5)	300	36.8	1.03 (0.14)	1.00 (0.11)	0.95	1.58	39.89
4% Croscarmellose/MCC:lactose (62.5:37.5; Run # 1)	410	44.8	0.98 (0.13)	0.97 (0.12)	0.80	1.59	49.87
4% Croscarmellose/MCC:lactose (62.5:37.5; Run # 2)	410	44.8	1.04 (0.14)	0.99 (0.12)	0.81	1.59	48.75
4% Croscarmellose/MCC:lactose (62.5:37.5; Run # 3)	410	44.6	0.98 (0.12)	0.97 (0.13)	0.81	1.58	48.93
8% Croscarmellose/MCC:lactose (62.5:37.5)	500	50.0	0.92 (0.14)	0.92 (0.16)	0.69	1.60	56.54
MCC:lactose (25:75)	194	36.4	0.99 (0.17)	1.04 (0.15)	1.05	1.61	34.58
4% Croscarmellose/MCC:lactose (25:75)	277	34.1	0.98 (0.14)	1.01 (0.14)	0.91	1.60	43.08
8% Croscarmellose MCC:lactose (25:75)	360	40.2	1.01 (0.13)	1.03 (0.13)	0.83	1.60	48.11
4% Crospovidone-XL/MCC	650	56.8	0.99 (0.16)	0.93 (0.13)	0.94	1.55	39.38
8% Crospovidone-XL/MCC	675	27.6	0.99 (0.11)	0.91 (0.14)	0.90	1.56	41.90
4% Sodium starch glycolate/MCC	670	56.5	0.99 (0.11)	0.93 (0.13)	0.85	1.59	46.45
8% Sodium starch glycolate/MCC	750	59.7	1.00 (0.18)	0.93 (0.16)	0.65	1.64	60.65

[a] Standard deviation (S.D.).
[b] IMC, initial moisture content.
[c] Freeze-dried bead.
[d] MCC, microcrystalline cellulose.

beads to a greater extent than crospovidone, as reflected in their corresponding regression coefficients. Moreover, an increase in the porosity of the freeze dried beads was observed with increasing the MCC/lactose ratio. Beads with higher IMC's exhibited higher porosities. Increasing the IMC of the granulations prior to extrusion–spheronization resulted in a proportional increase in the porosity of the corresponding freeze-dried beads. The slope of this relationship was estimated to be around 0.478 ($P = 0.05$).

4.4. Effect of formulation variables on the compactibility of dried beads produced by extrusion–spheronization

The effect of the MCC/lactose ratio at 0 and 8% croscarmellose sodium levels on the compaction of freeze-dried beads containing MCC can be found in Figs. 1 and 2, respectively. Fig. 3 represents the effect of superdisintegrants at 0 and 8% levels on the compaction of freeze-dried beads containing MCC.

The effect of the different variables on the tensile strength of the compacted tablets cannot be studied unless identical compression pressures are used in the generation of the different compaction profiles. Though tablets were collected at 40, 60, 80, 100, 120, 140 and 160 MPa, these compression pressures were approximate. For accuracy reasons, the compaction pressure/tensile strength data for each formulation was fitted to a straight-line model from which the tensile strengths of each compact at particular compaction pressures can be predicted. The predicted tensile strengths of the different formulations at a compression pressure of 60 MPa were calculated and are listed in Table 2. This compression pressure was chosen because such pressures are commonly encountered in tablet production.

Table 2 reveals that the strongest tablets (tensile strength of 1.99 MPa) were produced by using the formulation composed of 8% croscarmellose sodium in MCC. Statistical analysis of the different variables affecting the predicted tensile strength of the tablets compressed at 60 MPa can be seen in Table 3.

