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TABLETABILITY OF MALTODEXTRINS AND ACETAMINOPHEN MIXTURES

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ABSTRACT

Tabletability of five types of maltodextrin, a filler/binder excipient, was studied by testing their loading potentials with acetaminophen. The formulations consisted of excipient and acetaminophen at five different ratios and magnesium stearate at a 0.5% concentration. These mixtures were compacted employing an Integrated Compaction Research System at a constant punch velocity of 100 mm/sec. under varying applied pressures from 50 to 450 MPa. Compaction data were evaluated using the total work of compaction vs applied pressure plots whilst the post-compaction tests included the measurements of crushing force, disintegration time, and friability of the resulting tablets. Both the energy involved during the compaction of a formulation and the crushing force values of the resulting tablets decreased as the amount of the maltodextrin in a formulation was reduced. Maltodextrins exhibited adequate binding potential at acetaminophen drug loading levels of only up to twenty-five percent. The disintegration times of the tablets containing maltodextrins were generally prolonged and this was found to be due to the formation of a "gel" layer around the tablet which formed on immersion into water. The tabletability of maltodextrins were also compared to that of Fast-Flo lactose, and the compactability of these excipients were found to be similar.

INTRODUCTION

The evaluation of a material for use as a direct compression filler/binder excipient is primarily concerned with that material's ability to flow and to form coherent compacts when used in formulations, especially with poorly compacting drug substances. The maltodextrins are a class of materials that have the potential to be useful filler/binder excipients and are starch conversion products which contain a relatively small amount of dextrose and maltose and have dextrose equivalent values not substantially above twenty. There are three general physically processed types of maltodextrin products available as direct compression filler/binders and the maltodextrins examined in this study differed from each other mainly by their method of manufacture; spray drying, fluidized bed agglomeration, and roller compaction (Mollan and Çelik (1)).

Acetaminophen has been previously used as a standard reference material to test the binding potential of excipients. Acetaminophen is a material that forms weak compacts at best, and undergoes capping easily even at low applied pressures. Wells and Langridge (2) described the loading capacity or compressibility potential of a compression aid as the proportion of a noncompressible or poorly compressible drug which can be incorporated into the vehicle to produce satisfactory tablets. They used acetaminophen with a combination of microcrystalline cellulose and dicalcium phosphate dihydrate, and characterized various properties of drug and excipient. Krycer et al. (3) used acetaminophen as a substrate in the evaluation of five potential pressure binders. They used binder levels of 20, 50, and 80 percent by weight and described the usefulness of tablet crushing strength vs pressure profiles as indicators of binding ability. Baykara et al. (4) used acetaminophen in mixtures with some direct compression excipients and evaluated the data by means of the Heckel and Kawakita equations. Yu et al. (5) examined mixtures of acetaminophen and Avicel PH101 and found that intact tablets could be produced with as little as 15% w/w of microcrystalline cellulose with acetaminophen.

The aim of this study was to determine the binding potential and tableting properties of the maltodextrins and to compare those values to that of a commonly used filler/binder excipient, Fast-Flo lactose.

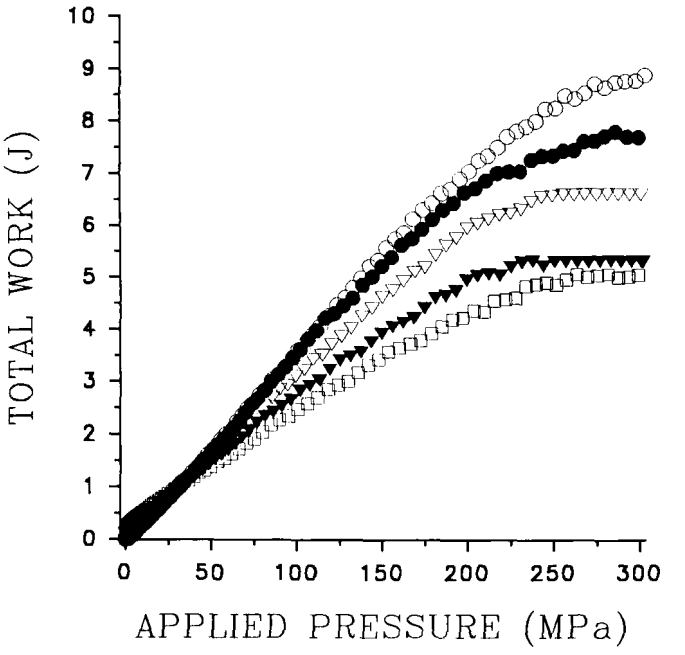

FIGURE 1. Total Work of Compaction vs Applied Pressure for the compacts of Experimental Maltodextrin/Acetaminophen Mixture
○ = 99.5% ; ● = 75% ; ∇ = 50.0% ; ▼ = 25.0% ; □ = 0.0%

