DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 19(17&18), 2335-2358 (1993)

CHARACTERIZATION OF DIRECTLY COMPRESSIBLE MALTODEXTRINS MANUFACTURED BY THREE DIFFERENT PROCESSES

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ABSTRACT

Five types of maltodextrins which were physically processed by the methods of spray drying, fluidized bed agglomeration, and roller compaction were compared in terms of their pre-, during and post-compaction properties. The maltodextrins all had relatively high moisture contents, and small surface areas. Intrinsic compaction testing found that the maltodextrins all formed stronger tablets than Fast-Flo lactose, and had longer disintegration times which were found to be insensitive to pressure. The roller compacted material had the most fragmentary behavior of the five types of maltodextrins examined. Dissolution testing showed that the maltodextrins had longer release rates than Emdex or Fast-Flo lactose, however the maltodextrin formulations were able to pass a modified USP dissolution test.

INTRODUCTION

The search for new materials which can be used as direct compression filler/binders has led to the introduction of maltodextrins in tablet formulations. Maltodextrins are composed of water soluble glucose polymers which are produced from the reaction of starch with acid and/or enzymes. Wartman et al. (1), defined a maltodextrin as "a purified concentrated aqueous solution of nutritive saccharides obtained from edible starch or the dried product derived from said solution, and having a dextrose equivalent value of less than twenty". The FDA defines maltodextrins, $(C_6H_{10}O_5)_n*H_2O$, (CAS #9050-36-6), as "non-sweet nutritive saccharide polymers that consist of D-glucose units linked primarily by alpha 1-4 bonds, and having a D.E. value of less than twenty". Maltodextrin is generally recognized as safe, (GRAS), as a direct human food ingredient at levels consistent with current good manufacturing practices (21CFR 184.1444). The term, dextrose equivalent value, of a starch hydrolysate is an expression for describing the total reducing sugars content of a material calculated as dextrose, and expressed as percent dry basis. A starch conversion product having a dextrose equivalent value above twenty is generally referred to as a corn syrup solid, whereas starch conversion products having only a trace amount of dextrose are referred to as dextrins. A starch conversion product having a measurable D.E. value of about twenty, and also having a trace amount of dextrose is known as a hydrolyzed cereal solid or maltodextrin. Thus far, only a few papers have appeared in the literature concerning the use of maltodextrins as direct compression excipients (2-5).

Characterization of pharmaceutical solids has been outlined by Jones (6), and more recently by Brittain (7). The methodology of the latter worker is used here and physical properties are classified as being associated with the molecular level (properties associated with individual molecules), the particulate level (properties pertaining to individual solid particles), or the bulk level (properties associated with an assembly of particulate species).

The aim of this study was to characterize the powder and compact properties of five types of maltodextrins which were manufactured by three different methods and to compare the results with a commonly used soluble filler/binder, Fast-Flo lactose.

MATERIALS AND METHODS

The maltodextrins used were: Maltrin M510 Lt#A3533, DE = 9-12, which is a spray dried product, and Maltrin M500 Lt#094906, DE = 9-12, which is a fluidized bed agglomerated material, both by Grain Processing Co; Malta*Gran TG Lt#A1009 and Malta*Gran 10 Lt#A1500, DE = 10, which are fluidized bed agglomerated products by Zumbro/IFP Inc; and Experimental Maltodextrin Lt#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 filler/binder excipients used for comparison studies included: Lactose USP hydrous (Fast-Flo lactose) Lt#1RM912 by Foremost Whey Products; Dextrates, NF, Hydrated (Emdex), Lt# J22X by Edward Mendell Co.; Dibasic Calcium Phosphate Dihydrate, USP, (Emcompress), Lt# 3083X by Edward Mendell Co. The active drug substance used was Propranolol HCl, Lt# 4149 by Forum Chemical Co.. Magnesium Stearate N.F., Lt# 2256KCCA by Mallinckrodt Co., was used as a lubricant in the dissolution experiments.

The powders were used as received, and humidity control was achieved by storing the materials in desiccators above saturated salt solutions of magnesium nitrate which maintained 52.8% relative humidity, as per Nyqvist (8), for at least two weeks prior to testing.

The flowability of the powders were tested with an automated powder flow tester, (Powder Flow Tester, Type PTG, Pharmatest, Hainburg, Germany), with a circular aperture opening of 10 mm. The moisture content was determined by the loss on drying method at 100°C (Computrac Max 50, Arizona Instr. Co., Tempa, AR). The bulk and tap densities of the powders were determined (100 taps in 100 ml glass cylinder with JEL apparatus, J. Engelsmans, Germany), while the true density was found by helium pycnometer, (Quantachrome Multipycnometer, Syossett, N.Y.). The reported results for flow, density, and moisture content are a mean of three replicates.

Particle size analysis was performed using a sonic sifter (ATM Co., Milwaukee, WI) for the individual filler/binder excipients tested.

Surface area measurements were performed by the nitrogen adsorption multi-point BET method (Quantasorb Sorption System, Quantachrome Corp., Syosset, N.Y.). The powders were vacuum dried for six hours at 60°C, then degassed with nitrogen for a minimum of one hour prior to testing.

The photomicrographs of the materials in powder form were taken using a scanning electron microscope (Amray 1400, Amray Inc., Bedford, MA, USA). The photomicrographs were all taken at 100X, 400X, and 1200X magnifications.

