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Determination of size distribution of lactose, glucose and mannitol granules by sieve analysis and laser diffractometry

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Summary

The granule size distributions of three tablet excipients, lactose, glucose and mannitol, were studied. The granules were produced in a high-shear granulator, and granule size was determined by both sieve analysis and laser light diffractometry For all excipients, the granule size increased with increase in the amount of granulation liquid. Both the shapes and the size distributions of granules produced from the three excipients differed, and the results of the two methods for determining granule size also clearly differed. Due to the low measuring range of laser light diffractometry, sieve analysis appeared to be a more reliable method for measuring mean size and size distribution of granule samples.

Introduction

Due to its good compactibility and low price, lactose is commonly used as an excipient for tablet formulations. However, because lactose intolerance is rather common, there has been pressure to replace lactose with some other excipient. The frequency of lactose intolerance varies among populations and the degree of lactose intolerance also differs in different individuals. Bedine and Bayless (1973) observed that with only 3 g of lactose, 10% of the lactose-intolerant individuals studied had symptoms, and with 12 g of lactose, 75% had symptoms. Lactose in pharmaceutical formulations produces an extra strain on the lactose-intolerant patients. Therefore, it is important to study possible excipients that could be substituted for lactose in oral solid formulations.

Glucose and mannitol are both used as tablet excipients, so far mainly in chewable tablets. Glucose is highly soluble (1:1) in water and also tastes good. Mannitol dissolves slowly in chewable formulations and produces a pleasant feeling in the mouth. The water solubility of mannitol is similar to that of lactose: 1 g of lactose or mannitol dissolves in 6 g of water. Mannitol, however, is known to have poor flow characteristics and is relatively expensive.

The aim of this study was to compare three tablet diluents: lactose, glucose and mannitol.

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Mannitol was chosen for this study because it has the same solubility as lactose and thus would be expected to behave similarly in the granulation process. On the other hand, glucose was chosen because of its greater solubility in water, which may result in granule properties that differ from those of lactose granules. Several investigations have been performed on granulation of lactose (Lindberg and Jönsson, 1983; Holm et al., 1985; Schæfer et al., 1986) but only rarely has the granulation of glucose or mannitol been studied. In addition, these three excipients have not previously been compared thoroughly.

Granule size and size distribution are probably essential properties of granules, for example, with regard to compactibility, flowability and weight variation of tablets (Marks and Sciarra, 1968; Kassem et al., 1972). Sieve analysis has frequently been used for determining granule size distribution. In addition to this traditional method, laser diffraction measurements, which are rapid and reproducible, have recently become more popular for determination of size distribution. Therefore, the second purpose of this study was to determine how the amount of granulation liquid affects granule size and granule size distribution, as determined by both sieve analysis and laser light diffraction based on Fraunhofer diffraction.

Materials and Methods

Granulation

Granules were produced from α-lactose monohydrate (EP D 80, Meggle Milchindustrie GmbH, Germany), anhydrous α-glucose (Suomen Xyrofin Ltd, Finland) and D-(−)-mannitol (Merck, Germany) using a high-shear granulator, Fielder PMA 25/2G (T.K. Fielder Ltd, U.K.). Theophylline monohydrate (Böhringer Ingleback-mitter, Germany) was used as a model drug for further dissolution tests. The concentration of theophylline was 2% of the diluent. The median particle size as determined by laser diffractometry was 20 μm for lactose, 240 μm for glucose, 27 μm for mannitol and 30 μm for theophylline. The binder solution used was a 20% polyvinylpyrrolidone (Kollidon® K25) solution in distilled water. The binder solution was added at a speed of 150 ml/min to the three final amounts of 90, 105 and 120 ml/kg. The batch size was 5 kg. In order to evaluate the reproducibility of the granulation process, lactose granules were produced in duplicate with 120 ml/kg of binder solution. After granulation the granules were forced through a 2 mm sieve with an oscillator (Erweka FGS, Erweka Apparatebau GmbH, Germany). Granules were dried on trays at room temperature for at least 48 h, and the granule size distributions of these granules were measured. Other granule properties were determined from the sieved granule size fraction that was under 2 mm in diameter.