MATERIALS & METHODS

The maltodextrins used were: Maltrin M510 Lot# A3533, DE = 9-12, which is a spray dried product, and Maltrin M500 Lot# 094906, DE = 9-12, which is a fluidized bed agglomerated product, both by Grain Processing Co.; Malta*Gran TG Lot# A1009, DE = 10, and Malta*Gran 10 Lot# A1500, DE = 10, which are fluidized bed agglomerated products by Zumbro/IFP Inc.; and Experimental Maltodextrin Lot # I2169X, DE = 15, which is a roller compacted material by Edward Mendell Co. Experimental Maltodextrin is not yet a marketed product, and the final mean particle size has not yet been determined. For this reason, sieve cuts of Experimental Maltodextrin were used which gave a theoretical mean particle size of 182 μm. The other materials used in this study were: Lactose USP Hydrous (Fast-Flo lactose) Lot# 1RM912 by

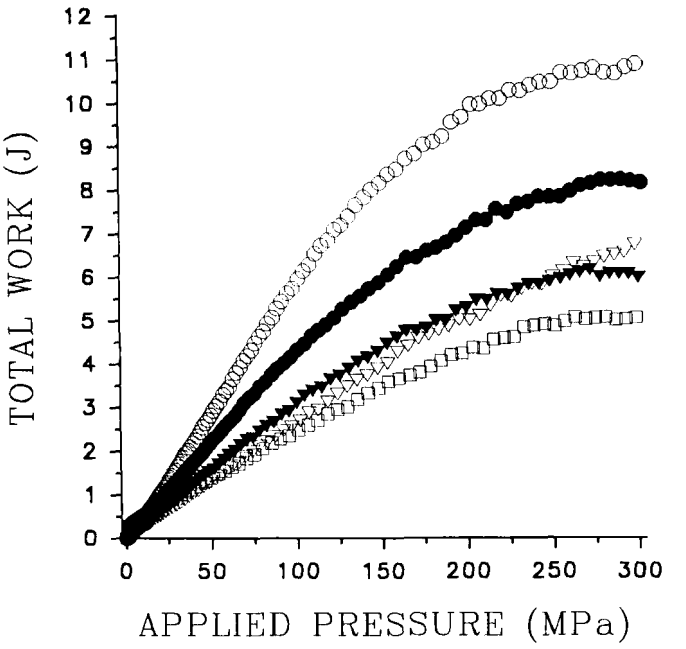

FIGURE 2. Total Work of Compaction vs Applied Pressure for the compacts of Maltrin M510/ Acetaminophen Mixture

○ = 99.5% ; ● = 75% ; ▽ = 50.0% ; ▼ = 25.0% ; □ = 0.0%

Foremost Whey Products; acetaminophen USP powder Lot# J22395P11 by Ruger Chem. Co.; and magnesium stearate Lot# 2256 by Mallinckrodt Co.

Formulations were made of filler/binder excipient, acetaminophen, and magnesium stearate. Acetaminophen was prescreened through a 30 mesh (595 μm) screen to minimize large agglomerates. The other powders were used as received. The blending procedure was to mix filler/binder excipient and acetaminophen for 10 minutes, then add 0.5% of magnesium stearate and mix for an additional 2 minutes. The formulations were mixed in a Turbula T2C mixer (Glen Mills Inc., N.J., USA). The batch size was 100 grams. The formulations were then stored above magnesium nitrate saturated salt solutions, which maintained 52.8% humidity, for at least two weeks prior to compaction.

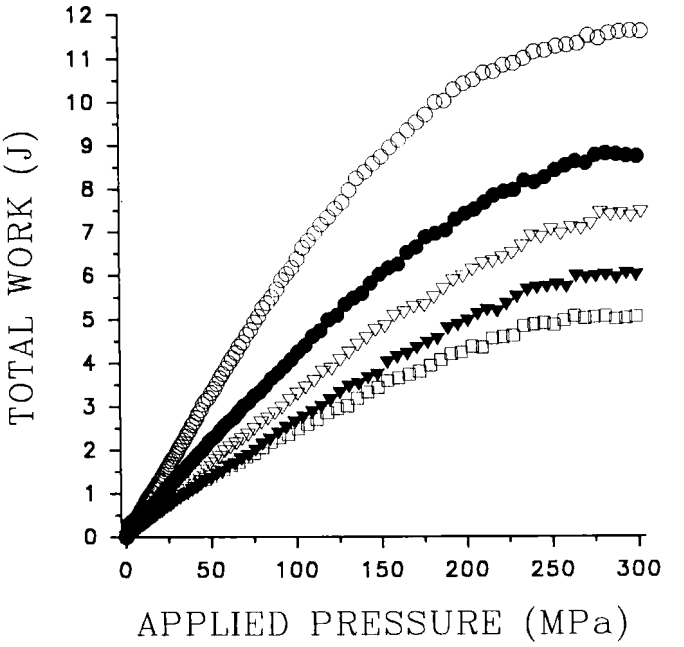

FIGURE 3. Total Work of Compaction vs Applied Pressure for the compacts of Maltrin M500/ Acetaminophen Mixture

○ = 99.5% ; ● = 75% ; ∇ = 50.0% ; ▼ = 25.0% ; □ = 0.0%

The true densities of the formulations were determined by helium pycnometry (Multipycnometer, Quantachrome Co., Syossett, N.Y., USA).