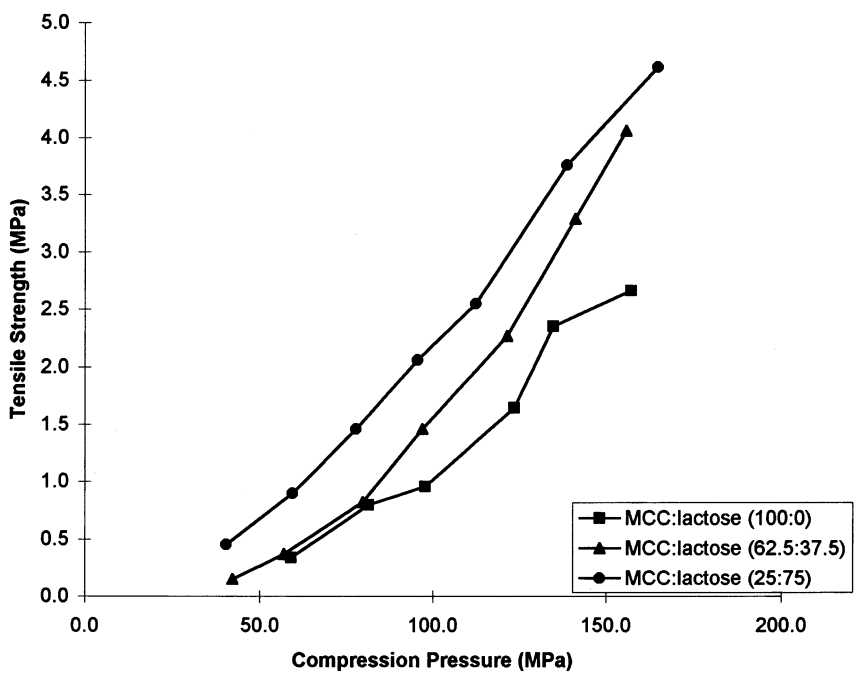

Fig. 1. Effect of MCC:lactose ratio on the compactibility of freeze-dried beads containing 0% croscarmellose sodium.

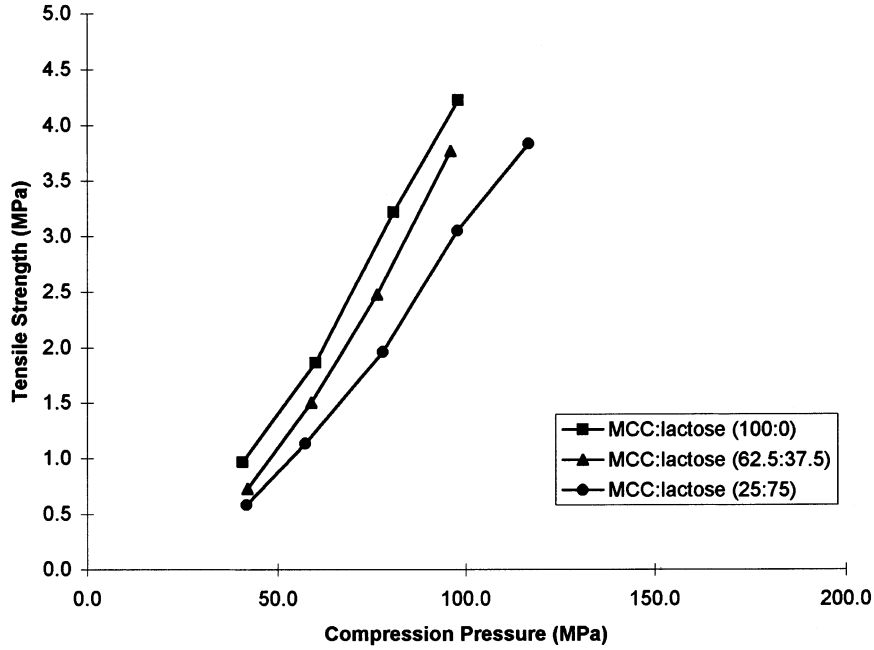

Fig. 2. Effect of MCC:lactose ratio on the compactibility of freeze-dried beads containing 8% croscarmellose sodium.