Granule size and shape

Granule size distributions were determined both by sieve analysis and by the laser diffraction method. The sieves used had mesh sizes of 75, 106, 150, 300, 425, 600, 1000, 2000 μm (F. Kurt Retsch GmbH & Co., Germany). Samples of dried granules (20 g) were vibrated for 12 min at a frequency of 70 Hz (Retsch Vibro VM 1, F. Kurt Retsch GmbH & Co., Germany). All tests were made in triplicate. The granule size distributions and the mean granule diameters were calculated according to the method of Meshali et al. (1983).

A Malvern 2600 C particle sizer laser diffractometer (Malvern Instruments, U.K.) was also used to measure granule size distribution. The focal length was 1000 mm and the active beam length 13 mm. A 14 mm beam expander was used. The granules were suspended in the air during measurement and were measured in triplicate. The median and the 10 and 90% fractiles of the size distributions were also determined using a model-independent method. Data were also fitted to the Rosin-Rammler, logarithmic normal, normal and model-independent models, and the values for logarithmic differences were calculated according to the formula

$$\text{log difference} = \log \sum_{j=1}^{n} (\text{light calculated}_j - \text{light measured}_j)^2 \quad (1)$$

where n is the number of size classes (Malvern, 1986).

To investigate the shape of the granules, scanning electron micrographs were taken using a Jeol JSM-840A scanning electron microscope (Japan).

Results and Discussion

Sieve analysis

The effect of the amount of granulation liquid is seen clearly in the granule size distributions determined by sieve analysis (Fig. 1a–c). Mean granule size increased with increasing amount of granulation liquid, and the amount of granulation liquid affected the granule size of all excipients studied. Opakunle and Spring (1976) previously found that the total volume of binder solution strongly affected the average size of the granules. In addition, they reported that at a concentration of 4–6%, the amount of polyvinylpyrrolidone dissolved in granulating solvent contributed slightly to granule size. In the current study, the concentration was higher: 20%. Therefore, both the concentration of polyvinylpyrrolidone and the amount of liquid would have affected the granule size. Nevertheless, with this experimental design, it is not possible to distinguish between the influence of the binder and that of the amount of solvent.

The size distributions found for lactose granules were broad and rather symmetrical. The largest sieve fraction was 150–300 μm. The size distributions for glucose granules were narrower than those for lactose, and the proportion of granules under 150 μm in diameter was very small. The amount of granulation liquid affected the size of glucose granules most, due to the high water solubility of glucose and recrystallization during drying.

The shapes of size distributions for mannitol granules clearly differed from those of the other fillers. Two separate peaks can be seen for mannitol, one at the large size fraction and another at the small size fraction. With an increased amount of granulation liquid, the proportion of larger granules increased. The bimodality of the size