The formulations were mixtures of filler/binder excipient with acetaminophen and magnesium stearate, in five ratios, respectively: 99.5/0.0/0.5, 75.0/24.5/0.5, 50.0/49.5/0.5, 25.0/74.5/0.5, and 0.0/99.5/0.5 (w/w) percentage. The formulations were compacted into tablets employing an Integrated Compaction Research System (Mand Testing Ltd., Stourbridge U.K.) which utilized a "sawtooth", ie. constant velocity waveform, of double ended design operating at a punch velocity of 100 mm/second. This type of profile was chosen because it allowed all of the materials to be subject to the same punch velocity during the compaction event, without the need of adjusting the

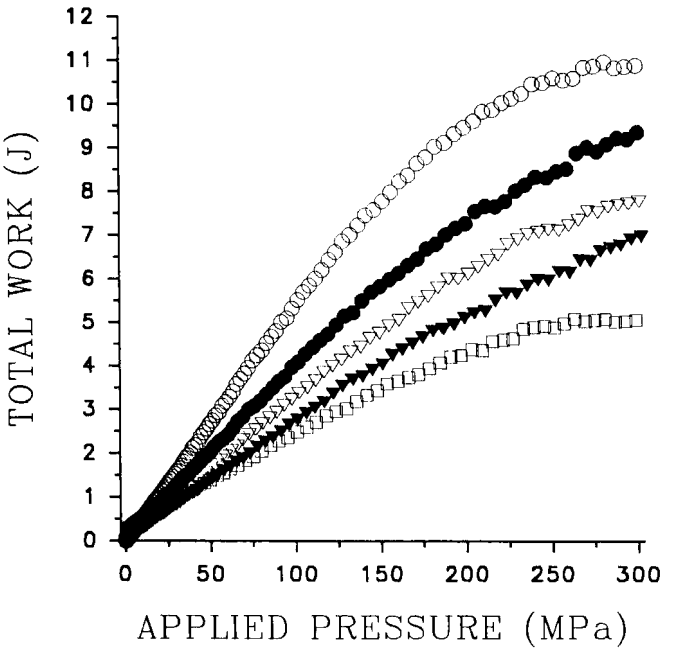

FIGURE 4. Total Work of Compaction vs Applied Pressure for the compacts of Malta*Gran TG/ Acetaminophen Mixture
○ = 99.5% ; ● = 75% ; ▽ = 50.0% ; ▼ = 25.0% ; □ = 0.0%

punch profiles for each formula due to variations in the bulk densities. A standard flat-faced round 10.3 mm set of BB tooling was used. Comparisons between formulations were made with the amount of powder compacted as 0.2 cm^3 in constant true volume at zero percent porosity. The deformation of the system, ie. punches, load cells, and other components in linear series with the punches, was accounted for by a "punch on punch" method. Deformations of the upper and lower punches were determined up to 40 kN, and these values were then fitted to polynomial equations which best described the phenomena. These equations were then used to compensate for system deformation in order to obtain accurate displacement measurements during compaction testing. The tablets were compacted to four predetermined mean pressures for comparison purposes: 75, 150, 300, and 450 MPa.

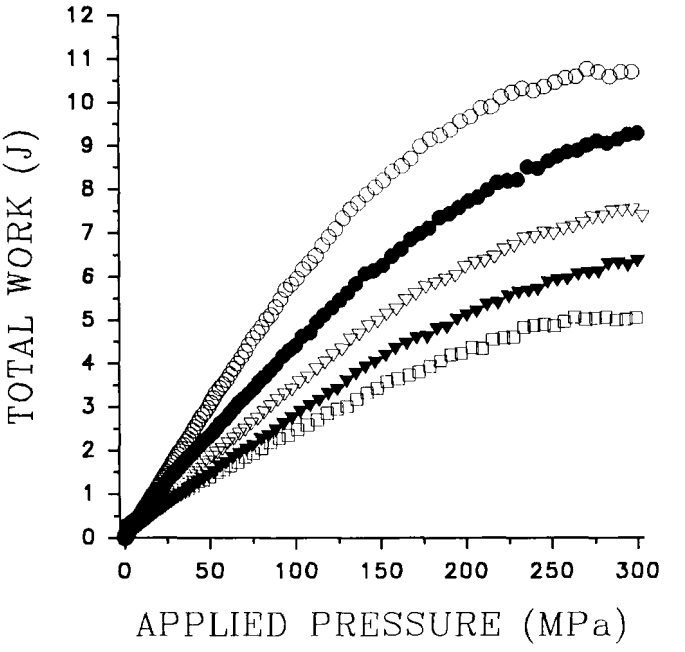

FIGURE 5. Total Work of Compaction vs Applied Pressure for the compacts of Malta*Gran 10/ Acetaminophen Mixture

○ = 99.5% ; ● = 75% ; ▽ = 50.0% ; ▼ = 25.0% ; □ = 0.0%

The physical testings of the tablets were performed 24 hours after ejection to allow for viscoelastic expansion. These included: weight (model 100A XE series, Denver Instrument Co., Arada, Col., USA); compact thickness and diameter, by micrometer (Material Control Inc., USA); crushing force (VK 2000, VanKel Ind., Edison, N.J.,USA); friability (Erweka Co.,Germany); and disintegration time (Type PTZ1, Pharma Test, Germany). The crushing force reported is a mean of ten tablets. The disintegration times are a mean of five tablets in distilled water at 37° C, without the use of disks. The friability value is that of a single run of ten tablets, with the friabulator revolving at 25 rev/min for 4 minutes. The Total Work of Compaction data reported are means of three separate compaction replicates.

