International Journal of Pharmaceutics, 33 (1986) 81–87
Elsevier

IJP 01103

Granulation and compaction of a model system. I. Granule properties

Teresa Cutt [1], John T. Fell [2], Peter J. Rue [3] and Michael S. Spring [2]

[1] *Pfizer Central Research, Sandwich, Kent, CT13 9NJ (U.K.),* [2] *Department of Pharmacy, University of Manchester, Manchester, M13 9PL (U.K.) and* [3] *Glaxo Group Research Limited, Ware, Hertfordshire, ST12 0DJ (U.K.)*

(Received 11 April 1986)
(Accepted 23 May 1986)

Key words: Granulation – Binder – Granule property – Granulation of a model system

Summary

A model material, glass ballotini, has been used to investigate the influence of surface hydrophobicity, binder type and concentration on granule properties. Distribution of the binder solutions was found to be independent of the surface properties of the glass. The mixing process was clearly sufficient to spread the material over a hydrophobic surface and the binder properties suitable to prevent "dewetting". Differences in the adhesion of the dried binder to the glass surfaces were observed and these differences influenced granule size distribution, binder concentration, friability and resistance to crushing.

Introduction

The function of the binding agent used in granulation is primarily to maintain the integrity of the granules prior to compression. However, it has been shown (Seager et al., 1979, 1981; Rue et al., 1980) that the distribution of the binding agent within the granule not only controls the intragranular particulate adhesion, but also the intergranular bonding achieved during tabletting and hence the resultant tablet properties, such as tensile strength, disintegration and dissolution. Although much research has been carried out on the individual processes of granulation and compression, there has been little work linking the two processes and examining the influences that the binding agent can have on the tabletting process and the resultant tablets.

The object of this study was to examine the relationship between the properties of the binding agent and the process mechanisms of granulation and compression. To isolate the role of the binding agent from other complicating factors, glass spheres were chosen as a model system for this study since they are insoluble, non-porous and of uniform sphericity.

Materials and Methods

Materials

Lead glass ballotini (Dragonit 30, Grade 20, Englass Ltd., Leicester, U.K.) with a size range of 0–60 μm were used. Size fractionation of this material was performed using a zig-zag classifier (Multi-Plex 100MZR, Alpine Ltd., Augsburg,

Correspondence: J.T. Fell, Department of Pharmacy, University of Manchester, Manchester M13 9PL, U.K.

F.R.G.) to give size fractions of mean size 26 and 40 μm, standard deviations 7 and 8 μm (by microscopy) respectively for batches I and II.

The binding agents used were: polyvinylpyrrolidone (PVP), weight-average molecular weight 25,000 (Kollidon 25, B.A.S.F., Ludwigshafen, F.R.G.); hydroxypropylmethylcellulose (HPMC), low viscosity grade (Methocel E15, Colorcon, Orpington, U.K.); hydrolysed gelatin, average molecular weight 10,000–12,000 (Byco C, Croda Foods, Widnes, U.K.).

Granulation

Prior to granulation the ballotini were cleaned using a 1% v/v solution of a water soluble detergent (Decon 90, Decon Labs., Hove, U.K.) followed by rinsing in 10 changes of distilled water. This method was chosen in preference to chromic acid which gave rise to a precipitate on the glass surface which could not easily be removed. A sample of the ballotini were rendered hydrophobic by treatment with dimethylsilane following the method of Mohammad and Fell (1982). 500 g of the glass beads (batch II) were premixed with the dry binder for 2 min in a small Z-blade mixer (Winkworth Ltd., Staines, U.K.) 40 ml of distilled water was added at a constant rate of 20 ml/min with the mixer running, and mixing was continued for 3 min after all the liquid had been added. A 20 ml volume was used for Byco as the larger volume of liquid produced a paste. The damp granules were passed through a 1180 μm screen on an oscillating granulator (Jackson, Crockatt, Glasgow, U.K.), dried at 60°C for 2 h in a hot air oven, and rescreened after cooling through the same size of screen. Samples of the granules were stored at 44% relative humidity at 25°C.