The powders were compacted into tablets employing an Integrated Compaction Research System (Mand Testing Ltd., Stourbridge, U.K.) which utilized a "sawtooth", i.e. 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 subjected to the same punch velocity during the compaction event, without needing to adjust the punch profiles for each excipient due to variations in the bulk densities. A standard set of flat-faced, round, 10.3 mm, BB tooling was used. Comparisons between materials 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, i.e. punches, load cells, and other components in linear series with the punches, was accounted for by a "punch on punch" method. Deformation of the upper and lower punch was determined up to 40 kN, and these values 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 in the intrinsic compaction experiments were made without any lubrication. This was accomplished by manually cleaning the punch and die set with alcohol after every three compaction tests.

The physical testing of the tablets was performed 24 hours after ejection to allow for viscoelastic expansion. The physical measurements and tests 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 values are the mean of 10 tablets. The disintegration times are a mean of 5 tablets in distilled water at 37° C,

without the use of disks. The friability value is that of a single run of 10 tablets, with the friabilator revolving at 25 rev/min for 4 minutes.

The formulations used in the dissolution testing were made with a batch size of 35 grams. The formula's were composed of; filler/binder 84.5%, propranolol HCl 15%, and magnesium stearate 0.5%, by weight. The blending procedure was to mix the propranolol HCl and filler/binder for 10 minutes in a Turbula T2C mixer (Glen Mills Inc., N.J., USA), then add the magnesium stearate and mix for an additional 2 minutes. The formulations were compared to each other by compacting the mixtures to two mean pressures of 50 and 150 MPa.

The dissolution testing was performed per the USP XXII (9) requirement for propranolol HCl tablets, with the exception that Apparatus Type II, paddle method at 50 rpm, was used instead of Apparatus Type I. (Vankel VK 6010 Dissolution Prep Center, and VK 3000 Intelligent Fraction Collector, Vankel Industries, Edison, NJ). Propranolol HCl concentration was determined spectrophotometrically (Lambda 3B Spectrophotometer, Perkins Elmer).

RESULTS AND DISCUSSION

Powder Properties

Particulate Level

Scanning electron photomicrographs of the maltodextrins examined are shown in Figures 1-5. The photomicrographs are at 100X, 400X, and 1200X magnification, from top to bottom, respectively. Figure 1 is of experimental maltodextrin, the roller compacted material. It shows a very dense structure, as compared with the other maltodextrins, and has many small particles adhering to the surface. There does not appear to be as many large pores as with the other maltodextrins, which were spray dried or fluidized bed agglomerated. Figure 2 is of Maltrin M510, which is spray dried, and shows a relatively smooth surfaced material with a generally round shape. At the higher magnifications, large pores are distinctly seen. Figure 3 is of Maltrin M500, a fluidized bed agglomerated maltodextrin, and appears as a very large porous mass with many irregularities. The photomicrograph indicates that the powder has a very smooth surface,