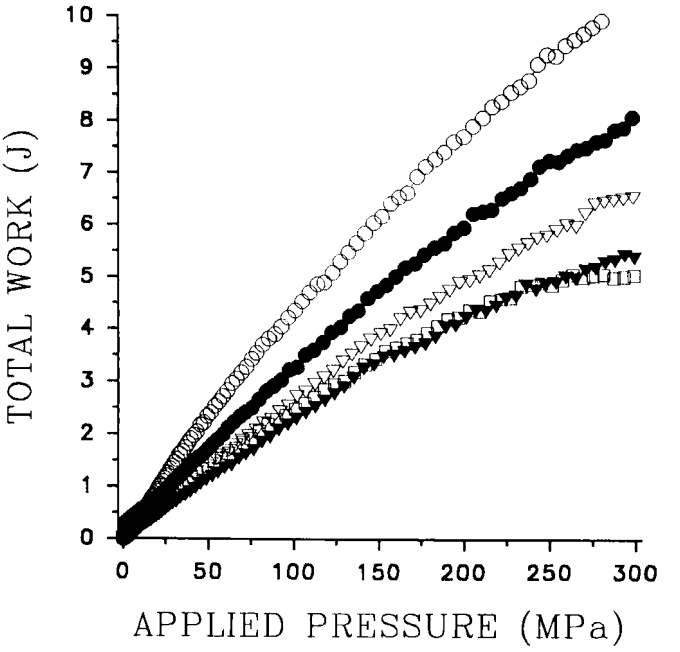

FIGURE 6. Total Work of Compaction vs Applied Pressure for the compacts of Fast-Flo lactose/ Acetaminophen Mixture
○ = 99.5% ; ● = 75% ; ∇ = 50.0% ; ▼ = 25.0% ; □ = 0.0%

RESULTS AND DISCUSSION

The energy transferred by the upper and lower punches to the powder bed is utilized for particle rearrangement, elastic-plastic deformation, and/or brittle fracture as well as for the formation of new bonds within the tablet matrix. The total work of compaction, TWC, can be calculated as per Çelik and Marshall (6)

$$TWC = \left(\int_{x=0}^{x_{max}(up)} F_{up} * dX_{up}\right) + \left(\int_{x=0}^{x_{max}(lp)} F_{lp} * dX_{lp}\right)$$

when F_{up} and F_{lp} are the forces on the upper and lower punches respectively; X_{up} and X_{lp} are the contribution of the upper and lower punches respectively to the decrease in

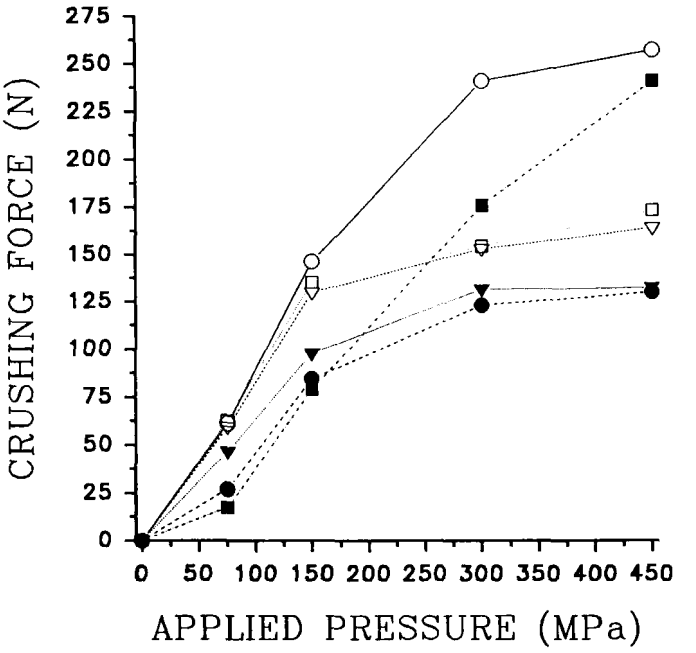

FIGURE 7. Crushing Force vs Applied Pressure for the compacts containing excipients at 99.5% concentration.

○ = Experimental Maltodextrin ; ● = Maltrin M510 ; ▽ = Maltrin M500

▼ = Malta*Gran TG ; □ = Malta*Gran 10 ; ■ = Fast-Flo lactose

the distance between them; X = 0 is the point where porosity equals the initial porosity and the maximum applied load was reached at $X_{max\ (up)}$ and $X_{max\ (lp)}$.

The higher the work input involved during the compaction of a powder system, the stronger the compact is expected to be formed due to the larger amount of energy utilized in the formation of bonds, providing that die wall friction is minimal.

