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TABLET PROPERTIES AND DISSOLUTION CHARACTERISTICS OF COMPRESSED CELLULOSE ACETATE BUTYRATE MICROCAPSULES CONTAINING SUCCINYL SULFATHIAZOLE

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ABSTRACT

Cellulose acetate butyrate microcapsules of succinyl sulfathiazole were prepared by a modified emulsion-solvent evaporation method and formulated for compression with microcrystalline cellulose and carboxymethyl starch. Tablet hardness decreased and friability increased as microcapsule content increased. Formulations containing up to 50% microcapsules produced satisfactory tablets, but at 70% microcapsules, the tablets were unacceptably fragile. Variation of microcapsule size fraction from 75 μm up to 428 μm had only a small effect on tablet properties when formulated at the 40% level. Tablet hardness increased with increasing compression

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pressure from 1.9 kg at 17.6 MPa to 14.9 kg at 210.7 MPa. Dissolution properties of the microcapsules were essentially unchanged at compression pressures up to 351 MPa with $T_{50\%}$ values ranging from 121 to 132 minutes. Uncompressed microcapsules had a $T_{50\%}$ value of 130 minutes.

INTRODUCTION

Compression of microcapsules into tablets raises legitimate concerns about damage to microcapsule walls with subsequent increased and perhaps unpredictable dissolution rates of sustained release tablets (1). On the other hand, decreased dissolution rates have been reported when microcapsules were compressed without formulation to assure the disintegration of the tablets (2,3,4,5). While many microcapsules are relatively fragile because of the thin walls of the encapsulating material, matrix microspheres containing drug dispersed in a polymer matrix are usually resistant to fracture or other damage. This work studies the effect of size, relative proportion in the formulation, and compression pressure on the physical parameters and dissolution properties of tablets made from matrix microspheres. The dissolution results are compared with results from uncompressed microspheres.

EXPERIMENTAL

Microcapsule Preparation - Succinyl Sulfathiazole as a model drug was encapsulated in cellulose acetate butyrate by a modified emulsion-solvent evaporation method. Microcapsules were dried

and separated into sieve fractions. Drug content ranged from 39.2% for microcapsules in the smallest (66-88 μm) size fraction to 55.5% in the largest (350-500 μm) size fraction. Average drug content for all size fractions combined was 48.9%.

Tablet Preparation - Tablets (500 mg) were compressed using a hydraulic press and flat-faced punches of 12.7 mm diameter. The required pressure was maintained for 30 seconds and then quickly released.

Three series of experiments were run:

1) The effect of microcapsule concentration; Tablets containing 20, 30, 40, 50, 60 and 70% microcapsules, 5% carboxymethyl starch and the remainder made up with microcrystalline cellulose, were compressed to 70.2 MPa pressure. The microcapsule size fraction was 250-350 μm.

2) The effect of microcapsule size fraction; Size fractions of 350-500 μm, 250-350 μm, 177-250 μm, 88-125 μm and 62-88 μm were compressed to 70.2 MPa. The formulations contained 40% microcapsules, 55% microcrystalline cellulose and 5% carboxymethyl starch.

3) The effect of compression pressure; Tablets containing 40% microcapsules, 55% microcrystalline cellulose and 5% carboxymethyl starch were compressed to 17.6, 35.1, 70.2, 140.4, 210.7, 280.9 and 351.0 megapascals. Microcapsules with a size range of 177 to 250 μm were employed in this formulation.

Determination of tablet thickness and density - The thickness of each tablet was determined by means of a micrometer. For each batch, fifteen tablets were measured. The tablet volume and density were calculated from the mean volume and mean weight of the tablets.

Determination of tablet breaking strength - Tablet breaking strength was determined by means of an Erweka hardness tester. The force required to break the tablet was recorded as its breaking strength.

Determination of tablet friability - The Roche Friabilator was used to measure friability. After five minutes treatment, the tablets were weighed and compared to their initial weight. The loss was expressed in percent as a measure of tablet friability.

Dissolution Studies - Dissolution studies were carried out at 37^{o} using simulated intestinal fluid containing 0.02% Tween 80 but no enzyme. The U.S.P. paddle method was employed at 100 rpm. Samples (5 ml) were withdrawn at intervals and assayed spectrophotometrically at 257 nm using fresh dissolution fluid as a blank. The 5 ml aliquots were replaced with fresh dissolution fluid. Results are reported as the mean of six tablets.

RESULTS AND DISCUSSION

Table I summarizes the effect of relative microcapsule content on physical properties of compressed tablets in a simple formulation containing microcrystalline cellulose diluent and a 5% disintegrant. Acceptable tablets were formed with all formu-

TABLE 1

Effect of Formula Microcapsule Content on Tablet Physical Properties

Microcapsule Content (%)	Tablet Thickness (mm)	Tablet Density (Gm/cm^3)	Tablet Hardness (kg)	Friability (% loss)
0.00	3.07±.03	1.286	15.00	0.00
20.00	3.15±.03	1.253	15.00	0.08±0.01
30.00	3.20±.03	1.233	15.00	0.16±0.04
40.00	3.20±.03	1.233	12.5±1.1	0.37±0.15
50.00	3.23±.03	1.222	6.6±0.7	1.32±0.14
60.00	3.28±0.2	1.203	3.5±0.2	3.64±0.14
70.00	3.35±.03	1.178	2.6±0.1	Tablet Fragmentation

Compression pressure was 70.2 megapascals, microcapsule size fraction was 250-350 μm.

lations up to 60% microcapsule content, although tablet hardness decreased with increasing microcapsule content. Friability also increased with increasing microcapsules content and tablets containing 70% microcapsules were unacceptably fragile. Tablet thickness increased while density decreased with increasing microcapsule content reflecting poorer compressibility as compared to the diluent.

