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CHANGES IN THE PARTICLE SIZE AND SIZE DISTRIBUTION DURING COMPACTION OF TWO PHARMACEUTICAL POWDERS WITH DISSIMILAR CONSOLIDATION MECHANISMS

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ABSTRACT

Five different size fractions (32-44 um, 53-63 um, 75-90 um, 105-124 um, and 124-177 um) of heavy magnesium carbonate and Avicel PH102 were compressed into 12.5 mm diameter compacts by means of a hydraulic press at two pressures. Compacts of the 75-90 um fraction of both substances and their binary mixtures in three different ratios were also prepared at eight different pressures. The subsequent compacts were disintegrated by sonication, and the size of the resultant particles analysed.It was found that the median particle diameter of both powders and disintegrated compacts was affected by sonication time and by the amount of water present in the ultrasonic bath. However a standard method was established.

The results showed that the particle size of the disintegrated compacts might be affected by both the initial particle size and the differences in the consolidation mechanisms of these two substances. However changes in the particle size of the binary mixtures are dependent on the relative concentration and the consolidation mechanism of the components in the mixtures.

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INTRODUCTION

The importance of changes in particle size and size distribution during the compression of pharmaceuticals has been recognized but the data shown in the literature are not always consistent [1,2]. This might be due to the use of different methods to recover the constituent particles of the disintegrated compacts, though experimental detail is lacking in both papers.

In a study of the changes in particle size distribution of sulphathiazole powder during tabletting, Carless & Sheak [3] showed that the bigger sizes are crushed, the fines are agglomerated and the intermediate sizes are not significantly affected. They postulated that there is a critical particle size when the effects of crushing and agglomeration cancel each other out, and this for sulphathiazole was 76 um. They also suggested that the critical size for a brittle compound is likely to be lower than that for a more deformable material.

Preceding studies in these laboratories [4,5] showed that magnesium carbonate consolidates by fragmentation, whereas Avicel PH102 consolidates both by fracturing and by plastic and elastic deformation. Thus magnesium carbonate is a comparatively more brittle compound, and Avicel PH102 is a more deformable substance. Accordingly, these two materials were chosen for the present study.

MATERIALS

Heavy magnesium carbonate B.P., magnesium stearate, acetone and glycerol, (B.D.H. Chemicals Ltd., U.K.); Avicel PH102 (Honeywell & Stein Ltd., U.K.); Isoton^{R} (1% w/v saline), (Coulter Electronics Ltd., U.K.)

METHODS

Preparation of narrow sieve fractions of powders

Heavy magnesium carbonate and Avicel PH102 were separated by an air-jet sieve (Alpine, West Germany) into five narrow fractions (32-44 um, 53-63 um, 75-90 um, 105-124 um and 124-177 um).

Preparation of mixtures

The required amounts of the 75-90 um fractions of heavy magnesium carbonate and Avicel PH102 were sieved through a 350 um sieve on to paper and mixed for 5 minutes with a spatula. The mixture was then transferred to a 30ml glass vial and tightly closed with a plastic cap. The vial was attached to the outside wall of a plexiglass cube fitted to a motor drive unit (Type AR400, Erweka Apparatebau GmbH, West Germany) and mixed for a further 15 minutes at 30 r.p.m. 3.0 g of each mixture was prepared according to the following proportions by weight; heavy magnesium carbonate : Avicel PH102 = 3:1; 1:1; 1:3.

Preparation of dispersing solution for powders and compacts

Isoton^{R} was saturated with magnesium carbonate and 0.1% sodium azide added to the solution, which was then filtered through a 0.45 um filter membrane (Oxoid Ltd., U.K.).

Preparation of electrolyte

The electrolyte was 1% saline in a 50/50 ratio by volume of glycerol and water saturated with magnesium carbonate. 0.1% w/v sodium azide was added before filtration through a 0.45 um membrane as before.