The TWC plots of the formulations used are shown in Figures 1-6. For any given excipient, it was observed that the total amount of energy involved during the compaction of the formulations decreased as the concentration of that excipient in the formulation was

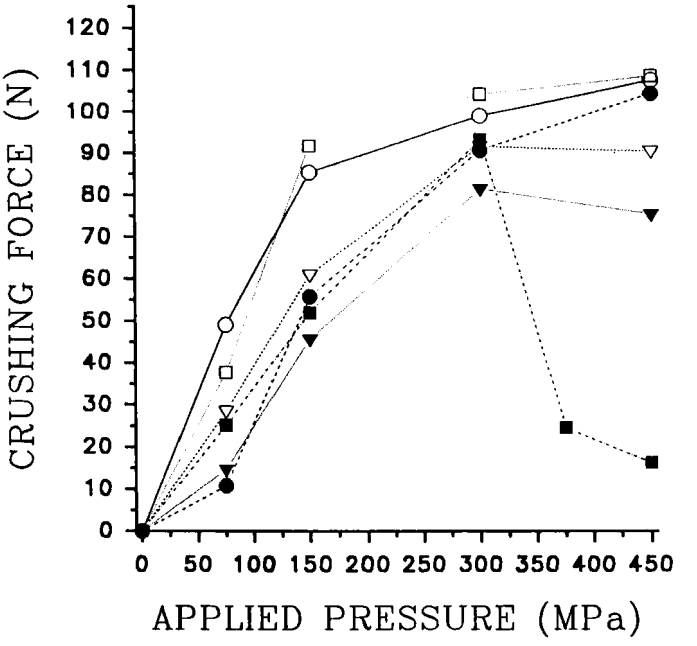

FIGURE 8. Crushing Force vs Applied Pressure for the compacts containing excipients at 75.0% concentration

○ = Experimental Maltodextrin ; ● = Maltrin M510 ; ▽ = Maltrin M500

▼ = Malta*Gran TG ; □ = Malta*Gran 10 ; ■ = Fast-Flo lactose

reduced. As can be seen from the crushing force data given below (Figures 7-10), a linear correlation was observed between the TWC values of the formulations and the crushing force values of their tablets, which is an evidence for the above assumption.

If a time element is used in conjunction with the force and displacement data, then the power utilized during the compaction of a powder system can be calculated using several methods. When the method of Çelik and Marshall (6) was applied to the compaction data obtained in this study, it was seen that the average power consumption during the compaction of the formulations also decreased as the concentration of a given excipient in the formulation was reduced, similar to the TWC data.

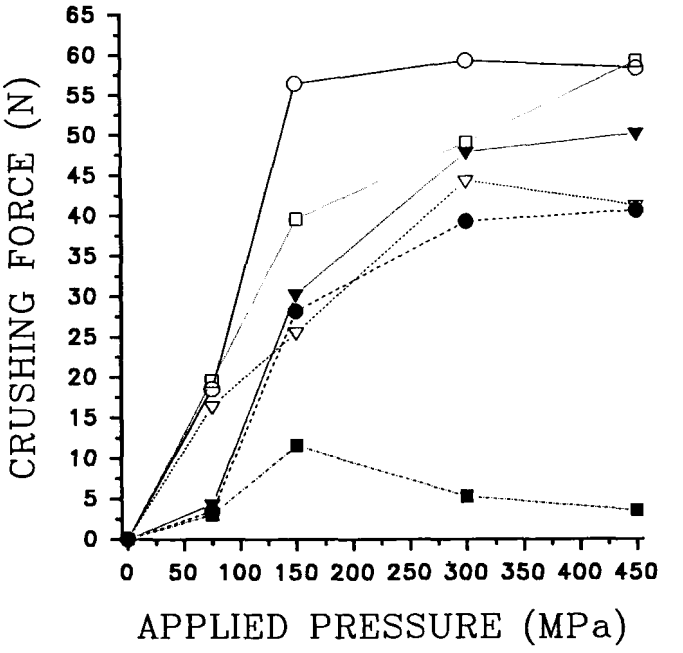

FIGURE 9. Crushing Force vs Applied Pressure for the compacts containing excipients at 50.0% concentration

○ = Experimental Maltodextrin ; ● = Maltrin M510 ; ▽ = Maltrin M500

▼ = Malta*Gran TG ; □ = Malta*Gran 10 ; ■ = Fast-Flo lactose

Figures 7-10 present the crushing force vs applied pressure plots of the compacts containing excipients and drug at the following levels (in addition to magnesium stearate at 0.5% concentration): 99.5:0.0 (Figure 7); 75.0:24.5 (Figure 8); 50.0:49.5 (Figure 9); 25.0:74.5 (Figure 10). Mollan and Çelik (1) previously observed similar crushing force profiles of the unlubricated compacts of the neat Experimental Maltodextrin, Maltrin M500, Maltrin M510, Malta*Gran TG, and Malta*Gran 10 powders, despite the fact that the surface area of Experimental Maltodextrin, a roller compacted material, was much larger than those manufactured by spray dried or fluidized bed agglomeration processes. However, in the present work, Experimental Maltodextrin generally exhibited higher crushing force values, especially at high pressures, when compared to the other maltodextrins and Fast-Flo lactose (Figure 7). This may be due to the presence of the