Granule size distribution

This was determined by sieve analysis using a sieve shaker (Rotap, Pascall Eng., Crawley, U.K.) and a sieving time of 5 min which was sufficient to effect separation without causing breakdown of the granules.

Granule friability

A 5 g sample of granules of the 1000–1180 μm size fraction was placed in a friabilator (Erweka, Offenbach, F.R.G.) and tumbled for 5 min at 30 rpm. The percentage loss in weight was recorded. These granules were stored at 12% R.H. to maximize differences between the binding agents.

Resistance to crushing

This was determined using a direct shear apparatus (E.L.E. Ltd., Hemel Hempstead, U.K.) modified to measure small loads in compression (Reading and Spring, 1984). Twenty granules of the 1000–1180 μm size fraction were individually crushed and the load to cause each granule to fail completely was taken as the resistance to crushing.

Binder content analysis

The binder concentrations in the various granule size fractions were determined by the following methods: PVP was determined by the method of Muller (1968), HPMC by a method based on that used for dextrans (British Veterinary Codex, 1965), and Byco by the method of Lakin (1978).

Results

The reproducibility of the granulation procedure was checked by preparing 4 replicate batches. The means and standard deviations of the size distributions are given in Table 1. Satisfactory

TABLE 1

THE VARIABILITY OF 4 BATCHES OF GRANULES PRODUCED USING THE DEFINED GRANULATION METHOD

Granule diameter (μm)	% Weight in size fraction	
	Mean	Standard deviation
< 125	16.1	2.5
125– 250	6.5	1.1
250– 355	4.9	1.2
355– 500	5.8	1.6
500– 710	5.0	1.0
710–1000	9.0	1.4
1000–1180	52.6	2.2
Mean granule friability (%)	5.60	0.58

Hydrophilic glass; 3% w/w PVP K-25; 40 cm^3 distilled water as granulating fluid.

reproducibility was obtained and this allowed single granulations to be used for the remainder of the work.

Binder type and concentration

Table 2 shows the effect of binder type and concentration on the mean granule size. There is a general increase in diameter with an increase in binder concentration. The size and mechanical properties of the granules are dependent on the distribution of the binder, both in the different size fractions, and at a microscopic level on the surface of the glass. The distribution of binder, even in such an ideal system of spherical, insoluble particles cannot be assumed to be uniform with respect to granule size. The distribution of binder in the various size fractions of the granules is illustrated in Fig. 1. HPMC granules showed a variation in binder content with granule size and a deficiency of binder in the smaller granules and fines, whereas PVP was only slightly deficient in the fines. Byco was distributed evenly amongst the granule size fractions (notable as only half the quantity of granulating fluid was used for these granulations).

The friabilities of the granules are shown in Fig. 2. An increase in binder concentration from 1.5 to 3% w/w decreased the friability of both the HPMC and Byco granules. The PVP granules were considerably less friable than the other granules at the lowest binder concentration, and increasing the concentration had little effect on their friability. Resistance to crushing results are shown in Fig. 3. The variation between individual results was high, nevertheless an increase in binder concentration produced an increase in the resistance to crushing of granules prepared from all 3 binders.

TABLE 2

THE EFFECTS OF CONCENTRATION AND TYPE OF BINDING AGENT ON THE MEAN DIAMETER OF GRANULATED GLASS BALLOTINI

Binder type	Binder concentration (% w/w)		
	1.5	3.0	4.5
PVP	718	1010	1015
HPMC	437	515	300
Byco	245	1002	1016

Values are in μm.