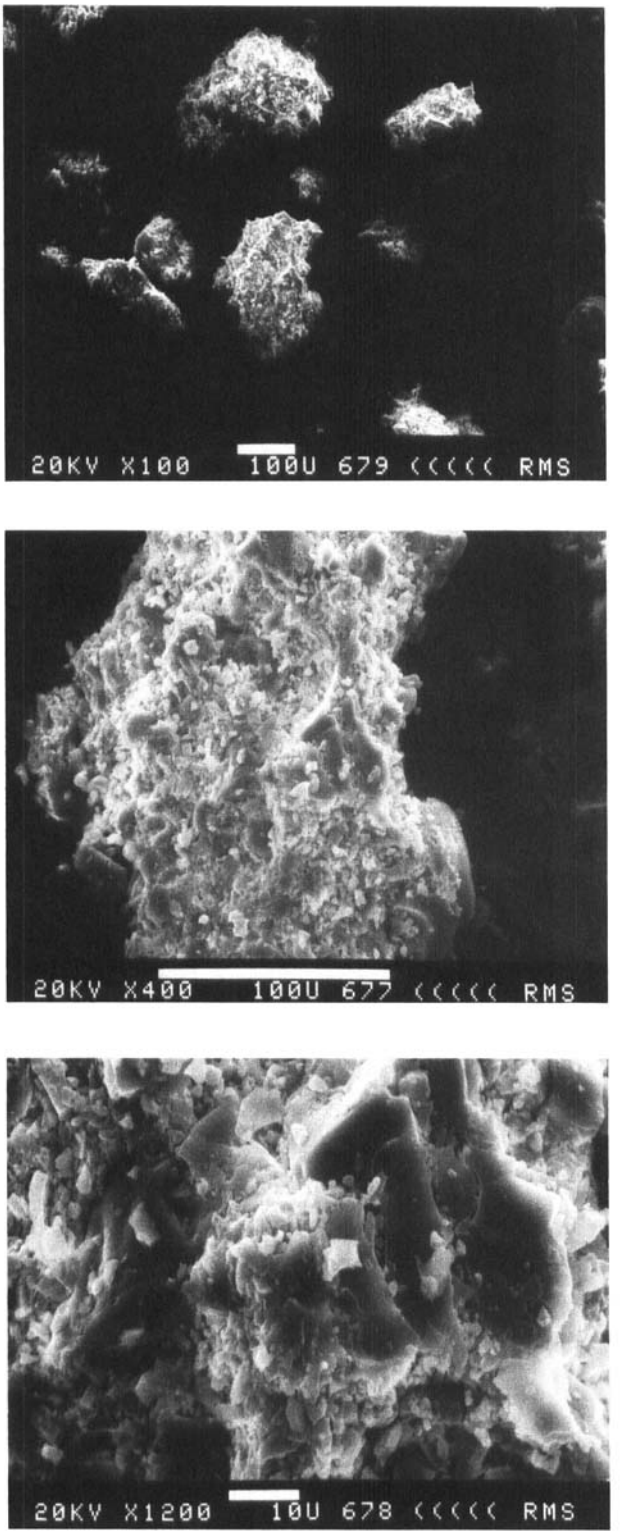

FIGURE 1
Scanning Electron Photomicrographs of Experimental Maltodextrin

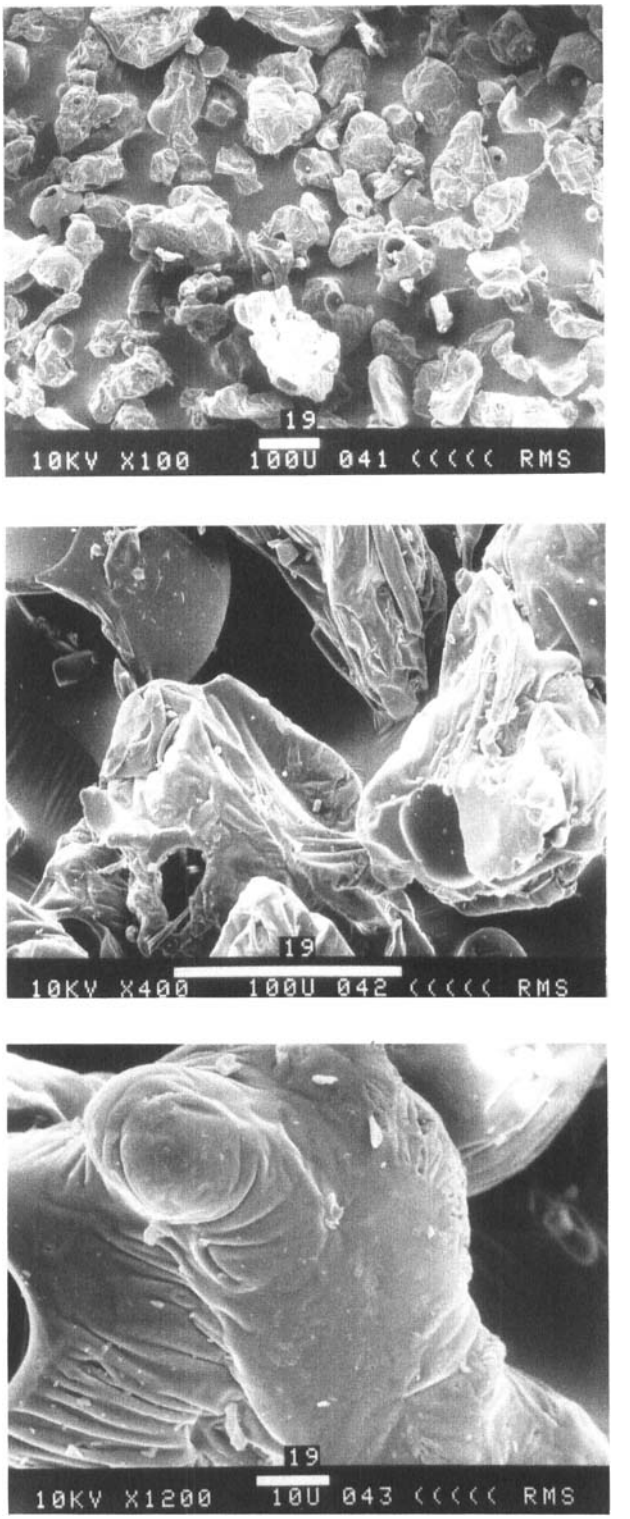

FIGURE 2
Scanning Electron Photomicrographs of Maltrin M510

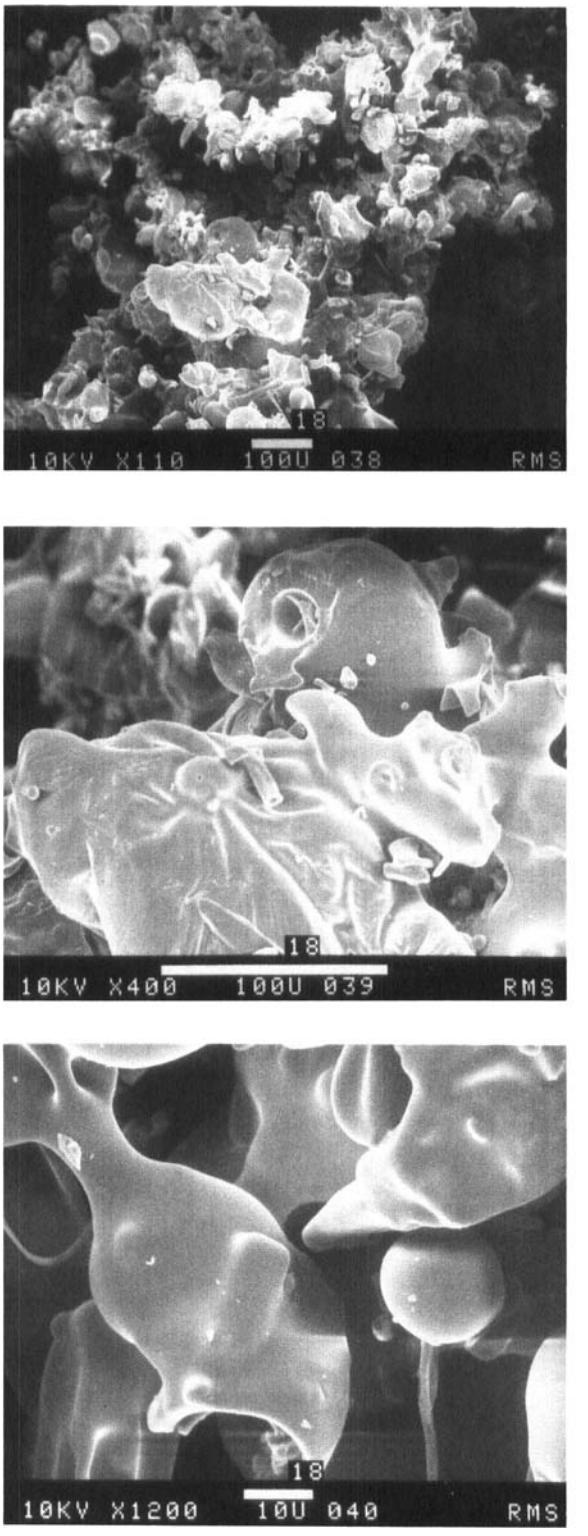

FIGURE 3
Scanning Electron Photomicrographs of Maltrin M500

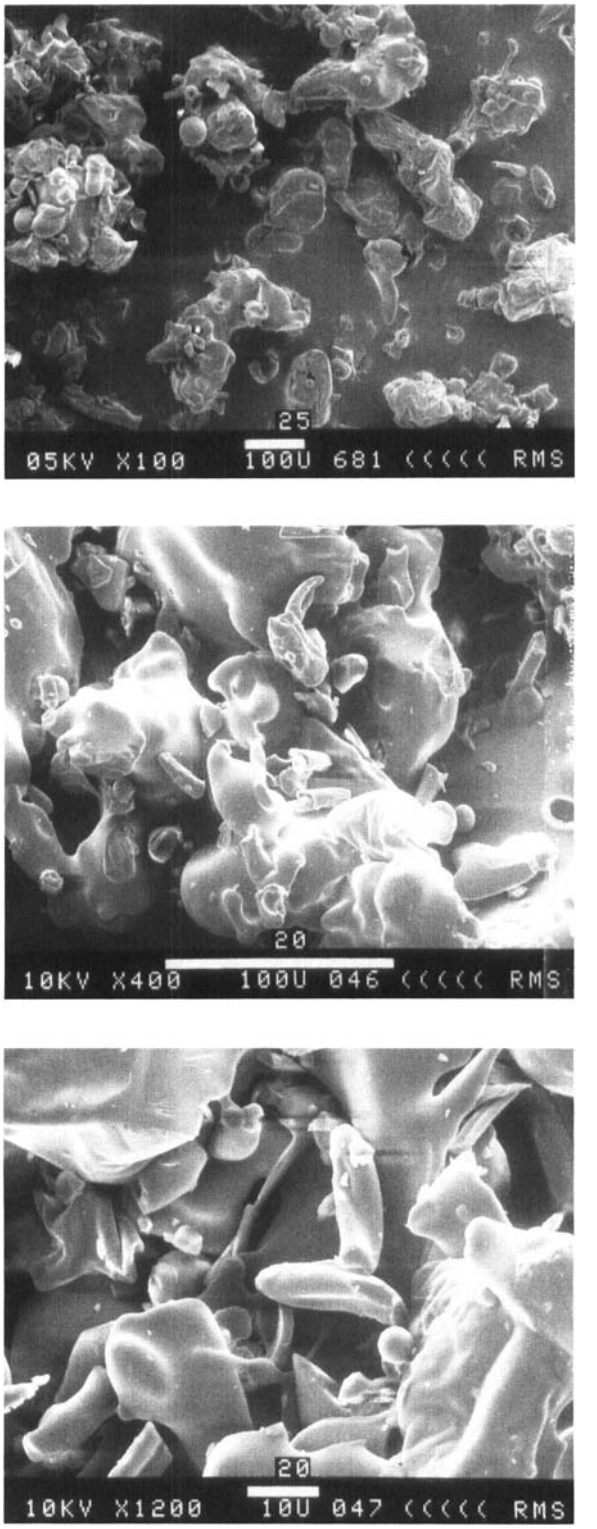

FIGURE 4
Scanning Electron Photomicrographs of Malta*Gran TG

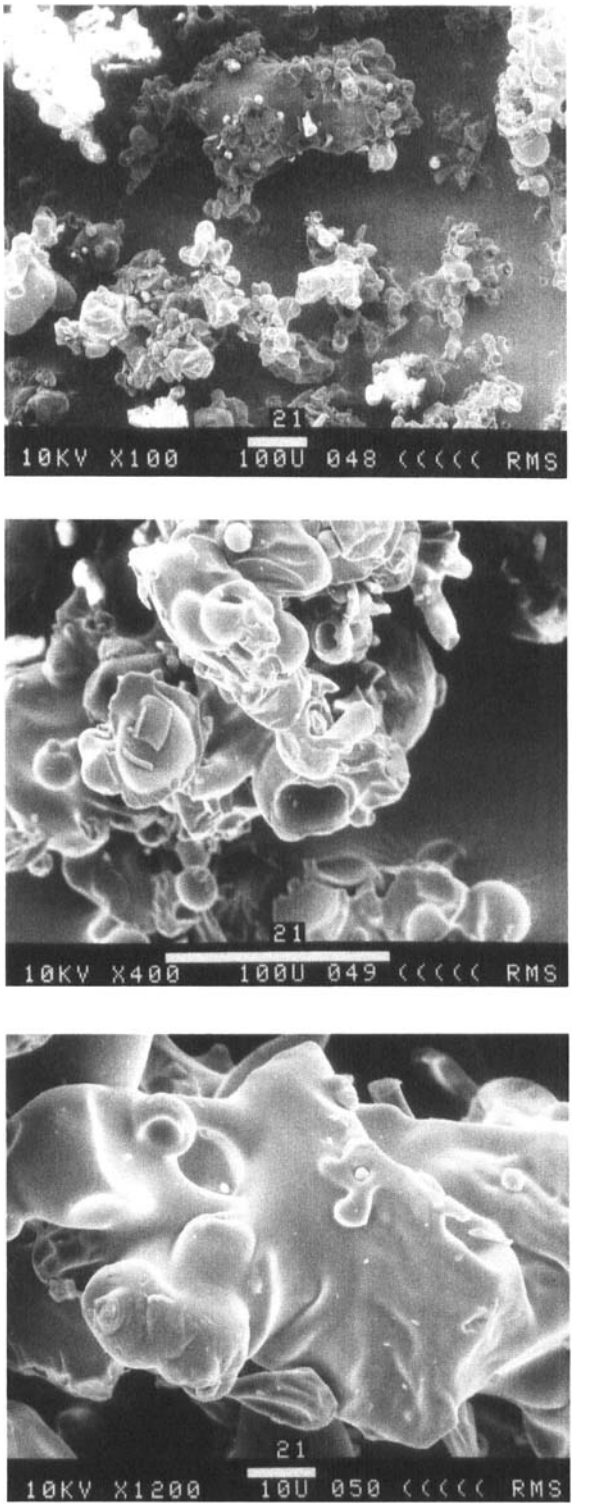

FIGURE 5
Scanning Electron Photomicrographs of Malta*Gran 10