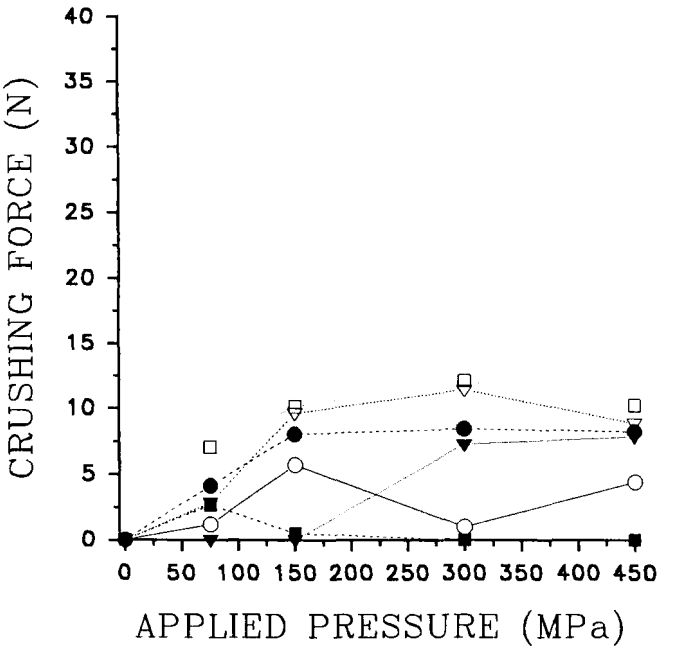

FIGURE 10. Crushing Force vs Applied Pressure for the compacts containing excipients at 25.0% concentration

○ = Experimental Maltodextrin ; ● = Maltrin M510 ; ∇ = Maltrin M500

▼ = Malta*Gran TG ; □ = Malta*Gran 10 ; ■ = Fast-Flo lactose

same amount of magnesium stearate available in all the formulations, thus the lubricant could have a detrimental effect on the crushing strength of the tablets compressed from the powders possessing low surface areas.

As can be seen from the Figure 8, the crushing force values of the tablets of all of the formulations containing excipients at 75% concentration decreased as compared to those containing excipients at 99.5% concentration. All of the tablets, except those containing Fast-Flo lactose, exhibited a similar trend of initially a large increase in the crushing force values up to 300 MPa above which the changes in these values were minimal. Fast-Flo lactose showed a very large decrease in the crushing force values at applied pressures above 300 MPa. This can be indicative of the inability of Fast- Flo lactose,

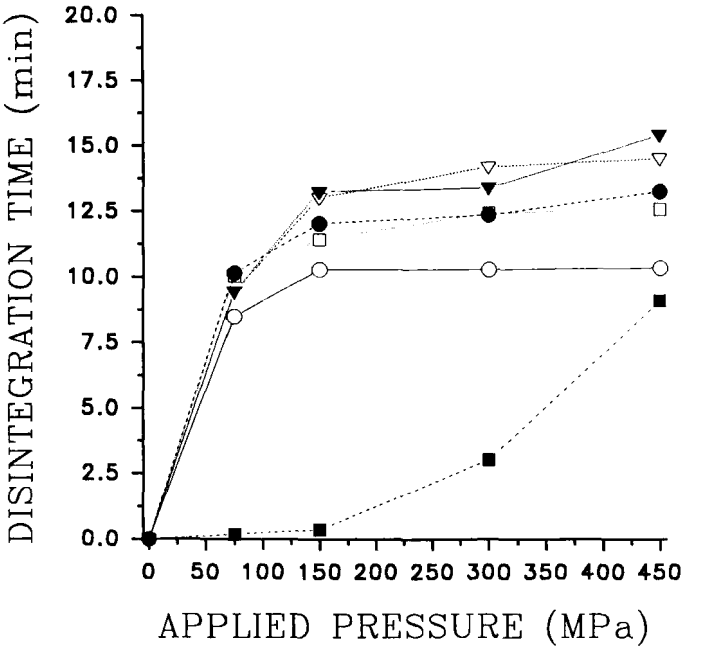

FIGURE 11. Disintegration Time vs Applied Pressure for the compacts containing excipients at 99.5% concentration

○ = Experimental Maltodextrin ; ● = Maltrin M510 ; ▽ = Maltrin M500

▼ = Malta*Gran TG ; □ = Malta*Gran 10 ; ■ = Fast-Flo lactose

primarily a brittle material by nature, to accommodate the increasing degree of stored elastic energy from the acetaminophen at very high pressures.