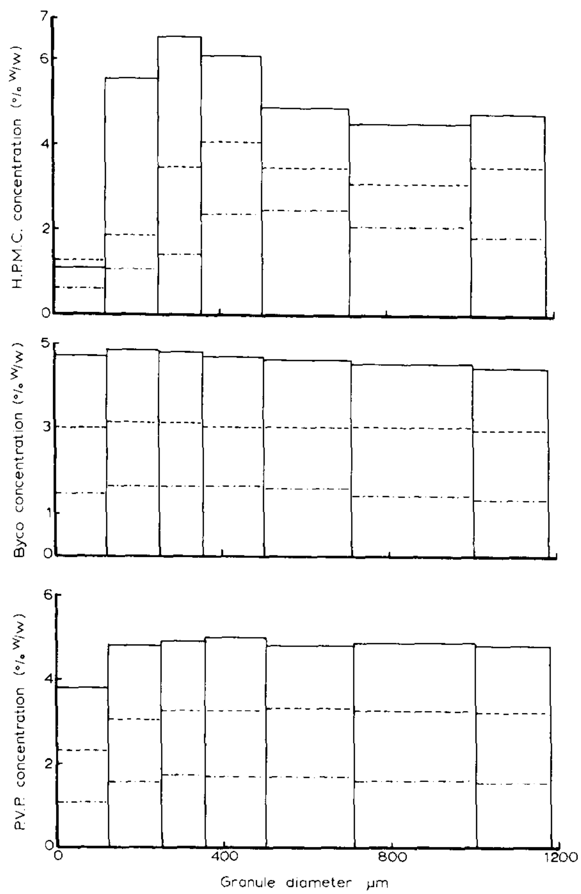

Fig. 1. The effect of binder concentration on the distribution of binders throughout the granules. ·–·–·, 1.5% w/w; - - - - - -, 3.0% w/w; ———, 4.5% w/w.

Wettability of the glass spheres

Granules were prepared from the glass spheres (batch I) which were either cleaned (hydrophilic), or cleaned and then treated to render them hydrophobic. Contact angles, against water, of ballotini that had been melted to form smooth surfaces and then treated in the same manner as the beads, gave results of 25° and 101° respectively. PVP was used as the granulating agent, and in this experiment only it was added as a 35% w/w aqueous solution (to give a total binder concentra-

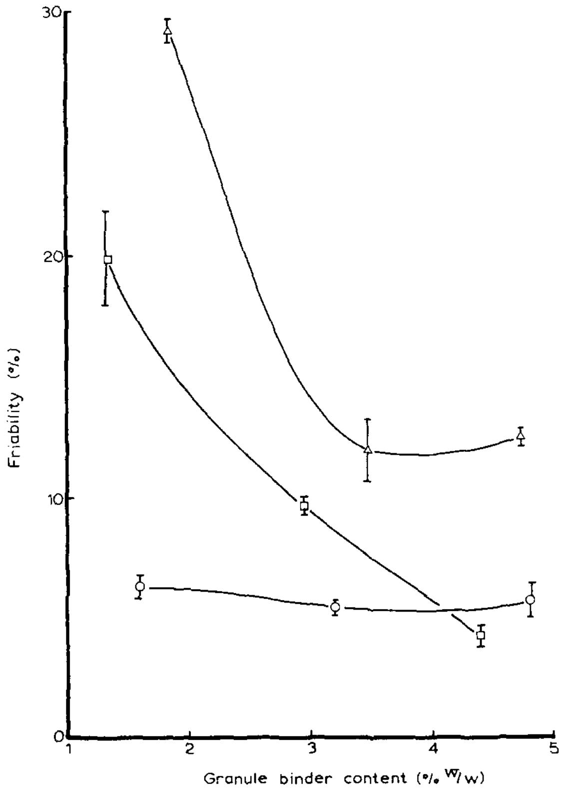

Fig. 2. The effects of concentration and type of binding agent on the friability of glass granules. △, HPMC; ○, PVP; □, Byco. Bars indicate 1 S.D.