Preparation of compacts

Compacts weighing 0.5g and 12.5mm in diameter were compressed on a hydraulic press (Model A, Apex Ltd., U.K.); the required pressure was maintained for a constant time of 8 seconds. The die wall, and faces of both upper and lower punches were lubricated with a 5% w/v suspension of magnesium stearate in acetone before the powder was added.

Particle size analysis

Dispersing solution (20 ml) was added to 3.0 g of either powder or compacts in a conical flask.This was then allowed to stand for 20 hours and then placed in an ultrasonic bath (Kerry Ltd., U.K.) containing either 50 ml or 200 ml water for various time intervals, after which samples were removed, diluted with electrolyte, and the particle size distribution determined (Coulter Counter model TA II, Coulter Electronics Ltd., U.K.).

RESULTS AND DISCUSSION

Effect of sonication

The particle size ranges of powders before and after sonication for various time intervals were found to have a log-normal distribution, and so the median particle diameter was used as the particle size parameter. The effect of the amount of water contained in the ultrasonic bath on the size of the particles recovered is shown in Tables 1 and 2. These represent the median particle diameter of the samples which have been agitated in an ultrasonic bath containing 50 ml or 200 ml of water respectively for various time intervals before the particle size distribution of the samples is determined. The median particle diameter of both magnesium carbonate and Avicel PH102 decreased with an increase in sonication time. However the agitation due to sonication was relatively smooth and much more uniform when there was 200 ml of water inside the ultrasonic bath. Hence this volume was used for in all further studies.

To ascertain if sonication had any effect on the particle size of disintegrated compacts as opposed to uncompressed powder, a 3.0 g sample of compacts was subjected to sonication for various time intervals. Table 3 shows that the median diameter of the particles from the compacts also decreases with increase in sonication time.

The results obtained for sonication times of 1 sec and 5 sec respectively do not represent the whole particle population of the samples. Under these conditions, the compacts were not fully disintegrated into their constituent particles, and big loose aggregates could be seen. During sampling, picking up the aggregates must be avoided. However after 30 seconds sonication, no large

TABLE I

Effect of sonication on the median particle diameter (um) of narrow sieve fractions (75-90 um) of magnesium carbonate and Avicel PH102. Mean of six determinations; SD : standard deviation; CV : coefficient of variation. The ultrasonic bath contained 50 ml of water.

	Magnesium carbonate			Avicel PH102		
Sonication Time	Mean (um)	SD (um)	CV (%)	Mean (um)	SD (um)	CV (%)
None	63	2.2	3.5	85	0.8	1.0
1 sec	60	1.5	2.5	82	1.3	1.6
5 sec	55	2.5	4.5	77	3.5	4.5
30 sec	42	4.6	11.0	42	2.0	4.8
1 min	33	1.9	6.1	27	1.7	6.3
2 min	26	5.0	19.0	23	1.3	5.7
5 min	22	2.9	13.6	20	1.0	5.0

aggregates were visible, and the data obtained thereby represent the whole population of the disintegrated compacts.

A 30 sec sonication time was selected as a reasonable length of time, as a small inaccuracy with timing will not give rise to a great effect on the measured value of particle size.

Effect of initial particle size

The changes in the distribution for all the five size fractions of magnesium carbonate and Avicel PH102 before and after compaction

TABLE 2

Effect of sonication on the median particle diameter (um) of narrow sieve fractions (75-90 um) of magnesium carbonate and Avicel PH102. Mean of four determinations. The ultrasonic bath contained 200 ml of water.

	Magnesium carbonate			Avicel PH102		
Sonication Time	Mean (um)	SD (um)	CV (%)	Mean (um)	SD (um)	CV (%)
None	61	1.0	1.6	85	0.8	0.9
1 sec	57	3.4	6.0	84	1.5	1.8
5 sec	50	5.4	11.0	83	0.6	0.7
30 sec	32	1.5	4.5	81	1.2	1.5
1 min	26	2.4	9.2	74	1.6	2.2
2 min	24	1.3	5.4	63	1.9	3.2
5 min	18	2.4	13.3	27	1.8	6.7

are depicted in Figures 1-6. The proportion of particles in the original size fraction is greatly reduced in all cases. Also after compression, particles smaller than the original size can be detected. However the most notable changes are in the proportion of particles greater than the original size. This proportion increases after compression at high pressure.