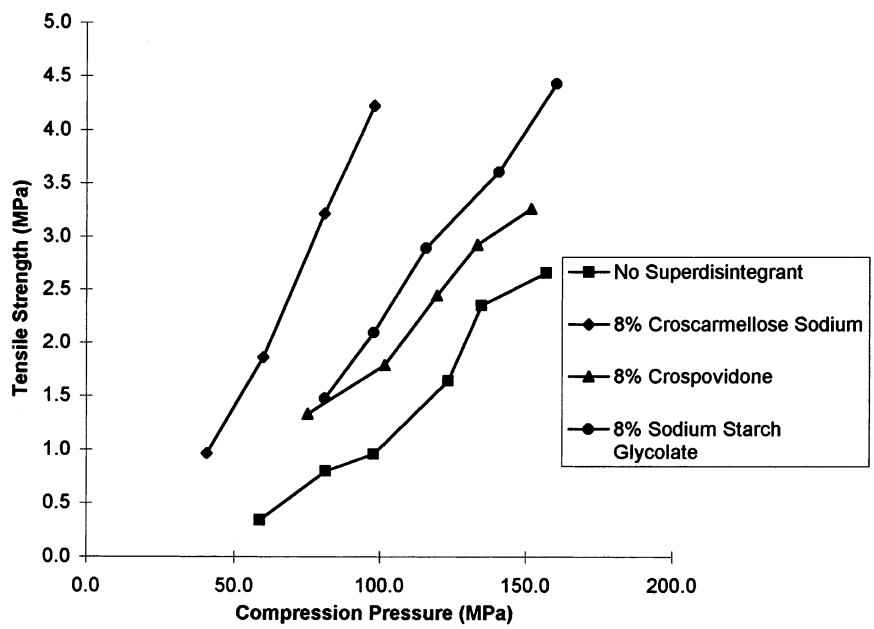

Fig. 3. Effect of different superdisintegrants on the compactibility of freeze-dried beads.

Table 2
Effect of formulation variables on the predicted tensile strengths of tablets and the mean yield pressures of freeze-dried beads

Formulation	Predicted tensile strength (MPa) at a compression pressure of 60 MPa	Mean yield pressure (MPa) at an upper punch speed of 100 mm/s
MCC	0.24	79.1 (1.2)[a]
4% Croscarmellose/MCC	1.12	78.2 (1.3)
8% Croscarmellose/MCC	1.99	80.5 (3.0)
MCC:lactose (62.5:37.5)	0.42	92.1 (3.0)
4% Croscarmellose/MCC:lactose (62.5:37.5; Run # 1)	1.09	103.0 (2.0)
4% Croscarmellose/MCC:lactose (62.5:37.5; Run # 2)	1.19	107.1(10.0)
4% Croscarmellose/MCC:lactose (62.5:37.5; Run # 3)	1.06	106.2 (8.7)
8% Croscarmellose/MCC:lactose (62.5:37.5)	1.65	101.2 (0.8)
MCC:lactose (25:75)	0.94	112.0 (1.4)
4% Croscarmellose/MCC:lactose (25:75)	1.05	115.4 (0.8)
8% Croscarmellose MCC:lactose (25:75)	1.30	112.6(0.9)
4% Crospovidone-XL/MCC	0.57	104.3 (7.4)
8% Crospovidone-XL/MCC	0.64	110.0 (1.4)
4% Sodium starch glycolate/MCC	0.38	112.7 (2.5)
8% Sodium starch glycolate/MCC	0.88	123.5 (2.4)

[a] R.S.D.

The MCC/lactose ratio is of significant importance in predicting the tablet tensile strength. Decreasing the level of MCC produced tablets with higher tensile strengths (Fig. 1). This is seen numerically in Table 2 when comparing the corresponding tensile strengths the plain MCC formulation, MCC/lactose (62.5:37.5) formulation, and the MCC/lactose (25:75) formulation. The tensile strengths for these formulations are 0.24, 0.42, and 0.94, respectively. This result of lower tablet tensile strength for higher MCC levels in the beads can be attributed to the MCC forming strong adhesive hydrogen bonding (Millili and Schwartz, 1990; Aulton et al., 1994). Hard beads containing MCC do not exhibit sufficient plastic deformation to produce hard tablets. Crospovidone and sodium starch glycolate had no statistically significant effect on the tensile strength of the compressed tablets.

A statistically significant interaction between croscarmellose sodium and the MCC/lactose ratio on the tensile strength of the compacts was also found (Table 3). Increasing the percentage of croscarmellose sodium in the formulation predominantly containing MCC produced compacts with higher tensile strength than if such an increase occurred in a lactose-predominant formulation. This is seen in Figs. 1 and 2, where, in the absence croscarmellose sodium, a higher MCC/lactose ratio produced tablets with lower tensile strengths (Fig.