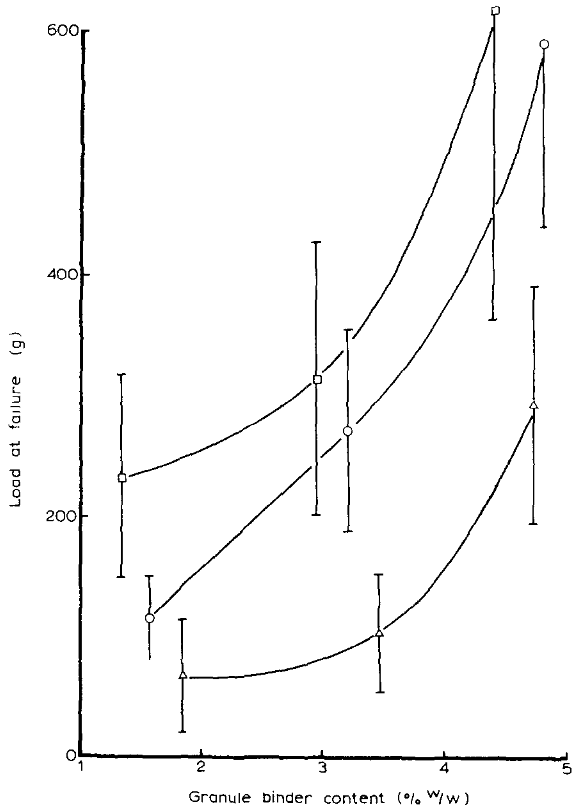

Fig. 3. The effects of concentration and type of binding agent on the resistance to crushing of the granules. Key as in Fig. 2.

tion of 2.72% w/w in the dried granules).

The granule size distributions are shown in Fig. 4. There was a higher proportion of small granules formed from the hydrophobic glass beads. The mean granule sizes for the hydrophilic and hydrophobic granulations were 295 and 195 μm respectively. Binder distribution throughout the various

TABLE 3

THE EFFECT OF WETTABILITY OF GLASS BEADS ON THE DISTRIBUTION OF PVP BINDER THROUGHOUT THE DRIED GRANULATE

Granule size fraction (μm)	Mean concentration of PVP (% w/w)	
	Hydrophilic glass	Hydrophobic glass
< 125	2.45	2.47
125–250	2.68	2.73
250–355	2.78	2.79
355–500	2.85	2.97
500–710	2.80	2.79
710–1000	2.76	2.77
1000–1180	2.80	2.80

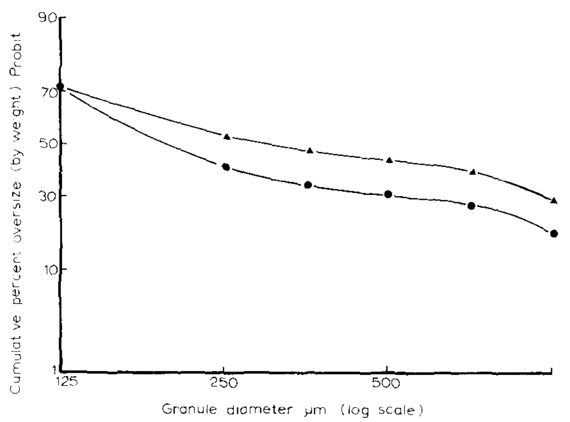

Fig. 4. The effect of wettability of the glass beads on the granule size distribution. ▲, hydrophilic; ●, hydrophobic.

TABLE 4

THE EFFECTS OF WETTABILITY OF GLASS BEADS ON THE MECHANICAL PROPERTIES OF GRANULES FORMED USING 2.72% w/w PVP BINDER

Glass surface	Granule friability (%)	Granule strength (load at failure, g)
Hydrophilic	5.18 (1.43)	202 (69)
Hydrophobic	13.78 (4.69)	115 (47)

Values are means (± S.D.).

granule size fractions is shown in Table 3. The distribution of PVP was independent of the nature of the substrate.

The friabilities of the granules and their resistance to crushing are shown in Table 4. Granules prepared from the hydrophilic glass were more resistant to crushing and less friable than those produced from the hydrophobic glass.

Discussion

During wet granulation, the binder fluid is distributed over the surface of the particles. A uniformly distributed binder is preferred, to optimise bonding and hydrophilisation of hydrophobic constituents and also to promote granule strength. However, the occurrence of agglomeration will influence the binder distribution and result in variations in binder content uniformity. In normal circumstances, spreading of fluids on hydrophobic surfaces would be limited. In the granulation process, however, spreading will be encouraged by the shearing action of the mixer and the (normally) low surface tension of the binder fluids. Once spread, whether the fluid will drain away from the surface will depend on a variety of factors including the viscosity and the contact angle. On drying, the binder will form bonds between the particles. The strength of these bonds and the adhesion of the binder to the particles will determine the amount of attrition that occurs during the dry screening stage and the friability and the resistance to crushing of the granules. Storage conditions after this screening will also influence these latter properties. The use in this study of an inert insoluble material for granulation, glass ballotini, enables the influence of the binding agent to be examined separately.