The effects of initial particle size and compaction pressure on the median particle size of the disintegrated compacts are shown in Table 4. The median particle diameter of all samples is reduced at 65 MNm^{-2}. However, the decrease in the median particle diameter of the finer size fractions (32-44 um and 53-63 um) is much smaller than that

TABLE 3

Effect of sonication on the median particle diameter (um) of disintegrated compacts (65 MNm^{-2}) of magnesium carbonate and Avicel PH102 respectively. Mean of six determinations.

	Magnesium carbonate			Avicel PH102		
Sonication Time	Mean (um)	SD (um)	CV (%)	Mean (um)	SD (um)	CV (%)
None	55	9.6	17.5	84	3.7	4.4
1 sec	38	4.6	12.1	84	1.3	1.5
5 sec	26	3.5	13.5	77	4.6	6.0
30 sec	19	1.0	5.3	63	1.8	3.0
1 min	17	1.8	10.6	42	4.4	10.5
2 min	15	1.3	8.7	36	5.3	14.7
5 min	12	2.1	18.0	27	5.1	18.9

of the coarse fractions (75-90 um, 105-124 um, and 124-177 um) for both magnesium carbonate and Avicel PH102.

Leigh *et al* [6] and Hersey *et al* [7] have suggested that there is a tendency for yield stress to increase with decreasing particle size. Rearrangement is also greater in the case of fine particles [8,9]. This may explain why, although comminution is the main process at low pressure (65 MNm^{-2}), the decrease in the median particle diameter of the finer size fractions is much smaller than that of the coarse fractions for both magnesium carbonate and Avicel PH102.