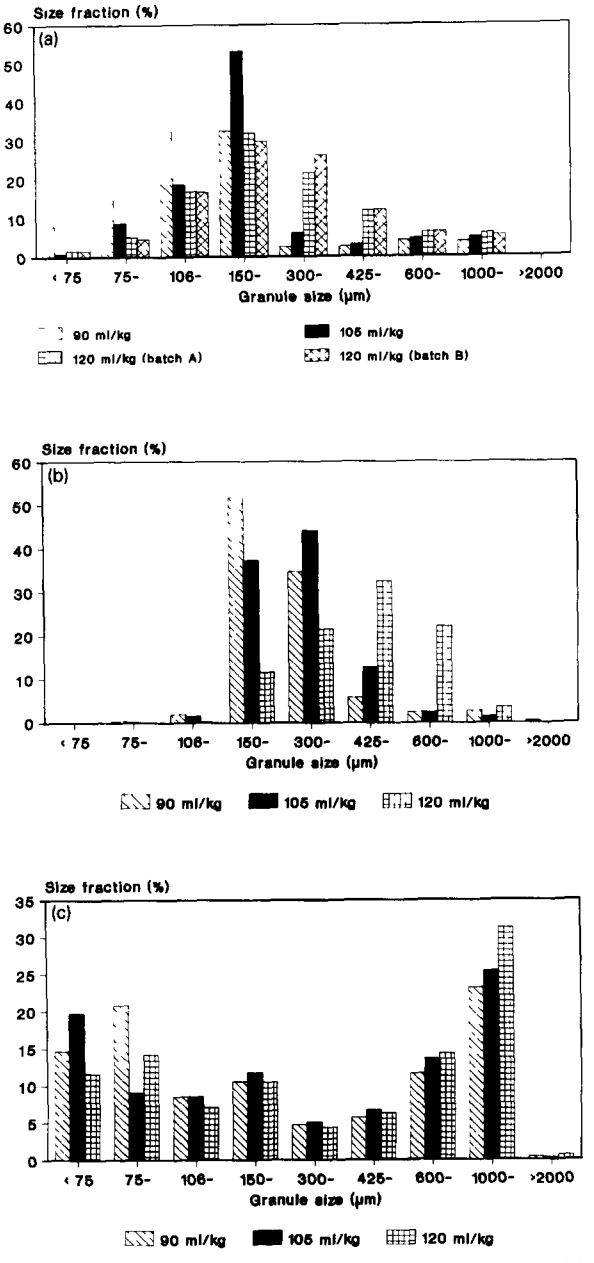

Fig. 1. Granule size distributions of lactose (a), glucose (b) and mannitol (c) granules determined by sieve analysis. Batches A and B were replicates.

distributions of mannitol granules can be explained by the poor wettability of mannitol. However, the shape of the distribution, for example, bimodality, is dependent on the sieve sizes used.

TABLE 1

Median and 10 and 90% fractiles of granule size distributions determined with laser diffractometer (n = 3)

Diluent	Amount of granulation liquid (ml/kg)	Median (μm)		Fractile 10% (μm)		90% (μm)	
		Mean	S.D.	Mean	S D.	Mean	S D.
Lactose	90	160	6	66	2	910	210
	105	220	7	84	1	840	340
	120	380	41	120	9	910	170
	120 [a]	400	8	140	1	880	190
Glucose	90	340	17	230	11	650	32
	105	410	27	270	21	740	64
	120	650	31	350	11	1110	230
Mannitol	90	420	190	55	21	1360	150
	105	550	160	65	18	1440	10
	120	760	210	78	7	1480	42

[a] Replicate batch

Theophylline is probably easier to wet than mannitol, because when mannitol is dry it is electrically charged. During the granulation process, theophylline works as a granulation nucleus, around which mannitol particles adhere or partly dissolve and recrystallize. As a result, large lumps and granules are formed, and the rest of the mannitol particles remain separate or form small granules.

Laser diffractometry

The results from the laser diffractometer are presented in Table 1 and Fig. 2. According to the median and fractile values, the effect of the amount of granulation liquid was similar to that found in the sieve analysis.

The shapes of the granule size distributions found with laser diffractometry were similar to those with sieve analysis, except that the slight bimodality of the mannitol granule size distribution was not observed. The electrical charge of mannitol granules and their cohesiveness during suspension of the granules in the air may have affected the determination. In addition, the laser diffractometer results should generally be viewed with caution, since the measurements were carried out near the upper limit of the measurement range, which may distort the results.

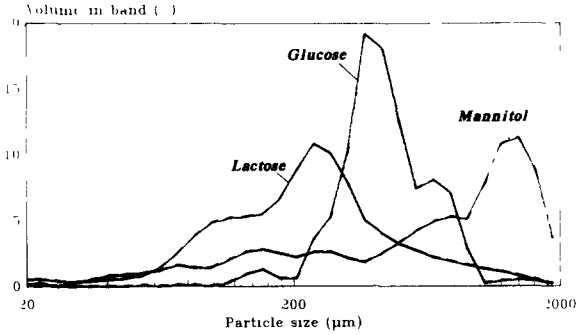

Fig 2 Granule size distributions of lactose, glucose and mannitol granules determined by laser light diffractometry. The amount of granulation liquid was 105 ml/kg.

According to the model fittings for granule size distributions (Table 2), the smaller the value for the logarithmic difference, the better was the fit to the model. Logarithmic differences less than 5 indicated a good fit (Malvern, 1986). Distributions of pharmaceutical powders commonly show a good fit to the logarithmic normal model. However, the lactose and glucose granule size distributions also fitted the Rosin-Rammler model very well (Table 2). The size distribution for glucose granules also fitted the normal model