Figures 9 and 10 present the crushing force profiles of the tablets containing excipients at 50% and 25% concentrations, respectively. The graph in Figure 9 illustrates the further decrease in tablet crushing force values at 50% concentration, with approximately the same trend followed for the maltodextrins as at 75% concentration. Experimental Maltodextrin had the highest profile, followed by the other maltodextrins. Fast-Flo lactose at 50% concentration showed a dramatically different trend to that at 75% concentration, and the formulation exhibited a very low strength at all the applied pressure ranges. It appeared that lactose does not have the degree of binding ability needed to overcome the detrimental elastic effects of the acetaminophen, and so can be

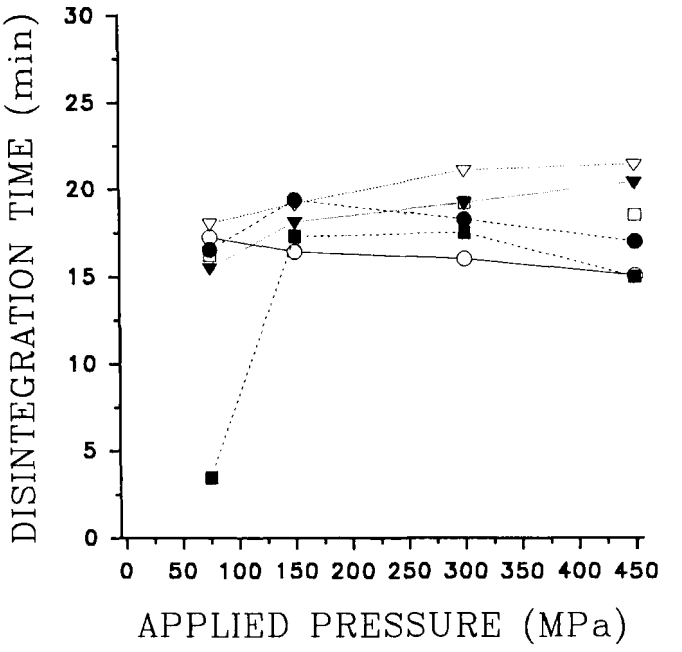

FIGURE 12. Disintegration Time vs Applied Pressure for the compacts containing excipients at 75.0% concentration

○ = Experimental Maltodextrin ; ● = Maltrin M510 ; ▽ = Maltrin M500

▼ = Malta*Gran TG ; □ = Malta*Gran 10 ; ■ = Fast-Flo lactose

considered to have a lower loading potential than the maltodextrins. At 25% filler/binder excipient concentration (Figure 10), all of the excipients have lost most of their binding ability and they produced very weak compacts.

The disintegration time of the tablets of the formulations are shown in Figures 11-14. Figure 11 is a plot of the excipients at 99.5% concentration and shows all the maltodextrins exhibiting similar disintegration behavior. Up to 150 MPa there is an increase in disintegration time with applied pressure, after which no significant changes in disintegration times occurred in spite of increases in compaction pressure. Experimental Maltodextrin had a slightly shorter disintegration time than the other maltodextrins tested. No linear correlation was observed between the crushing force values and disintegration times of the tablets containing maltodextrins. Such a correlation

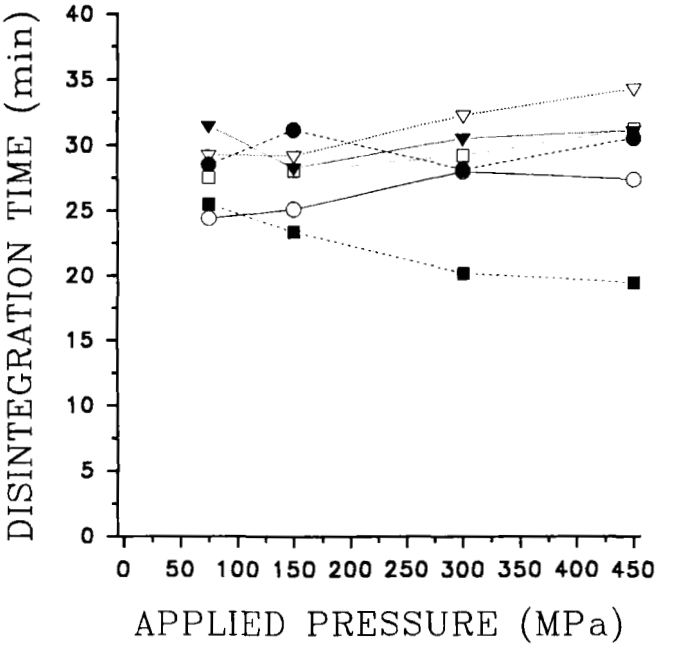

FIGURE 13. Disintegration Time vs Applied Pressure for the compacts containing excipients at 50.0% concentration

○ = Experimental Maltodextrin ; ● = Maltrin M510 ; ▽ = Maltrin M500

▼ = Malta*Gran TG ; □ = Malta*Gran 10 ; ■ = Fast-Flo lactose

was seen in the case of tablets containing Fast-Flo lactose which exhibited a very different disintegration profile than the maltodextrins. The disintegration time of the tablets containing lactose was very short and insensitive to the applied pressure up to 150 MPa, above which it increased with further increases in applied pressure.

An explanation of the relatively long disintegration times of the maltodextrins tablets was probably because of the formation of a visible "gel" layer around the tablet which formed on immersion into water. This layer seemed to be the rate controlling step, and was the main reason for all the maltodextrins to exhibit similar disintegration behavior, in spite of differences in applied pressure, tablet crushing force, and method of manufacture. It must also be kept in mind that soluble excipients often do not disintegrate, they dissolve.