Table 3
Statistical analysis of the effect of formulation variables on the predicted tensile strengths of tablets produced using freeze-dried cushioning beads at a compression pressure of 60 MPa

Formulation variable	Coefficient	*P*-Value
Croscarmellose sodium experiments		
MCC:lactose ratio	−0.0090	0.0001
% Croscarmellose sodium	−0.0056	0.730
Interaction (MCC/lactose × % croscarmellose sodium)	0.0023	1.74E-05
Crospovidone experiments		
% Crospovidone	0.05	0.229
Sodium starch glycolate experiments		
% Sodium starch glycolate	0.08	0.200

Table 4
Disintegration time of tablets produced by compressing the freeze-dried beads at compression pressures of 15 and 20 MPa

Formulation	Disintegration time (s) at a compression pressure of 60 MPa	Disintegration time (s) at a compression pressure of 80 MPa
MCC	<5	<5
4% Croscarmellose/MCC	<5	14
8% Croscarmellose/MCC	31	110
MCC:lactose (62.5:37.5)	<5	68
4% Croscarmellose/MCC:lactose (62.5:37.5; Run # 1)	367	968
4% Croscarmellose/MCC:lactose (62.5:37.5; Run # 2)	462	890
4% Croscarmellose/MCC:lactose (62.5:37.5; Run # 3)	331	669
8% Croscarmellose/MCC:lactose (62.5:37.5)	667	848
MCC:lactose (25:75)	65	164
4% Croscarmellose/MCC:lactose (25:75)	550	1334
8% Croscarmellose MCC:lactose (25:75)	659	673
4% Crospovidone-XL/MCC	<5	<5
8% Crospovidone-XL/MCC	<5	<5
4% Sodium starch glycolate/MCC	<5	<5
8% Sodium starch glycolate/MCC	7	29

1). As the concentration of croscarmellose sodium increased to 8%, an increase in the MCC/lactose ratio produced tablets with higher tensile strengths (Fig. 2). For beads containing water soluble materials such as lactose, it is not unreasonable to anticipate that the dissolution of the soluble component during the wet massing stage will contribute to bonding. Water removal from those beads during drying could lead to the formation of solid bridges between primary powder particles by recrystallization. On the other hand, the type of bonds associated with MCC beads are different from the solid bridges encountered with lactose (Aulton et al., 1994; Dyer et al., 1994). These bonds are mainly hydrogen bonds (Huttenrausch, 1971; Nakai, 1977) which tend to produce stronger beads than those of lactose. Thus, pure MCC beads are stronger and less easily deformable resulting in compacts with lower tensile strengths (Fig. 2). In the presence of 8% croscarmellose sodium in MCC, the high porosity associated with the high granulation fluid requirement could have decreased the hydrogen bonding between adjacent MCC molecules resulting in softer beads, which deform more readily upon the application of pressure to give hard tablets.

Fig. 3 shows the superiority of croscarmellose sodium over both crospovidone and sodium starch glycolate in improving the compactibility of the freeze dried beads.

Thus, combining both MCC and croscarmellose sodium in the production of freeze-dried cushioning beads by extrusion–spheronization produced the most highly compactible beads, which upon compaction produced tablets with the highest tensile strengths.

Regression analysis also revealed that increasing the porosity of the freeze-dried beads by 1% tends to increase the tensile strength of their corresponding compacts by 0.046 MPa ($P = 0.00145$).

4.5. Disintegration

The disintegration times of the tablets produced by compressing the freeze-dried beads of different

formulations at compression pressures of 60 and 80 MPa can be found in Table 4. At higher compression pressures, longer disintegration times were encountered. As the MCC/lactose ratio decreased, the disintegration time was prolonged because lactose is a non-disintegrating soluble excipient.

The effect of different formulation variables on the disintegration time cannot be statistically analyzed because tablets of similar tensile strength should be compared. Unfortunately, the compaction study necessitated that compression pressure be varied, resulting in variable tensile strengths.

4.6. Studies to monitor changes in bed density

An increase in bulk density of the compacts formed by compressing the cushioning beads of the different formulations was observed with an increase in the applied pressure. The relationship between the applied pressure and density or porosity (Athy–Heckel equation, see Eq. (2)), measured inside the die, appeared to be linear over almost the entire range of the applied pressure studied. The appearance of only a minimal initial curvilinear region, which is attributable to particle rearrangement, is not surprising since the freely-flowing spherical beads are likely to assume a near maximal packing arrangement upon filling the die.