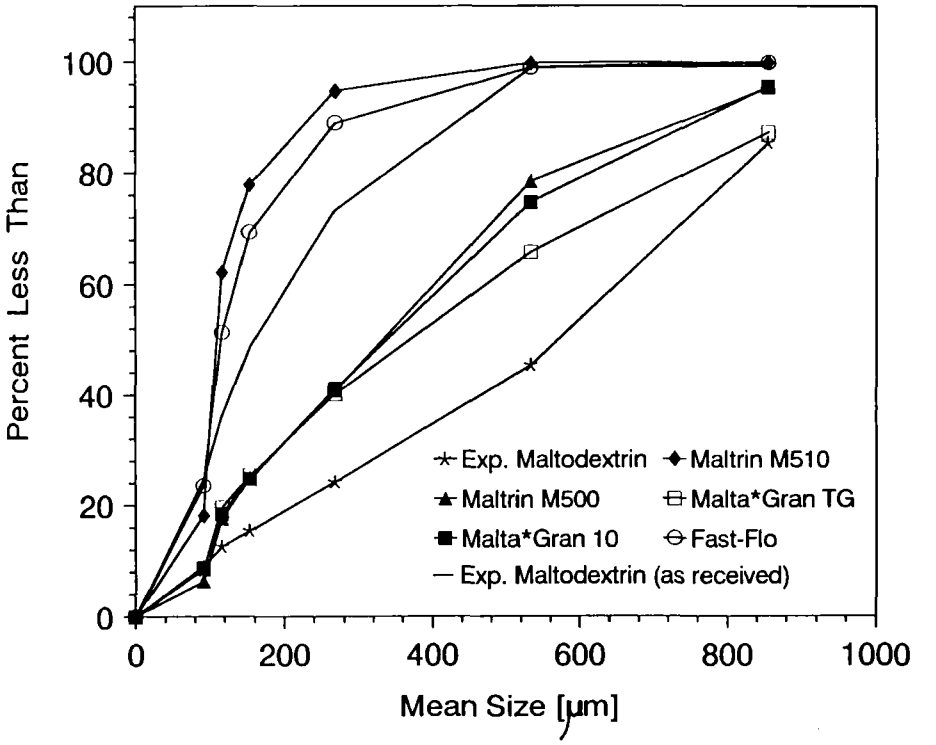

FIGURE 6
Particle Size Distribution of the Excipients Used

especially when examined at high magnification. Figure 4 is of Malta*Gran TG, another fluidized bed agglomerated material, and the powder exhibits a similar structure to the other agglomerated maltodextrins, with a smooth surface and numerous large pores are evident. Figure 5 is of Malta*Gran 10, also a fluidized bed agglomerated material, and it appears to be structurally similar to the other agglomerated maltodextrins.

The particle size distributions of the filler/binders are shown in Figure 6. The mean geometric weight size of the materials from log probability plotting of the data is shown in Table 1. The maltodextrins are of a particle size larger than is generally found in direct compression tableting, 50 μm to 200 μm is the average, with the exception of Maltrin M510. Experimental maltodextrin is shown both "as received" as well as the distribution of the fraction which was used in the remainder of the study.