Increasing microcapsule size from 75 μm (mean) to 428 μm (mean) had only a small effect on tablet hardness, friability and

TABLE II

Effect of Microcapsule Size on Physical Properties of Tablets

Microsphere Size Fraction (μm)	Tablet Thickness (mm)	Density (Gm/cm^3)	Hardness (kg)	Friability (% loss)
350-500	3.28±.03	1.203	11.0±0.7	0.32±0.05
250-350	3.20±.03	1.233	12.5±1.1	0.37±0.15
177-250	3.23±.03	1.222	10.0±0.6	0.56±0.12
125-177	3.25±.03	1.199	9.5±0.5	0.60±0.12
88-125	3.25±.03	1.199	8.8±0.5	0.94±0.08
62-88	3.25±.03	1.199	9.5±0.4	0.65±0.06

Compression pressure, 70.2 megapascals, microcapsule content, 40%

TABLE III

Effect of Compression Pressure on Physical Properties of Tablets

Compression Pressure MPA	Tablet Thickness (mm)	Tablet Density (Gm/cm^3)	Tablet Hardness (kg)	Friability (% loss)
17.6	4.55±.05	0.868	1.9±0.1	Fragmentation
35.1	3.86±.03	1.023	4.5±0.3	2.2±0.5
70.2	3.23±.03	1.222	10.0±0.6	0.56±0.12
140.4	3.02±.03	1.307	13.5±0.7	0.23±0.08
210.7	2.95±.03	1.338	14.9±0.1	0.23±0.05
280.9	3.92±.03	1.352	14.7±0.4	0.25±0.05

Microcapsule content, 40%; Microcapsule size, 177-250 μm.

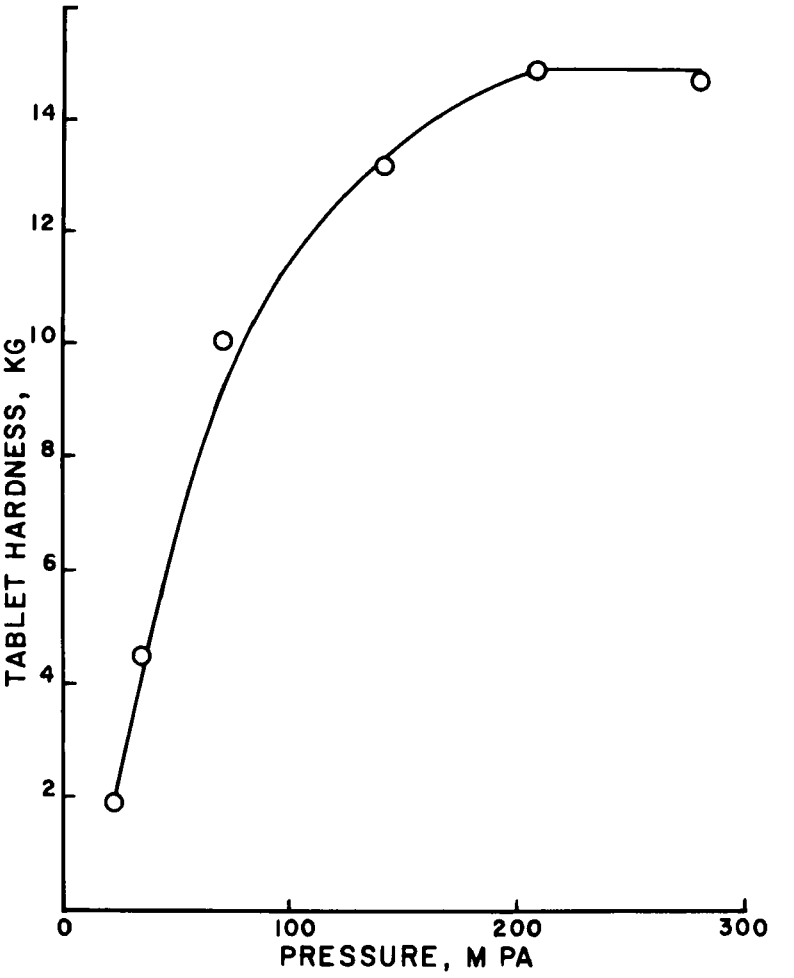

FIGURE 1

Effect of Compression Pressure on Hardness of Tablets with 40% Microcapsule Content.

density when the microcapsules were present in the formula at a concentration of 40% of the total. This data is summarized in Table II.