TABLE 2

Model fittings of granule size distributions

Diluent	Amount of granulation liquid (ml/kg)	Log difference			
		Rosin-Rammler	Log normal	Normal	Model independent
Lactose	90	4.48	4 48	5 66	4.46
	105	4 73	4.01	5.94	3.85
	120	5 26	4.85	6 27	4 09
	120 [a]	4.99	4.62	6 28	4 49
Glucose	90	4.08	4.46	4 06	4 25
	105	3.83	5.02	3 72	4 32
	120	3.72	4 50	4.38	2 75
Mannitol	90	5.28	5.55	6.50	3.65
	105	5.22	5 81	6.58	3.10
	120	5.35	5.37	6.41	3 70

[a] Replicate batch.

well, which is rarer for pharmaceutical materials. Due to their broadness and to possible bimodality, the size distributions for mannitol granules did not fit any model other than the independent model, which is the unknown 'black box' model constructed in the apparatus by the supplier.

Comparison of sieve analysis and laser diffractometry

From the median granule size measured by laser diffractometry and the mean granule diameter calculated according to Meshali et al. (1983), it can be seen that the order of the granules differed (Figs 3 and 4). For all three types of granules the median values were higher than the mean granule diameter. Mannitol granules had the largest medians because of their broad distribution and the high proportion of larger granules (Fig. 3). Glucose granules had the second largest medians and mannitol granules the smallest. On the other hand, the mean granule diameters of glucose granules seemed to be largest at all levels of granulation liquid (Fig. 4). No clear difference was observed between lactose and mannitol granules.

We conclude that depending on the method used to determine the granule size, the results may be inconsistent. The granule size distributions determined by laser diffractometer and sieve analysis clearly differed from each other. According to these results, the measuring range of the laser diffractometer seemed to be too low to give

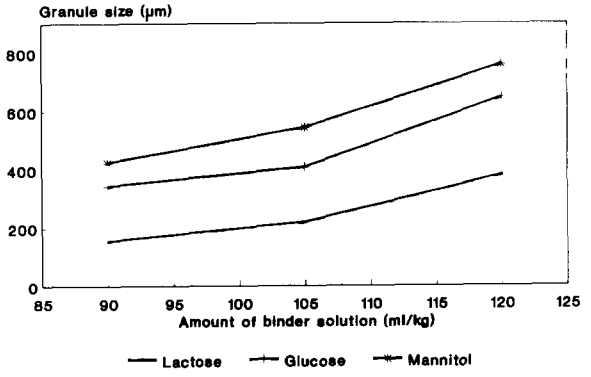

Fig 3. Effect of amount of granulation liquid on the median size of lactose, glucose and mannitol granules determined by laser light diffractometry

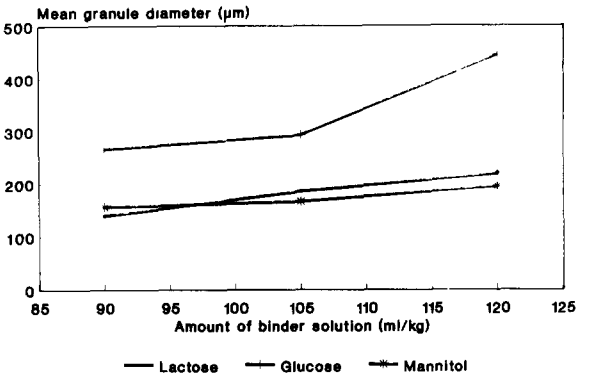

Fig. 4. Effect of amount of granulation liquid on the mean granule diameter of lactose, glucose and mannitol granules. Mean granule diameter was calculated from sieve analysis results according to the method of Meshali et al (1983)

reliable results for granule samples. Thus, of these two methods, sieve analysis is the more reliable method of measuring granule size and size distribution.

Shape of the granules

As seen in the scanning electron micrographs, the size of the granules increased with increasing amount of granulation liquid (Figs 5–7). Lactose granules became more spherical as greater amounts of granulation liquid were added (Fig. 5a, b). The lactose particles seemed to retain their shape and integrity during granulation and thus form an aggregate.

The glucose granules consisted of separate particles and crystals, which were attached to each other forming an aggregate (Fig. 6a, b). With an increasing amount of granulation liquid, the number of glucose particles per granule increased but their size decreased, resulting in a larger granule. With 120 ml/kg, these small particles had even fused together and formed a granule that was nearly round. As observed previously with sieve analysis, it was confirmed from scanning electron micrographs that the size distribution for mannitol granules is broad (Fig. 7a, b). The large granules were angular and elongated.