TABLE 1

Mean Particle Size of Excipients Studied

Excipient	Mean Particle Size (μm)
Exp. Maltodextrin (as received)	490
Exp. Maltodextrin	179
Maltrin M510	104
Maltrin M500	260
Malta*Gran TG	318
Malta*Gran 10	285
Fast-Flo Lactose	109

The moisture content of a filler/binder is an important physical characteristic, especially with regard to flowability and compactability of a powder. The moisture content, by the loss on drying method, of the "as received" materials, as well as the moisture content after equilibrium at 53% relative humidity for 2 weeks, are shown in Table 2. The maltodextrins all have a relatively high moisture content and all absorbed water when equilibrated at 53% humidity.

Bulk Level

The surface area results recorded by the multi-point BET method of nitrogen adsorption, as shown in Table 3, exhibited significant differences between the materials depending upon their method of processing. The roller compacted material, experimental maltodextrin, had a much larger surface area than the spray dried and fluidized bed agglomerated materials. This higher surface area was illustrated by the scanning electron micrographs, which showed a surface with many small agglomerates at all magnifications. The spray dried and fluidized bed agglomerated materials had very smooth surfaces, as shown by the photomicrographs, and this was quantified by the measurement of small surface areas.

TABLE 2

Moisture Content (%) of Measurements Using Loss on Drying Method

Excipient	Moisture Content	Moisture Content at 53% RH
Exp. Maltodextrin	7.39	7.81
Maltrin M510	6.22	8.20
Maltrin M500	6.10	8.84
Malta*Gran TG	6.53	8.46
Malta*Gran 10	4.86	8.83

TABLE 3

Specific Surface Area of Measurements Using BET Method

Excipient	Specific Surface Area (m^2/g)
Exp. Maltodextrin	1.73
Maltrin M510	0.31
Maltrin M500	0.54
Malta*Gran TG	0.40
Malta*Gran 10	0.50

The densities of the "as received" materials are shown in Table 4. The bulk densities show considerable differences between the various materials. The fluidized bed agglomerated maltodextrins, Malta*Gran TG, Malta*Gran 10, and Maltrin M500, have relatively low bulk and tap densities, which would be expected from their method of processing. The roller compacted maltodextrin has a higher density, and this is directly attributable to its method of processing. The roller compacted maltodextrin, as well as Fast-Flo lactose and Maltrin M510 show higher bulk and tap densities.

TABLE 4

Densities (g/ml) of the Excipients Studied

Excipient	Bulk Density	Tapped Density	True Density
Exp. Maltodextrin	0.54	0.65	1.503
Maltrin M510	0.48	0.54	1.425
Maltrin M500	0.26	0.32	1.410
Malta*Gran TG	0.37	0.43	1.424
Malta*Gran 10	0.28	0.34	1.417
Fast-Flo Lactose	0.57	0.66	1.525

TABLE 5

Flow Indices of the Excipients Studied

Excipient	Gravimetric (g/min)	Volumetric (ml/min)	Angle of Repose (°)	Carr's Index
Exp. Maltodextrin	237	436	36.1	15.7
Maltrin M510	363	759	28.4	11.0
Maltrin M500	166	643	35.2	17.8
Malta*Gran TG	263	707	32.4	14.3
Malta*Gran 10	188	665	34.3	17.0
Fast-Flo Lactose	505	881	29.7	12.9

The flow testing results are shown in Table 5. Flowability was tested by flow through an orifice and static angle of repose methods. Conversion from gravimetric to volumetric flow rates utilized the bulk densities of the materials tested. Carr's Compressibility Index (10) is:

$$\text{Percent Consolidation} = \frac{\text{Tapped Density - Bulk Density}}{\text{Tapped Density}} \times 100 \qquad \text{[Eq. 1]}$$

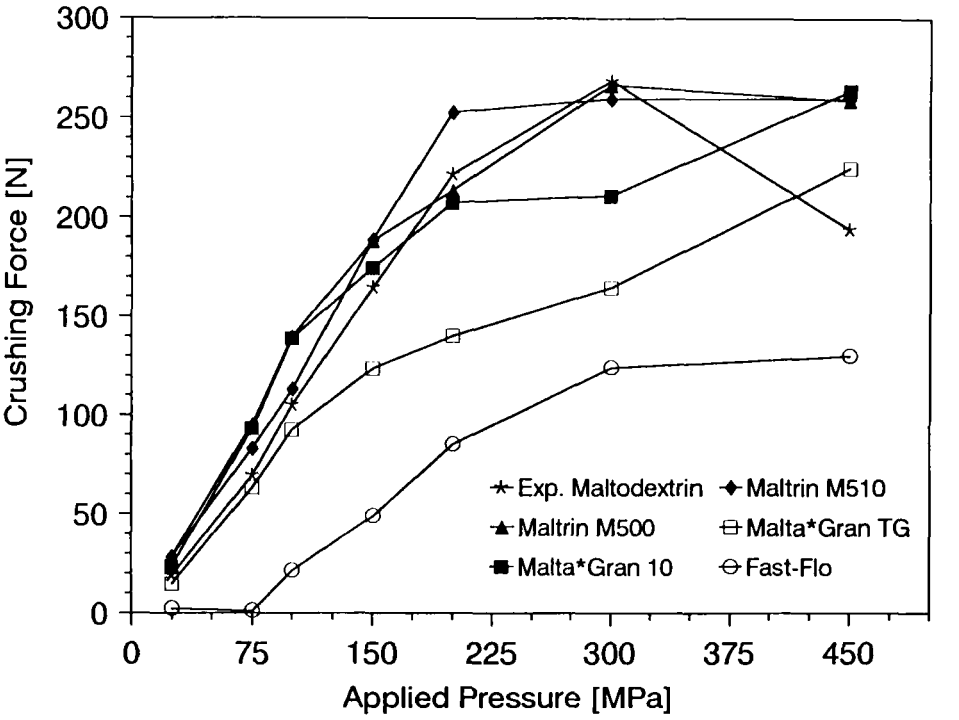

FIGURE 7
Crushing Force vs Maximum Applied Pressure for the Compacts of Unlubricated Excipients