Increased binder concentration leads to an increase in mean granule size (Table 2) increased resistance to crushing (Fig. 3) and a lower friability (Fig. 2). This is in keeping with the results of other workers (Chalmers and Elworthy, 1976; Harwood and Pilpel, 1968; Hunter and Ganderton, 1972). An increase in binder concentration strengthens bonds between the glass spheres as there is more binder per bond since the liquid volume was held constant. Failure of the binder during dry screening and in the mechanical tests may occur within the binder bonds or at the binder–particle surface. Binder distribution during granulation appears not to be a problem as can be seen from the coating achieved on the hydrophobic beads (Fig. 5). However, this photograph illustrates the poor adhesion of the binder (PVP) to the hydrophobic beads as compared to the hydrophilic ones, where failure occurs within the binder (Fig. 6). Hence granules from the hydrophobic beads exhibit a lower mean granule size, lower resistance to crushing and a higher friability than the comparable hydrophilic granules.

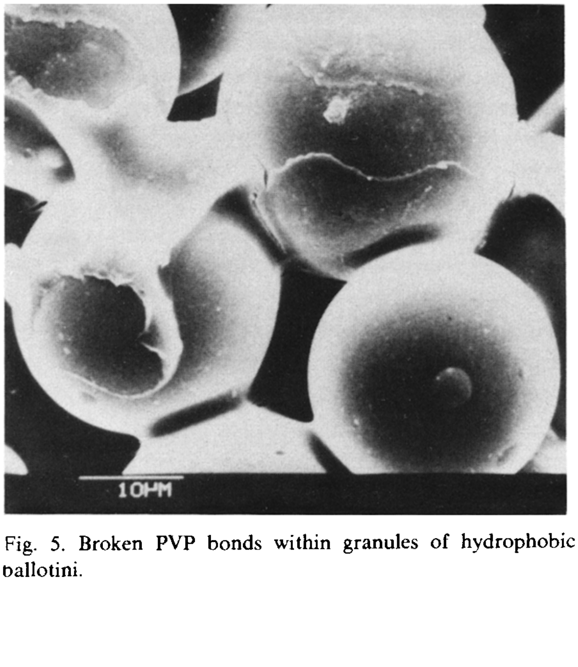

Fig. 5. Broken PVP bonds within granules of hydrophobic ballotini.

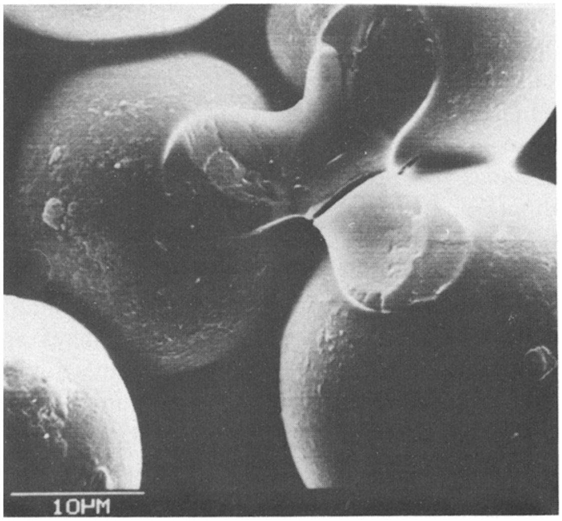

Fig. 6. Broken PVP bonds within granules of hydrophilic ballotini.