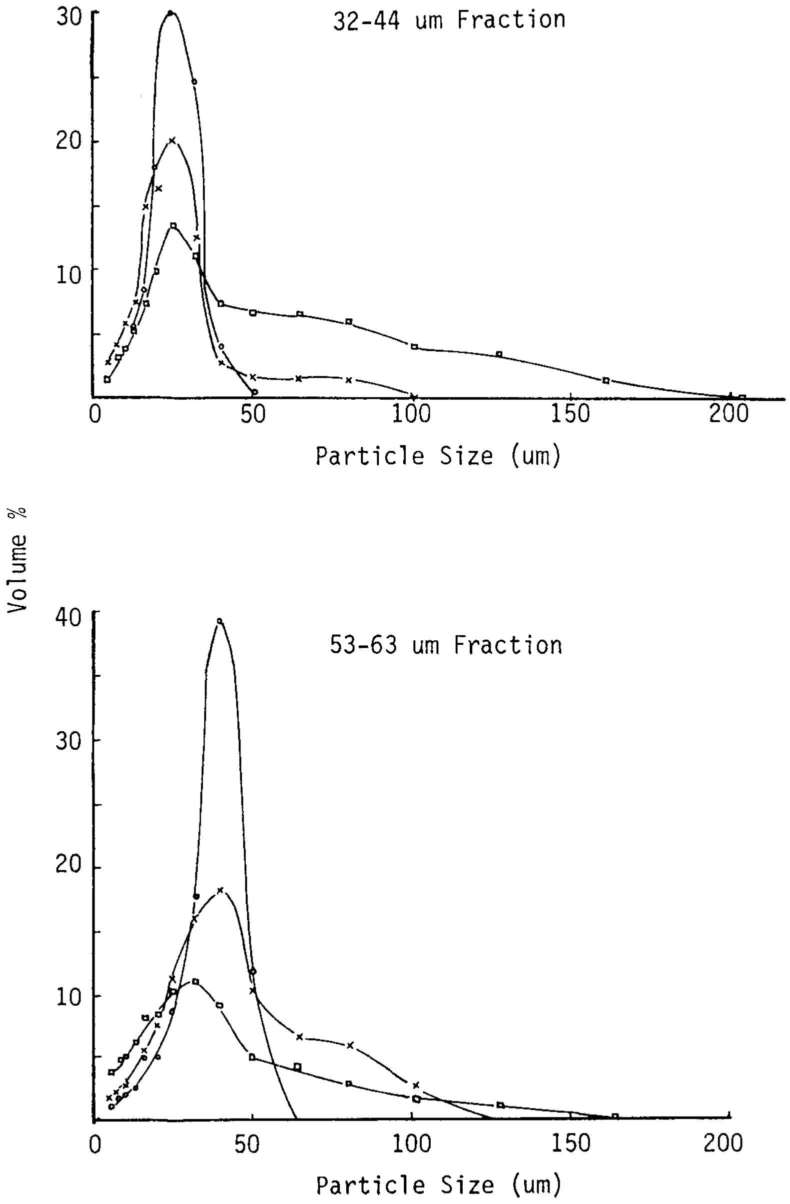

FIGURE 1

Particle size distribution curves for magnesium carbonate.

(○ , uncompressed powder; X , after compression at 65 MNm^{-2}; ◻, after compression at 260 MNm^{-2})

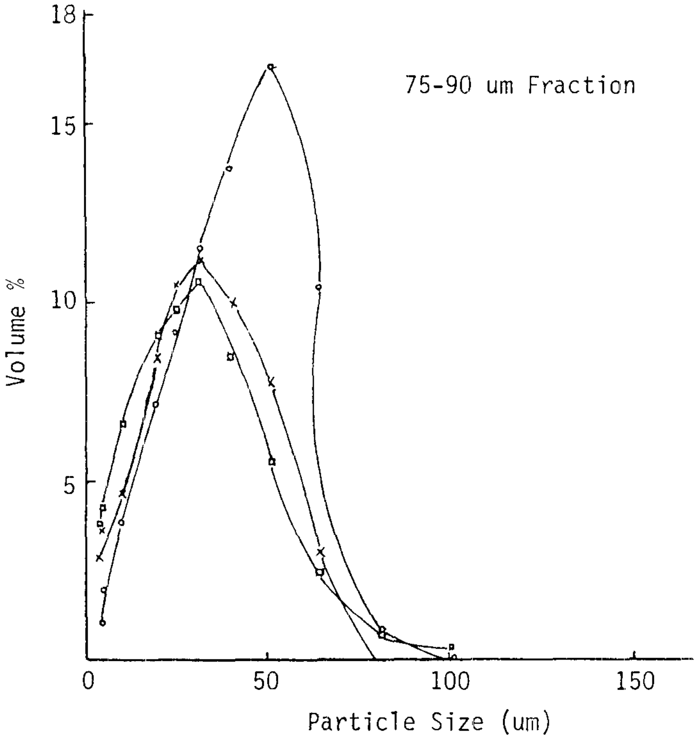

FIGURE 2

Particle size distribution curves for magnesium carbonate. (Symbols as in Figure 1)

Although comminution still takes place as the compression pressure is increased, recombination also takes place, the distribution curve covering a greater size range but becoming flatter. Thus the median particle diameter of the sample will depend on the balance of these two processes which, in turn, depends upon compression pressure. Also the particle size distribution and subsequent median particle diameter of the sample will depend on the agglomerates withstanding the standard deaggregation process.

An increase in the median particle diameter of the 32-44 um fraction of magnesium carbonate after compression at high pressure (260 MNm^{-2})