Comparison of granules

Due to their high water solubility, glucose particles readily formed the largest aggregates with

all the amounts of binder used. Although in this study glucose was easy to granulate, it should be noted that in practice granulation of glucose is difficult to control, due to the high water solubility and hygroscopic nature of glucose. The surface of the primary particles in the glucose gran-

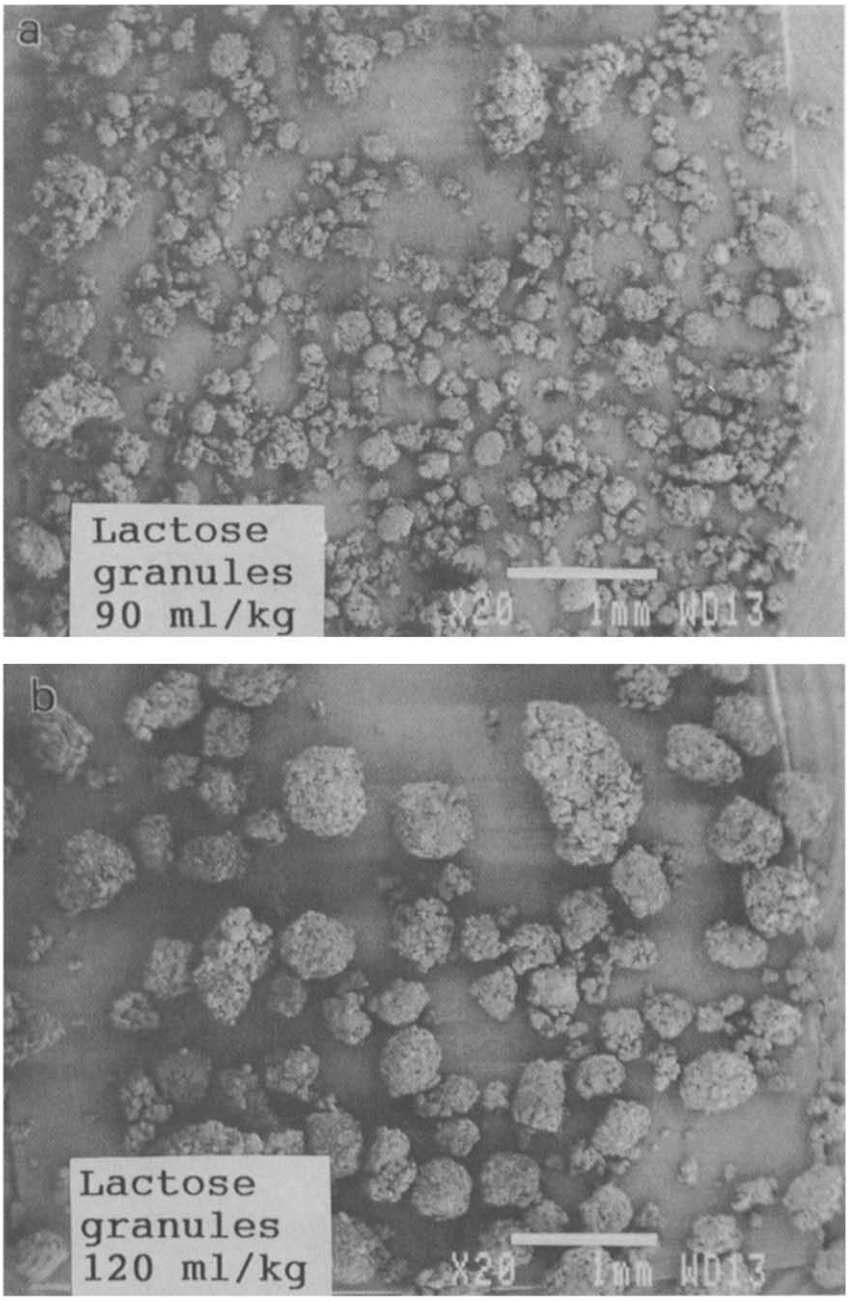

Fig. 5 Scanning electron micrographs of lactose granules Amount of granulation liquid· (a) 90 ml/kg and (b) 120 ml/kg. Bar, 1 mm

ules was rather smooth but the granules themselves were irregular. Since, in addition to a smooth surface, the size distribution of glucose granules was narrow, these granules can be expected to have good flowability.