Table III shows that maximum hardness in a 40% microcapsule formulation was achieved at about 210 MPa pressure but acceptable

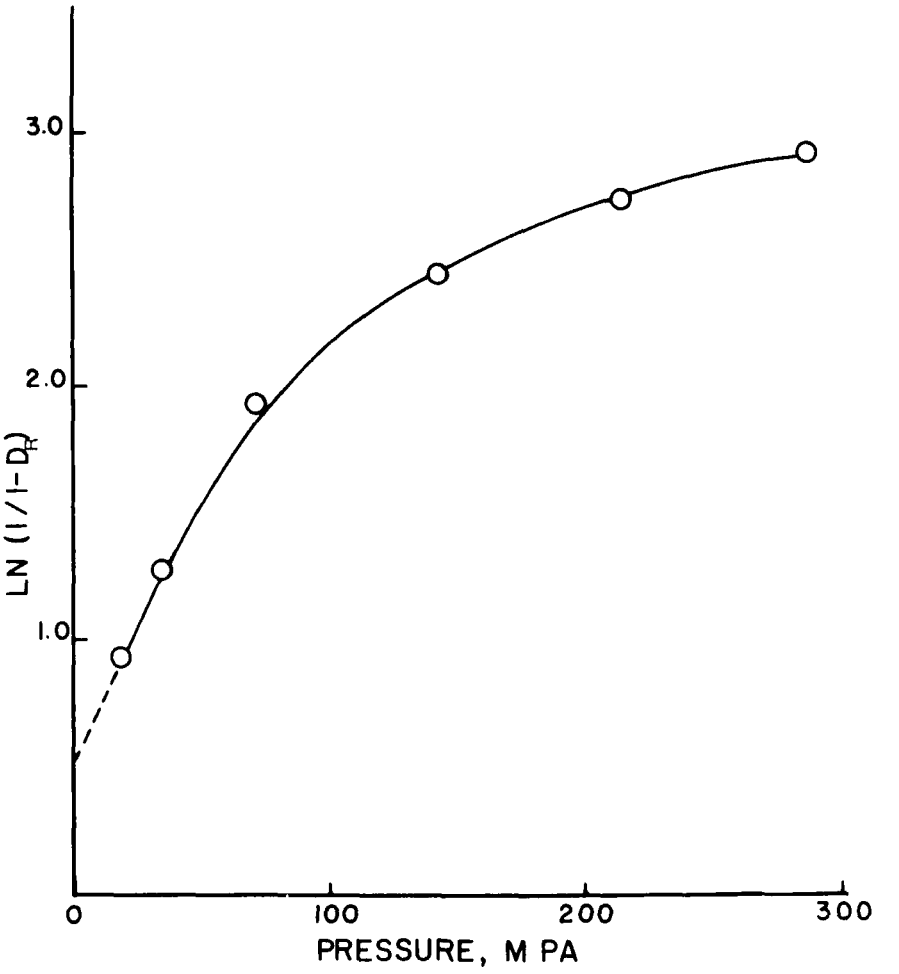

FIGURE 2

Heckel Plot of Tablet Compression Data from 40% Microcapsule Formulation, D_R = Relative Tablet Density.

tablets were formed at much lower pressure (35.1 MPa). A pressure hardness profile (Fig. 1) shows a rapid increase in tablet hardness with increasing pressure typical of formulations containing a high proportion of microcrystalline cellulose. A Heckel plot of the compression data (Fig. 2) shows curvature at

TABLE IV

Effect of Compression Pressure on the In Vitro Dissolution $T_{50\%}$ and $T_{80\%}$ Release of Succinyl Sulfathiazole from Tableted Microcapsules*+

Compression Pressure (MPA)	$T_{50\%}$(minutes)	$T_{80\%}$(minutes)
35.1	132	388
70.2	130	385
140.4	121	358
210.7	128	349
280.9	128	342
351.0	124	348

* Uncompressed microcapsules had a $T_{50\%}$ of 130 minutes, $T_{80\%}$ of 383 minutes
+ Microcapsule Size fraction was 250-350 μm.

higher pressures typical of results reported for pure microcrystalline cellulose (6).

Dissolution characteristics were typical of matrix microspheres and, as can be seen in Table IV, were not altered by compression of the 25-350 μm size fraction into tablets. The tableted microcapsules had virtually the same $T_{50\%}$ as the uncompressed microcapsules even at 350 MPa compression pressure. $T_{80\%}$ times were approximately 10% lower for the tablets with higher compression pressures, possibly indicating the breakup of agglomerated smaller microspheres.

CONCLUSIONS

1. Acceptable tablets could be formed with all microcapsule formulations up to 60% microcapsule content with microcrystalline cellulose diluent. Tablet hardness, however, decreased rapidly above 40% microcapsule content.
2. At 40% microcapsule content and 70 MPA compression pressure, microcapsule size (between 62 - 500 μm) had little effect on physical properties of the tablets.
3. Compaction data for formulas containing 40% microcapsules were similar to data reported for pure microcrystalline cellulose.
4. In Vitro dissolution characteristics remained almost constant at tablet compression pressures from 35 megapascals to 350 megapascals.

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