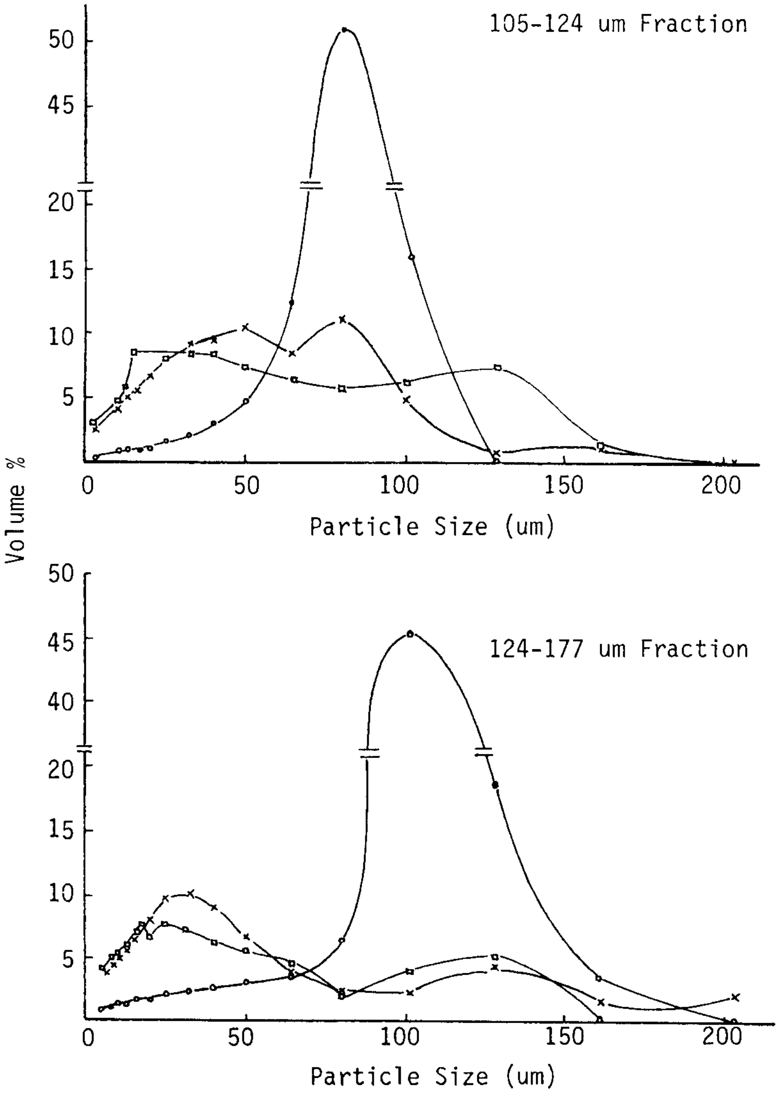

FIGURE 3

Particle size distribution curves for magnesium carbonate. (Symbols as in Figure 1)