Unlike lactose, mannitol is known to be an

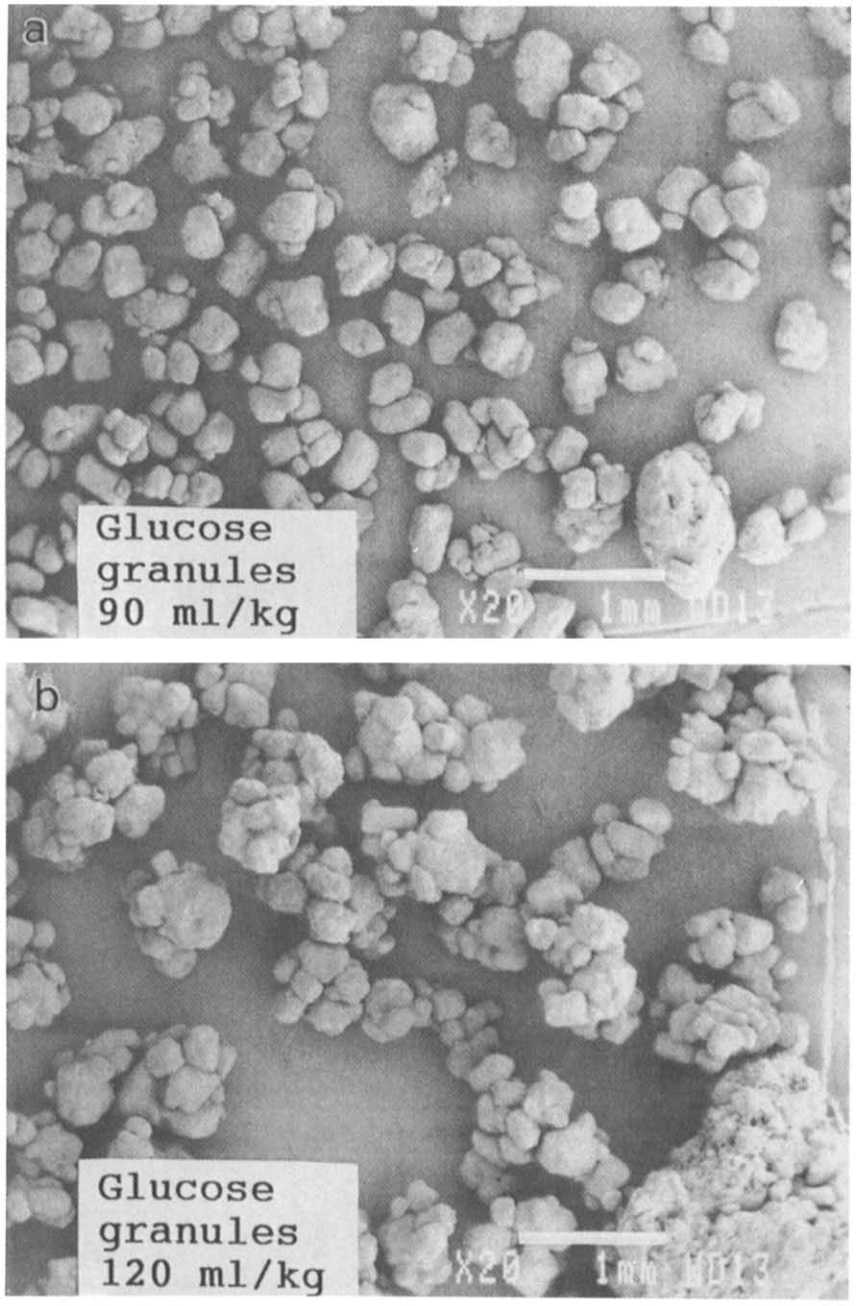

Fig. 6. Scanning electron micrographs of glucose granules. Amount of granulation liquid: (a) 90 ml/kg and (b) 120 ml/kg. Bar, 1 mm.

electrically charged and cohesive powder, which probably results in its poorer wettability. This might explain the angular shape of mannitol granules and the broad size distribution. The size distributions and shapes of lactose and mannitol granules differed from each other even though