The results from the gravimetric method of powder flow analysis showed great differences between the materials, with the high bulk density materials having a high flow rate, the low bulk density materials having a very low flow rate. Conversion from gravimetric to volumetric terms gave results in which the materials appear to behave similarly to each other. The angle of repose results generally correlated with the gravimetric results, however, because only very small differences existed between the repose angles, it is difficult to use this as a differentiating method. Carr's Flow Index correlated well with the gravimetric results and was an easy and useful method to differentiate flow behavior among the excipients tested.

Compact Properties

Intrinsic Compaction

One of the most common methods used to describe the compaction behavior of a material is to plot the tablet crushing force vs applied force or pressure. The maltodextrins examined are shown in Figure 7 along with Fast-Flo lactose which was used as a reference material. Unlubricated powders were compacted at seven different fixed pressures from 25 to 450 MPa mean pressure. Maltrin M500, Maltrin M510 and Malta*Gran 10 all exhibited similar behavior with a linear increase in crushing force values for pressures up to approximately 200 MPa, after which much smaller changes in these values occurred with further increases in pressure. Malta*Gran TG showed a profile which increased at a somewhat quadratic rate with no limiting pressure being reached. Experimental Maltodextrin had a similar profile to Maltrin M500, Maltrin M510, and Malta*Gran 10, up to 300 MPa, after which further increases in pressure caused a decrease in tablet strength. One potential reason could be because of increasing amounts of stored elastic energy which forms at high pressures and the release of this energy then overcomes the bond strength of the material on decompression. Another potential reason could be because of disruption of bond strength on ejection due to the lack of lubrication. Since edge chipping was noted after ejection, the lack of lubrication and disruption of bonds may be the most probable cause since stresses will be highest at the edges of the tablet. Fast-Flo lactose formed much weaker tablets than all the maltodextrins, with compact formation of zero strength at pressures up to 75 MPa. Tablet strength increased from 75 MPa up to 300 MPa, after which no further increases in strength occurred with increasing pressure.

The disintegration times of the tablets are illustrated in Figure 8. All of the maltodextrins exhibited similar behavior with a linear increase in disintegration times with pressures up to 75 MPa, after which little change in disintegration time was noted with further increases in pressure. This result is significant for the maltodextrins because of the lack of correlation with the crushing force values. The maltodextrins disintegration behavior was not controlled by the porosity of, or bonding within, the tablet, as shown by the lack of correlation with tablet crushing force profiles, but instead was controlled by a rate limiting "gel" layer which formed around the tablet on immersion into water. This layer is the controlling step in disintegration behavior and is the reason for the

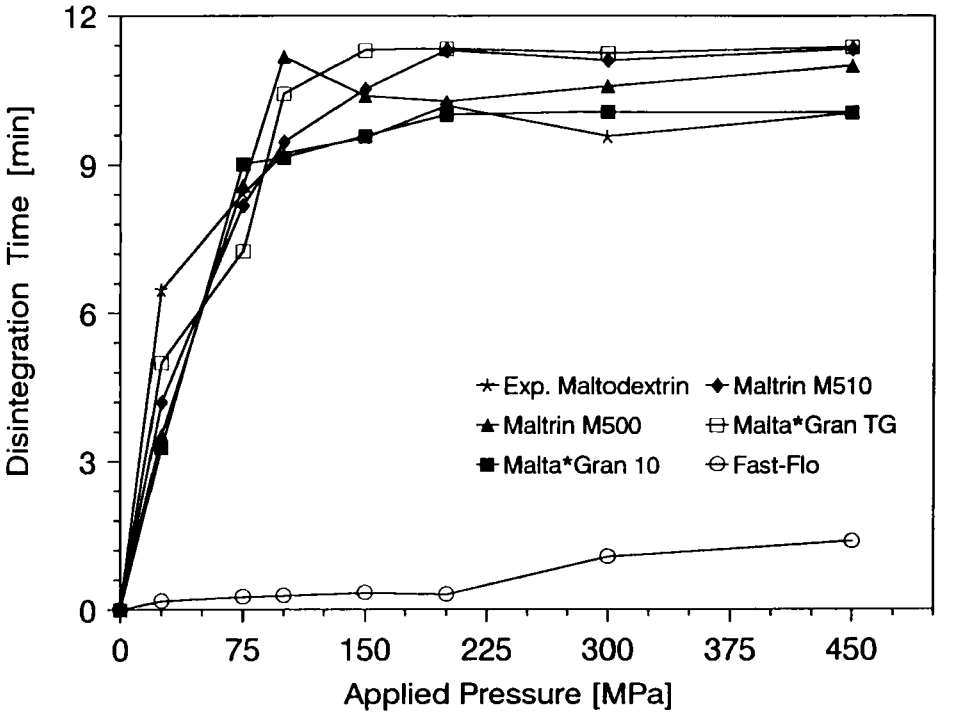

FIGURE 8
Disintegration Time vs Maximum Applied Pressure for the Compacts of Unlubricated Excipients

maltodextrins having almost identical disintegration behavior, in spite of differences in the method of processing or tablet crushing force values. Fast-Flo lactose had a totally different type of behavior, and all of the disintegration times for this material were very short.