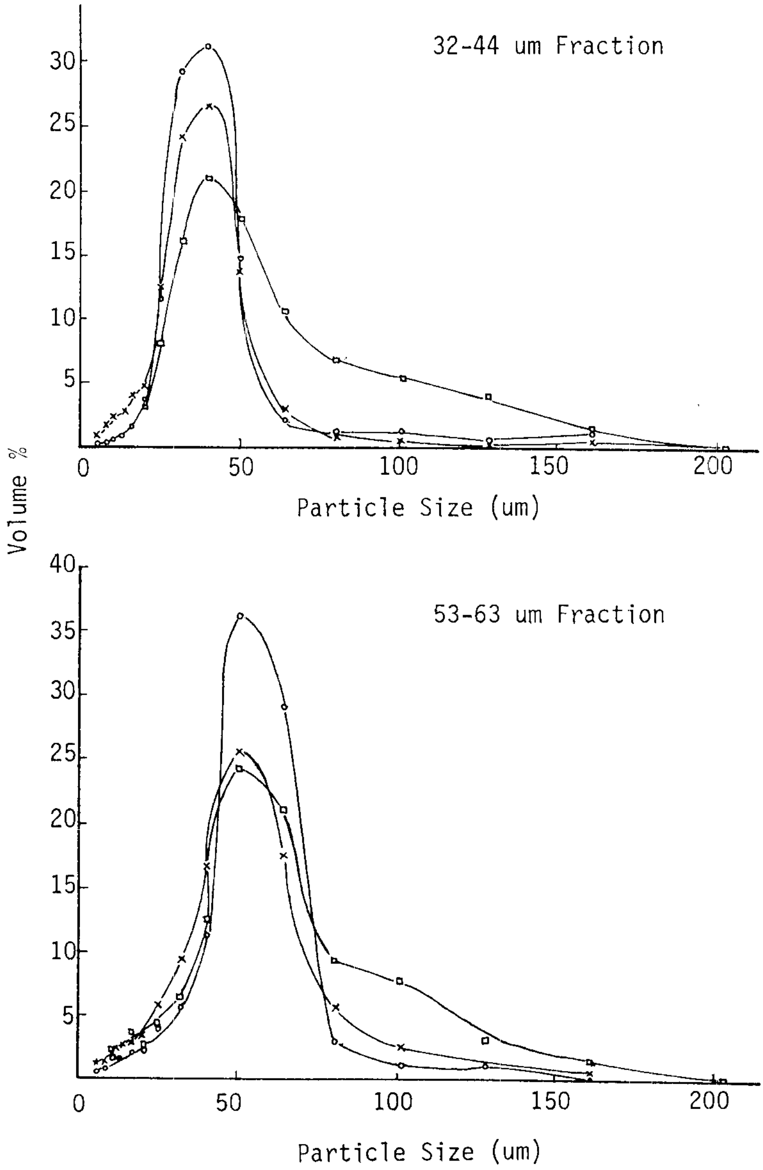

FIGURE 4

Particle size distribution curves for Avicel PH102. (Symbols as in Figure 1)

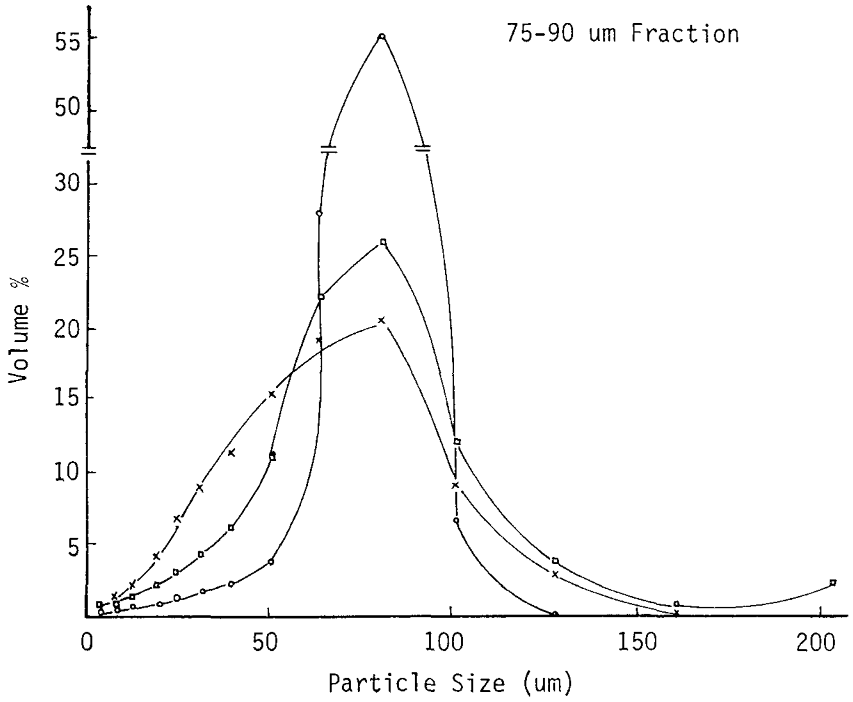

FIGURE 5

Particle size distribution curves for Avicel PH102. (Symbols as in Figure 1)

is presumably due to particle aggregation, and the bonding between particles is strong enough to withstand the standard deaggregation process. However, a decrease in the median particle diameter is obtained for the four other size fractions of magnesium carbonate at this pressure (Table 4). During compression of these samples at this pressure, both fragmentation and agglomeration will take place. A decrease in the median particle diameter of these four fractions of magnesium carbonate could be due to breakdown of interparticulate bonds during the deaggregation process.