The mean yield values for all freeze-dried formulations, measured in triplicate over a compression range of 50–150 MPa at an upper punch speed rate of 100 mm/s can be found in Table 2.

Results of the regression analysis investigating the effect of formulation variables on the yield value of freeze-dried beads showed that the only significant factor was the MCC/lactose ratio. As opposed to what was observed in the compactibility studies, the Athy–Heckel analysis revealed that as the MCC/lactose ratio is increased, beads with lower yield values and higher compressibility are produced. In MCC-predominant formulations, steeper slopes (thus lower yield value) than those of the lactose predominant formulations are observed. This can be explained by the fact that lactose has a higher yield value than MCC, thus formulations which are predominant in lactose tend to have higher yield values. Superdisintegrants had no effect on the yield value at the levels studied.

4.7. Determination of the deformation mechanism of freeze-dried beads

The changes in mean yield pressure as a function of punch speed and the calculated strain rate sensitivities Eq. (3) for the formulations studied can be found in Table 5. A difference in the yield pressure with changing punch speed indicates the existence of a time-dependent component to the deformation process (Roberts and Rowe, 1985) of

Table 5
Effect of punch speed on the mean yield pressures of freeze-dried beads

Formulation	Yield value (MPa) at an upper punch speed of 20 mm/s	Yield value (MPa) at an upper punch speed of 100 mm/s	Strain-rate sensitivity index
MCC	65.6 (0.8)[a]	79.1 (1.2)[a]	20.6
8% Croscarmellose/MCC	66.9 (1.0)	80.5 (3.0)	20.3
MCC:lactose (25:75)	91.1 (6.0)	112.0 (1.4)	23.0
8% Croscarmellose MCC:lactose (25:75)	98.7 (0.9)	112.6 (0.9)	14.1
8% Crospovidone-XL/MCC	70.8 (1.7)	110.0 (1.4)	55.4
8% Sodium starch glycolate/MCC	51.3 (0.7)	123.5 (2.4)	140.7

[a] R.S.D.

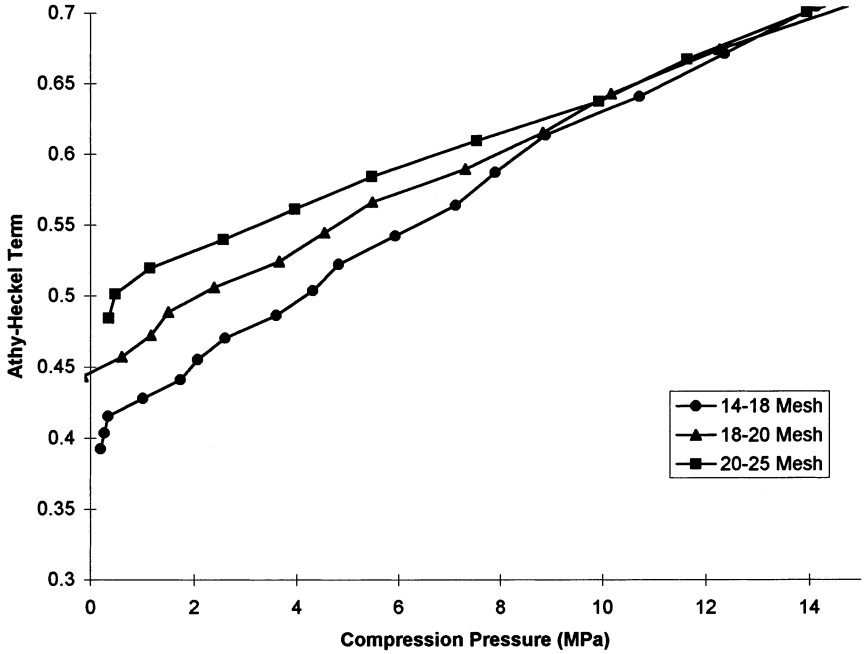

Fig. 4. Effect of bead size on the compressibility of freeze-dried beads containing plain MCC.

the freeze-dried beads. This can be attributed either to a change from plastic to brittle behavior or a reduction in the amount of time-dependent deformation (Rees and Rue, 1978). Thus, at the slower punch speeds of 20 mm/s the compacted beads exhibited more plastic flow than at 100 mm/s, resulting in statistically significant lower yield values ($P < 0.0001$). Moreover, the change in SRS indicates a time-dependent component to the deformation process, with the 8% sodium starch glycolate and the 8% crospovidone formulations showing the most strain-rate sensitivity.