The properties of the granules prepared from the 3 binders may be explained in a similar manner. Major differences in binder distribution are unlikely to occur (see above) so that prior to dry screening, the granules will be in a similar state. Subsequent behaviour will depend on the strength of the adhesive and cohesive bonds. Inspection of Fig. 7 shows that HPMC tends to fail due to poor adhesion of the binder to the glass. Byco and PVP appear to adhere more strongly and failure occurs within the bond (Figs. 6 and 8). This may account for the lower resistance to crushing and higher friability of the HPMC granules and their lower mean granule size. Failure at the surface rather than within the bonds will also account for the lack of correlation between binder concentration and mean granule size for this material. Similarly, the low concentration of HPMC in the sub-125 μm granules may be explained by the poor adhesion of HPMC to glass. During granule attrition, the outermost glass beads detach from the granule by surface fracture thus leaving the larger granules binder rich.

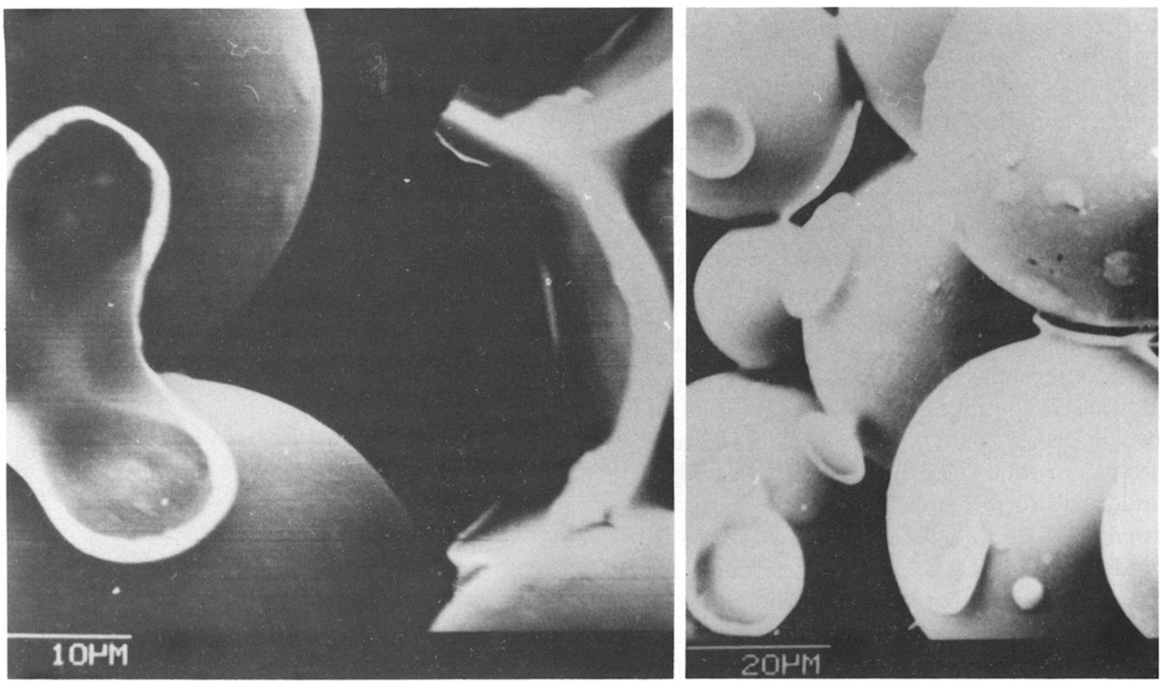

Fig. 7. Broken bonds in granules using HPMC (3% w/w).