Surface area analysis of different size fractions of magnesium carbonate under compression indicates that fragmentation is more severe for a larger size fraction than for a smaller size fraction [4].

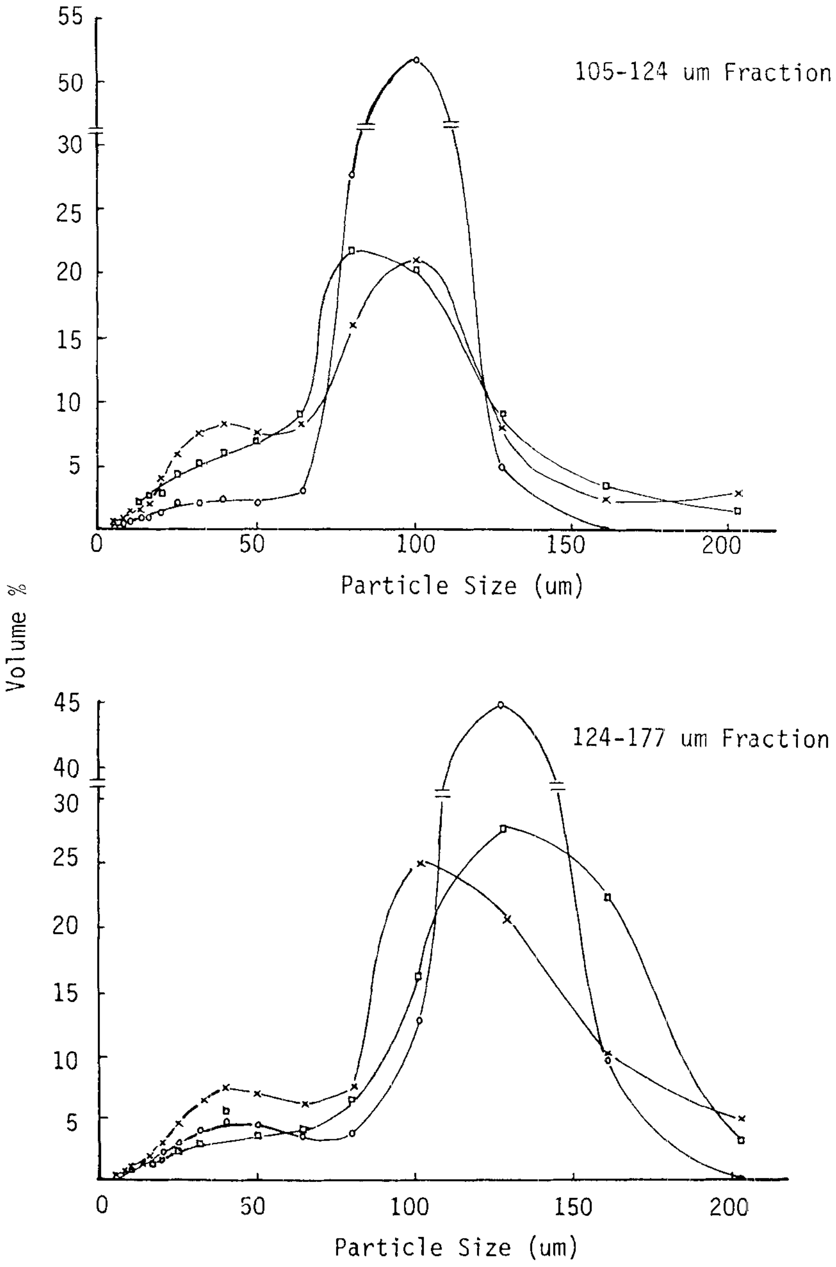

FIGURE 6

Particle size distribution curves for Avicel PH102. (Symbols as in Figure 1)

TABLE 4

Median particle diameter (um) of uncompressed powder and disintegrated compacts.