In the second study, the compression profiles (Athy–Heckel plots) were evaluated for different sieve cuts (14–18, 18–20, and 20–25 mesh cuts) at an upper punch speed rate of 100 mm/s. If the beads were to exhibit plastic deformation, the Athy–Heckel plots for different particle size fractions of the beads would be parallel. If brittle fracture is the predominant mechanism of deformation, the initial structure of the material is progressively destroyed so that above a certain pressure a common, coincident linear relationship would be obtained for all size fractions. Fig. 4 depicts the effect of particle size fraction on the Athy–Heckel compression profiles for the formulation containing 100% MCC. It is clear that brittle fracture is contributing to the deformation mechanism. The use of different size fractions to detect the predominant mechanism of deformation was not sensitive enough for all of the formulations tested. This could be due to the narrow size distribution of the beads which is an inherent advantage of the extrusion–spheronization process. If the size distribution was wider, sieve-cuts that differ significantly in size might have given different compression profiles from which the mechanism of deformation could have been elucidated.

Therefore, the freeze-dried beads exhibited both plastic deformation and some brittle fracture. The presence both deformation mechanisms is desirable because as the cushioning beads, mixed with drug-loaded beads, are compacted, initial fragmentation into primary powder particles would not only fill the voids between the drug-loaded beads but surround them. Plastic deformation of the fine particles would then enhance the excipi-

ent–excipient interaction producing stronger compacts.

4.8. Scanning electron microscopy

Selected scanning electron micrographs (SEM's) of a cross-section of the freeze-dried beads containing plain MCC (at a magnification = 100 ×) and 8% croscarmellose sodium in MCC (100 ×) are presented in Figs. 5 and 6, respectively. SEM's of the surface of tablet compacts at a compression pressure of 80 MPa containing freeze-dried plain MCC beads and 8% croscarmellose sodium in MCC (35 ×) are seen in Figs. 7 and 8, respectively.

Comparing Figs. 5 and 6, beads containing 8% croscarmellose sodium are more porous than plain MCC. This is attributable to the higher granulation fluid requirement associated with the presence of croscarmellose sodium. A similar trend is observed in the cross-sections of the beads containing MCC:lactose (25:75) and 8% croscarmellose sodium in MCC:lactose (25:75) for the same reason (SEM's are not presented).

The surfaces of tablets, produced by compressing plain MCC (Fig. 7) and 8% croscarmellose sodium in MCC (Fig. 8) to an equal force differ significantly. The latter have an obviously smoother surface than those containing plain MCC beads, where the boundaries of the component beads are still visible. This is because of the difference in porosities of the two bead systems which resulted in a difference in compactibility.

5. Conclusions

Inert cushioning beads of different compressibilities, compactibilities and disintegration properties were produced by freeze-drying. The presence of high levels of MCC and different superdisintegrants, especially croscarmellose sodium, generally increased the granulating fluid level requirement, thus producing freeze-dried beads with higher porosities and better compactibilities. Compacts made from such beads exhibited varying disintegration times ranging from less than 5 s, for MCC predominant formulations, to longer time periods, for lactose-predominant formulations.