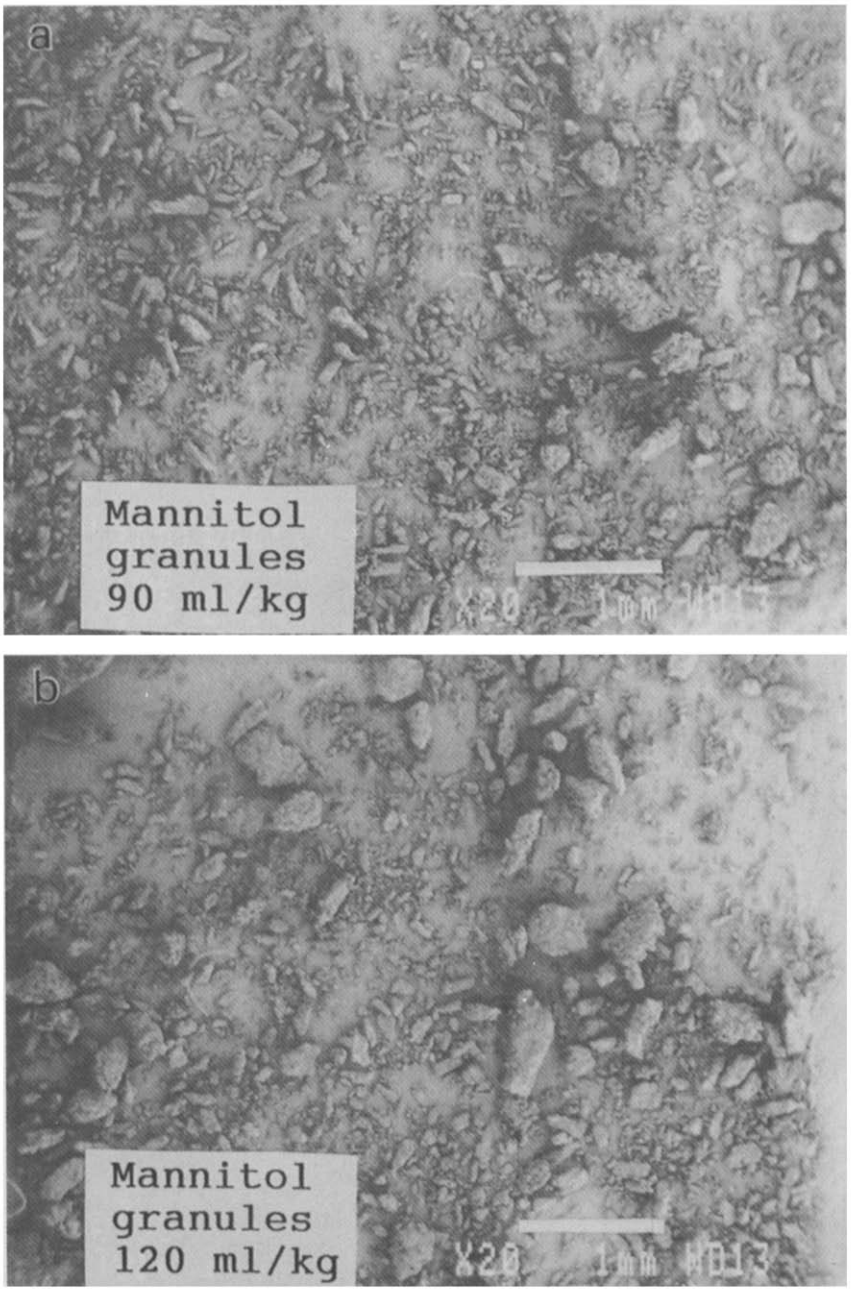

Fig. 7 Scanning electron micrographs of mannitol granules. Amount of granulation liquid: (a) 90 ml/kg and (b) 120 ml/kg. Bar, 1 mm.

lactose and mannitol have similar water solubilities. The mannitol granules produced also had a relatively strong static charge. This may decrease the flowability of the mannitol granules. On the other hand, it is assumed that the broad size distribution may result in good compactibility.

Without knowing the ultimate purpose for which the granules are to be used, it cannot be concluded with certainty on the basis of this study which of these granules has the best properties. Nevertheless, both mannitol and glucose are promising alternatives to lactose for use as tablet excipient. Further investigations, including compression studies, are needed.

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