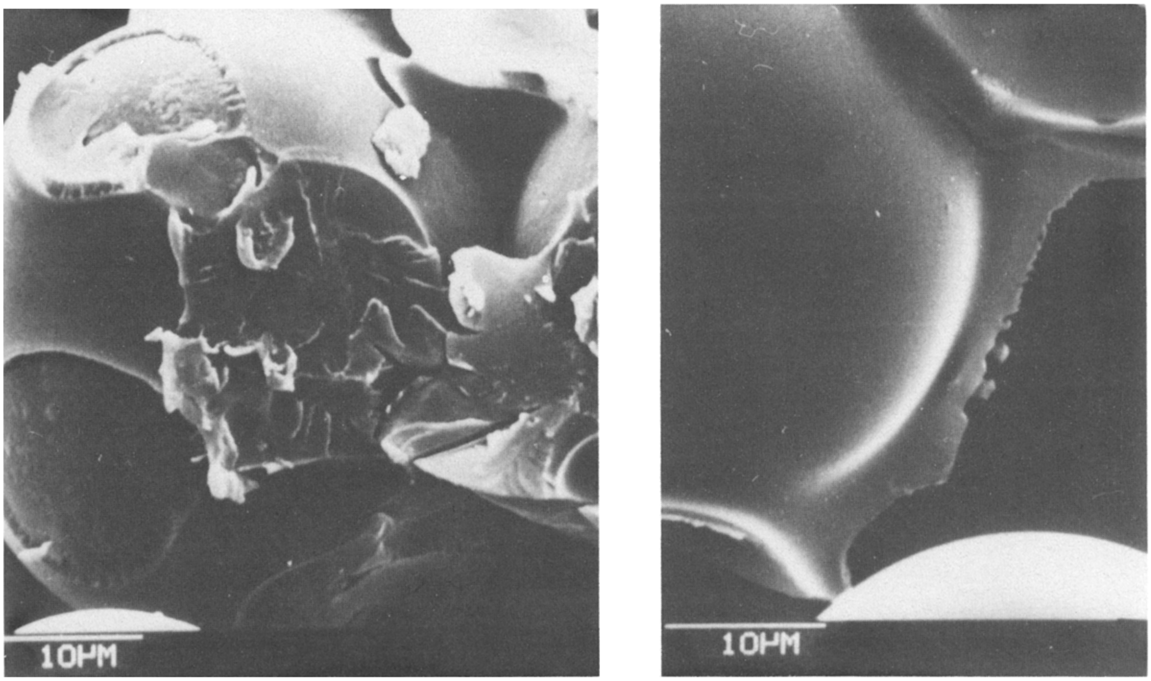

Fig. 8. Broken bonds in granules using Byco (3% w/w).

References

British Veterinary Codex 2nd edn., London Pharmaceutical Press, 1965, p 203.

Chalmers, A.A. and Elworthy, P.H., Oxytetracycline tablet formulations: effect of variations in binder concentration and volume on granule and tablet properties. *J. Pharm. Pharmacol.*, 28 (1976) 228–233.

Harwood, C.F. and Pilpel, N., Granulation of griseofulvin. *J. Pharm. Sci.*, 57 (1968) 478–481.

Hunter, B.M. and Ganderton, D., The effect of particle size on the granulation of lactose by massing and screening. *J. Pharm. Pharmacol.*, 24 (1972) Suppl., 17P-24P.

Lakin, A.L., Determination of nitrogen and estimation of protein in foods. In King R.D. (Ed.) *Developments in Food Analysis Techniques*, Applied Science Publishers, London, 1978, pp. 43–74.

Mohammad, H.A.H. and Fell, J.T., Contact angles of powder mixtures consisting of spherical particles. *Int. J. Pharm.*, 11 (1982) 149–154.

Muller, K., Nachweis und bestimmung von P.V.P. sowie bestimmung von wirkstoffen in P.V.P.- haltigen arzneimittelzubereitungen. *Pharm. Act Helv.*, 43 (1968) 107–122.

Reading, S.J. and Spring, M.S., The effects of binder film characteristics on granule and tablet properties. *J. Pharm. Pharmacol.*, 36 (1984) 421–426.

Rue, P.J., Seager, H., Ryder, J. and Burt, I., The relationship between granule structure, process of manufacture and the tabletting properties of the granulated product. Part II. *Int. J. Pharm. Tech. Prod. Mfr.*, 1 (1980) 2.

Seager, H., Burt, I., Ryder, J., Rue, P.J., Murray, S., Beal, N. and Warrack, J.K., The relationship between granule structure, process of manufacture and the tabletting properties of the granulated product. Part I. *Int. J. Pharm. Tech. Prod. Mfr.*, 1 (1979) 36–42.

Seager, H., Rue, P.J., Burt, I., Ryder, J. and Warrack, J.K., The relationship between granule structure, process of manufacture and the tabletting properties of the granulated product. Part III. *Int. J. Pharm. Tech. Prod. Mfr.*, 2 (1981), 41–50.