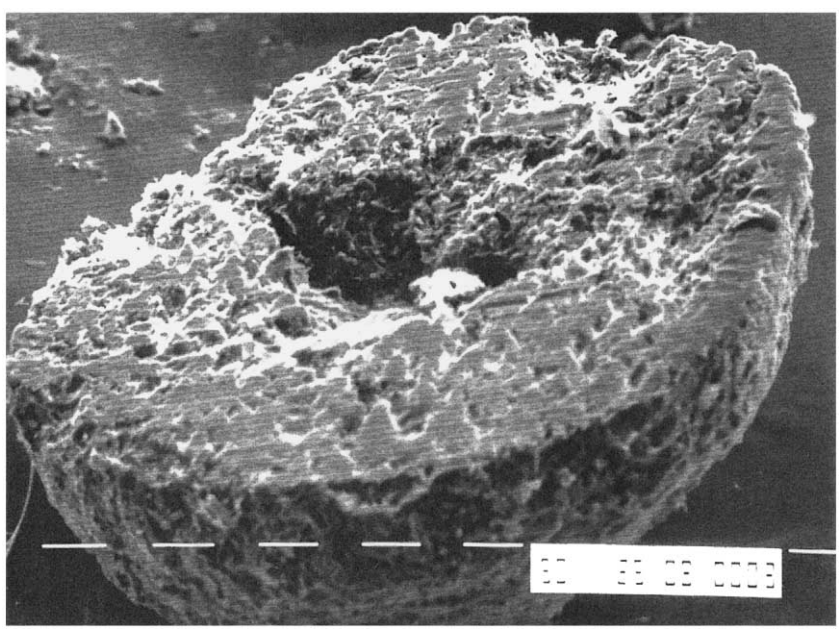

Fig. 5. Scanning electron photomicrograph of a cross section of freeze-dried beads containing plain MCC; magnification, 100 ×.

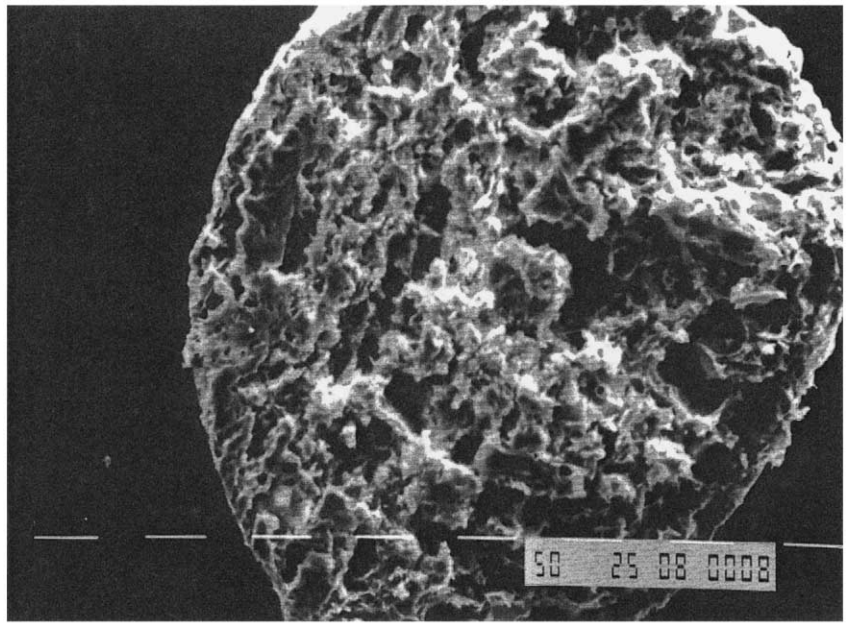

Fig. 6. Scanning electron photomicrograph of a cross section of freeze-dried beads containing 8% croscarmellose sodium in MCC; magnification, 100 ×.