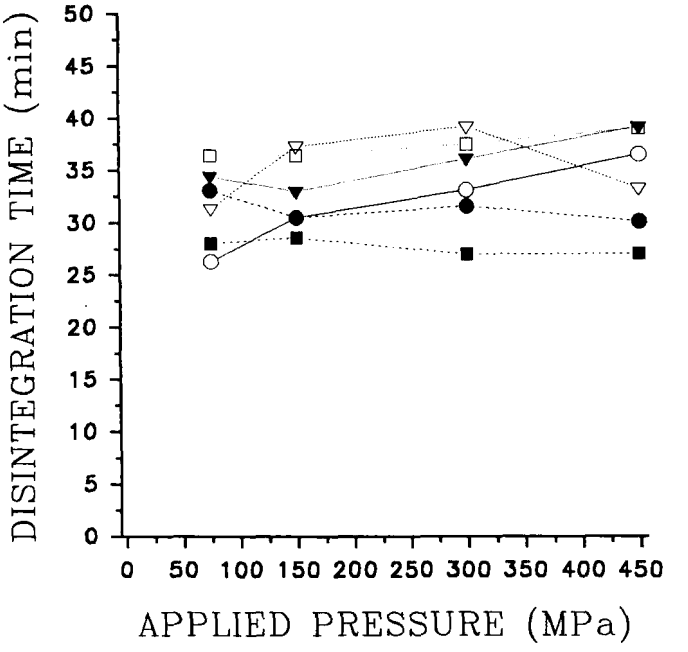

FIGURE 14. Disintegration Time vs Applied Pressure for the compacts containing excipients at 25.0% concentration

○ = Experimental Maltodextrin ; ● = Maltrin M510 ; ▽ = Maltrin M500

▼ = Malta*Gran TG ; □ = Malta*Gran 10 ; ■ = Fast-Flo lactose

This means that longer disintegration times may be seen with soluble materials as compared to insoluble materials which may "breakup" on disintegration testing. Figures 11-14 all show similar profiles to each other due to the mean tablet disintegration times depending on the solubility properties of acetaminophen. No significant differences were seen between the maltodextrins at each concentration, while Fast-Flo lactose had a slightly faster disintegration time than the maltodextrins at corresponding concentrations.

The friability testing values are shown in Table 1. When compressed above 150 MPa applied pressure, all formulations containing excipients at 99.5% concentration resulted in tablets with acceptable friability values of less than 1.0%. When drug loading was increased to 25% the friability values all increased, with Fast-Flo lactose having the greatest degree of friability over the range of pressures tested. Considering that flat-faced

TABLE 1. Percent Friability of the Tablets of the Formulations Used

Mixture Ratio Excipient/ Acetaminophen	Pressure (MPa)	Experimental Maltodextrin	Maltrin M510	Maltrin M500	Malta*Gran TG	Malta*Gran 10	Fast-Flo lactose
100/0	450	0.37	0.09	0.45	0.51	0.70	0.27
100/0	300	0.37	0.26	0.40	0.53	0.26	0.32
100/0	150	0.34	0.28	0.49	0.78	0.41	0.88
100/0	75	0.37	1.72	1.31	2.72	0.39	26.42
75/25	450	1.02	0.53	0.72	0.80	1.88	28.82
75/25	300	0.39	1.53	0.74	1.60	0.58	2.21
75/25	150	0.63	0.95	1.26	1.91	0.39	1.82
75/25	75	1.40	4.24	3.39	7.34	0.53	3.40
50/50	450	2.59	3.82	2.44	1.97	7.89	100.00
50/50	300	2.67	5.81	2.79	1.83	3.29	100.00
50/50	150	3.02	8.97	7.80	3.56	2.58	68.42
50/50	75	3.75	27.33	24.73	17.63	3.90	100.00
25/75	450	53.97	72.66	74.80	53.10	87.11	73.22
25/75	300	33.63	72.28	58.30	45.70	41.73	84.40
25/75	150	24.81	100.00	53.80	100.00	49.78	100.00
25/75	75	100.00	100.00	89.80	100.00	40.38	100.00

punches were used, instead of bevel edged, all of the materials have acceptable friability values when compacted above 150 MPa except for Fast-Flo lactose which has marginal values at best. At 50% concentration, all friability values were unacceptably high. At 75% loading of drug all the tablets almost completely broke, and this phenomena correlated well with the loss of tablet crushing force values (Figures 7-9).

CONCLUSIONS

Maltodextrins were found to be satisfactory filler/binder excipients in terms of their compaction properties and loading potentials. They exhibited adequate binding potential at acetaminophen drug loading levels of only up to twenty-five percent. Although the degree of binding ability and loading potential with acetaminophen differed from one type of maltodextrin to the other, all of them formed stronger compacts than Fast-Flo lactose. The energy involved during the compaction of a formulation and the crushing force values of the resulting tablets decreased as the concentration of the maltodextrin in that formulation was reduced.

Regardless of the magnitude of the applied pressure, the tablets containing maltodextrins exhibited prolonged disintegration times due to the formation of a "gel" layer around the tablet which formed on immersion into water.

ACKNOWLEDGEMENTS

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