	Magnesium carbonate			Avicel PH102		
		After compression			After compression	
Sieve fraction	Powder	$65MNm^{-2}$	$260MNm^{-2}$	Powder	$65MNm^{-2}$	$260MNm^{-2}$
32-44 um	26	22	30	40	38	48
53-63 um	40	37	23	58	54	58
75-90 um	31	20	18	90	60	75
105-124 um	87	38	25	100	80	90
124-177 um	115	27	20	135	100	130

Therefore, for a substance which consolidates mainly by fragmentation, a much greater reduction in the median particle diameter of the larger size fractions than that of the smaller size fractions after compression at 260 MNm^{-2} is not unexpected.

Table 4 also shows that there is an increase in the median particle diameter for the 32-44 um fraction, and a decrease in the median particle diameter for the three larger size fractions (75-90 um, 105-124 um, 124-177 um) when Avicel PH102 was compressed at 260 MNm^{-2}. However, the median particle diameter of the disintegrated compacts of the 53-63 um fraction remains the same as that of the uncompressed powder.

It seems that the initial size of a substance is an important factor to be considered in predicting particle size changes of the substance when compressed. The critical size [3] where bonding and fragmentation equal each other will vary from solid to solid, depending on the consolidation mechanism of the solid. Avicel PH102, which consolidates both by fracture and deformation, is likely to have a higher critical size than a more brittle material such as magnesium carbonate.

Effect of mixing

A study on the effect of mixing on the particle size of the final product will be more informative, as a pharmaceutical formulation usually consists of two or more components. Table 5 shows that there is a decrease followed by a subsequent increase in the median particle diameter of the three mixtures with increase in compression pressure. This indicates that at low pressures, comminution is the predominant process, leading to a decrease in the median particle diameter of the solids. The predicted values in Table 5 are those which would have been expected if each component in the mixture had behaved as if it were being compressed on its own. A comparison of the data shows that the experimental value is less than the predicted value for the mixtures at low pressures, indicating that particle crushing at this stage is more severe than that when the individual components are compressed separately.

For mixtures containing either a higher proportion of Avicel or magnesium carbonate, the median particle diameter increases with increase in compression pressure after a minimum has been reached. At higher pressures, the experimental value of the median particle diameter is greater than the predicted value for these two mixtures. The difference is more significant for the mixture containing a higher proportion of Avicel. This is presumably due to the formation of a continuous matrix of Avicel and the a possible trapping of fractured magnesium carbonate between the particles of Avicel.

TABLE 5

The median particle diameter of disintegrated compacts prepared over a range of pressures. A, B and C represent the binary mixtures of magnesium carbonate and Avicel PH102 containing 25%, 50% and 75% by weight of magnesium carbonate respectively.

Pressure (MNm^{-2})	Predicted Value (um)			Measured Value (um)		
	A	B	C	A	B	C
Powder	69	57	44	69	56	52
16	67	55	43	47	38	30
65	52	43	31	42	32	24
130	47	38	30	62	34	26
195	52	41	30	63	33	29
260	62	48	33	67	33	33
326	64	49	33	76	42	34
390	64	49	33	76	42	35
456	64	49	33	76	42	35

The median particle diameter of the 50% mixture also reaches a minimum at 65 MNm^{-2}. However this value remains fairly constant for the next three higher pressures studied. A subsequent increase in median particle diameter only occurs at pressures above 326 MNm^{-2}. It is in such a mixture that the chance of chemically different particles being adjacent to each other is greatest. Hence opportunities for bonding between identical chemical entities will be at a minimum. Also at any given pressure, the experimental value of the median particle diameter of the mixture is less than that predicted from the behaviour of the individual components. In such a mixture, the rebonding of fractured particles of Avicel and magnesium carbonate will be greatly reduced.

It is sugested that for compression of mixtures having different consolidation mechanism, the pressure at which aggregation predominates is dependent on the relative concentration of the components in the mixture. The value of the median particle diameter of the mixtures will be dependent on the consolidation mechanism of the components.

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