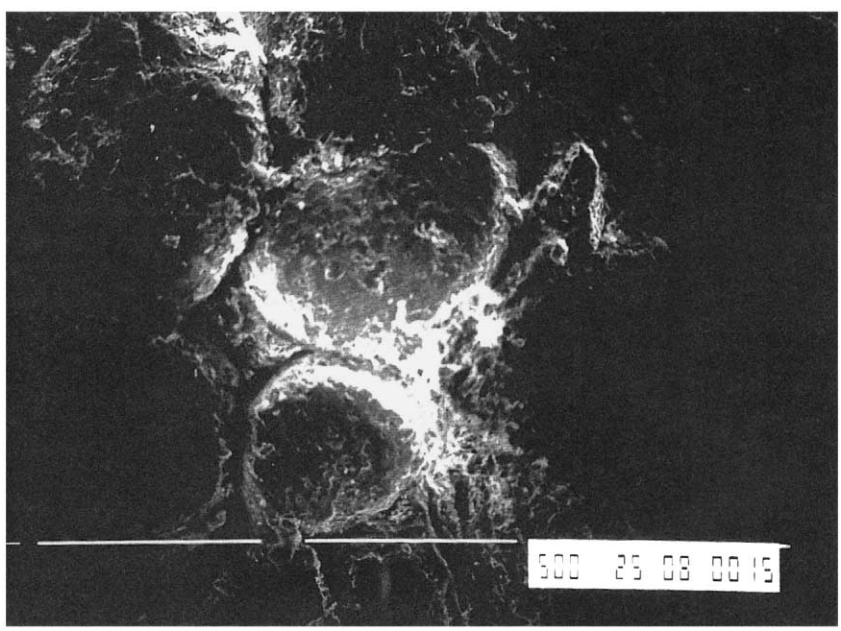

Fig. 7. Scanning electron photomicrograph of the surface of a tablet made by compressing freeze-dried beads containing plain MCC at a compression pressure of 80 MPa; magnification, 35 ×.

Compressibility studies revealed that formulations containing high levels of MCC exhibited lower yield values, and thus were more compressible, than those formulations containing high levels of lactose. Superdisintegrants had no effect on the compressibility of beads. Freeze-dried beads exhibited both plastic deformation and some brittle fracture.

The ultimate utility of the placebo cushioning beads produced by freeze drying must be practically evaluated by mixing and compacting them with drug-loaded membrane-coated sustained release beads. The cushioning beads should minimize the segregation propensity due to size and density differences, and should protect the coating of the drug loaded beads. Moreover, the compacts should disintegrate rapidly to release the intact drug-loaded beads with minimal change in the release kinetics of the drug.

6. In memoriam

It is with great sadness that Larry Augsburger and Yacoub Habib acknowledge the passing of Dr Ralph F. Shangraw, one of the most influential and most beloved contributors to pharmacy and the pharmaceutical sciences, and a significant contributor to this paper. Ralph's research won national and international recognition, and under his leadership the University of Maryland developed one of the most respected graduate programs in pharmaceutics in the country. That program won international recognition for its work in industrial pharmaceutical technology. However, despite his significant accomplishments, Ralph never became self-important. He was a warm, generous human being who took a genuine interest in those with whom he came into contact. To know Ralph was to be counted among his extended family. There are some in whose company we are always at our best, and Ralph was just such a person. Although Ralph will be missed, he lives on his scientific contributions and especially in the memory of those who knew him upon whom he has left his mark.

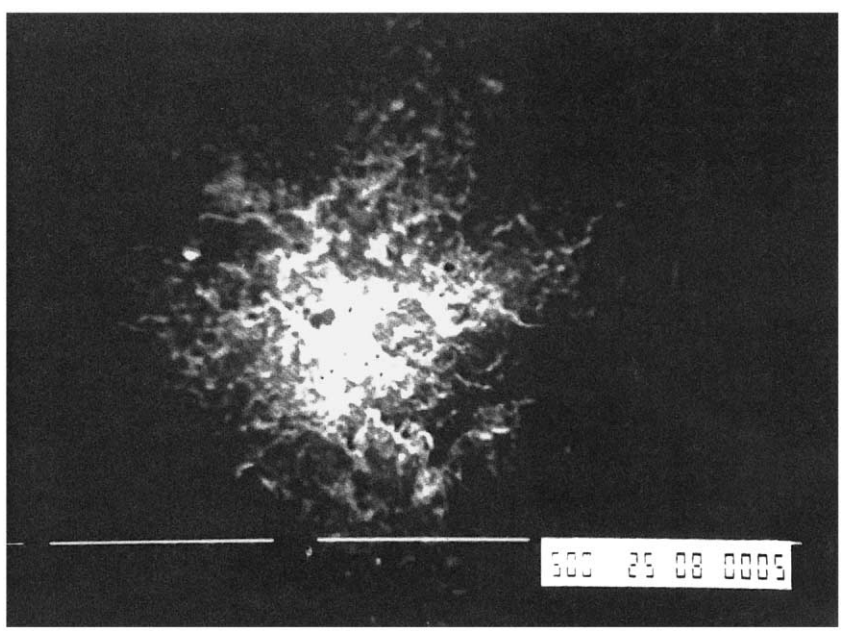

Fig. 8. Scanning electron photomicrograph of the surface of a tablet made by compressing freeze-dried beads containing 8% croscarmellose sodium in MCC at a compression pressure of 80 MPa; magnification, 35 ×.

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