Figure 9 is a graph of the log of tablet friability values vs maximum applied pressure. All the maltodextrins had satisfactory friability values, under one percent, in the range of 75 to 300 MPa. At low pressures, under 75 MPa, they had higher friability values, and additionally the Experimental Maltodextrin had a high friability value at 450 MPa which correlated with its loss of tablet strength. Fast-Flo lactose had a high friability value at all pressure ranges with obvious chipping occurring at the edges of the flat-faced tablets. The combination of weak tablets, and high friability values indicate

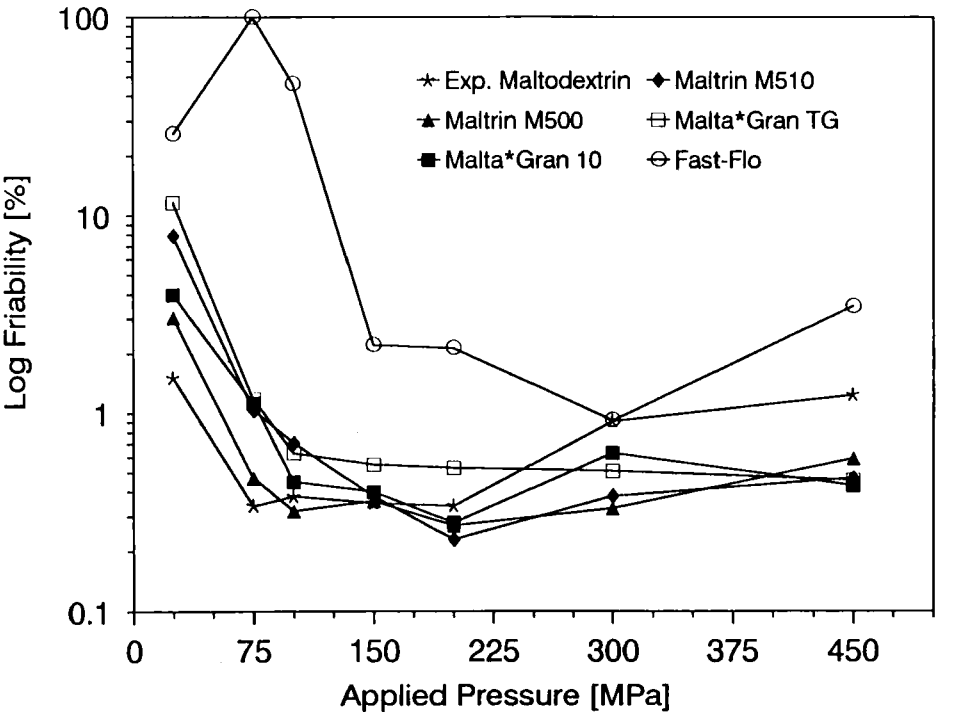

FIGURE 9
Log Friability vs Maximum Applied Pressure for the Compacts of Unlubricated Excipients

that experimental maltodextrin (at the higher pressures) and Fast-Flo lactose (at all pressures) were much more sensitive to the lack of lubricant than the other maltodextrins, and a disruptive effect on tablet bonds occurred on ejection. The friability values reinforce this theory due to the high stresses which occurred on the top and bottom edges of a tablet as it was ejected, and this is exactly the area that friability testing attempts to quantify.

The following equation was derived by Heckel (11,12) in order to interpret density-pressure relationships in compaction studies:

$$\ln [1/(1-\rho r)] = KP_a + A \qquad \text{[Eq. 2]}$$

TABLE 6

Yield Pressure (P_y) Values Calculated From "In-Die" and "Out-of-Die" Measurements

Excipient	In-Die Measurements			Out-of-Die Measurements		
	"F" Value	R^2	P_y (MPa)	"F" Value	R^2	P_y (MPa)
Exp. Maltodextrin	56270	0.999	143	1098	0.998	135
Maltrin M510	39328	0.998	97	11013	0.999	78
Maltrin M500	10107	0.992	63	18476	0.999	62
Malta*Gran TG	12436	0.997	64	292	0.990	86
Malta*Gran 10	10577	0.995	74	688	0.996	65
Fast-Flo Lactose	119830	0.999	181	373	0.992	194

where ρ_r is the relative density of the compact, P_a is the applied pressure, K and A are constants which can be determined from the slope and intercept of the extrapolated linear region of the plot. Hersey and Rees (13) related the constant K to the mean yield pressure (P_y) of a material by:

$$K = 1/P_y \qquad \text{[Eq. 3]}$$

Materials with high yield pressure values are classified as brittle fracturing or fragmentary, whereas materials with low values are classified as plastic/elastic deforming materials. The Heckel equation was calculated from the tablet dimensions, both during the compaction event, and after ejection, and the yield pressure values were determined by fitting linear sections of the slopes. The out-of-die data used mean porosity determined from the dimensions of 10 tablets at each maximum applied pressure, and from 4 to 7 data points per curve were used in the linear fitting procedure. The in-die data were determined from the mean of three compaction events. The results are shown in Table 6. The R^2 values and F-test values give confidence to the degree of fit to a

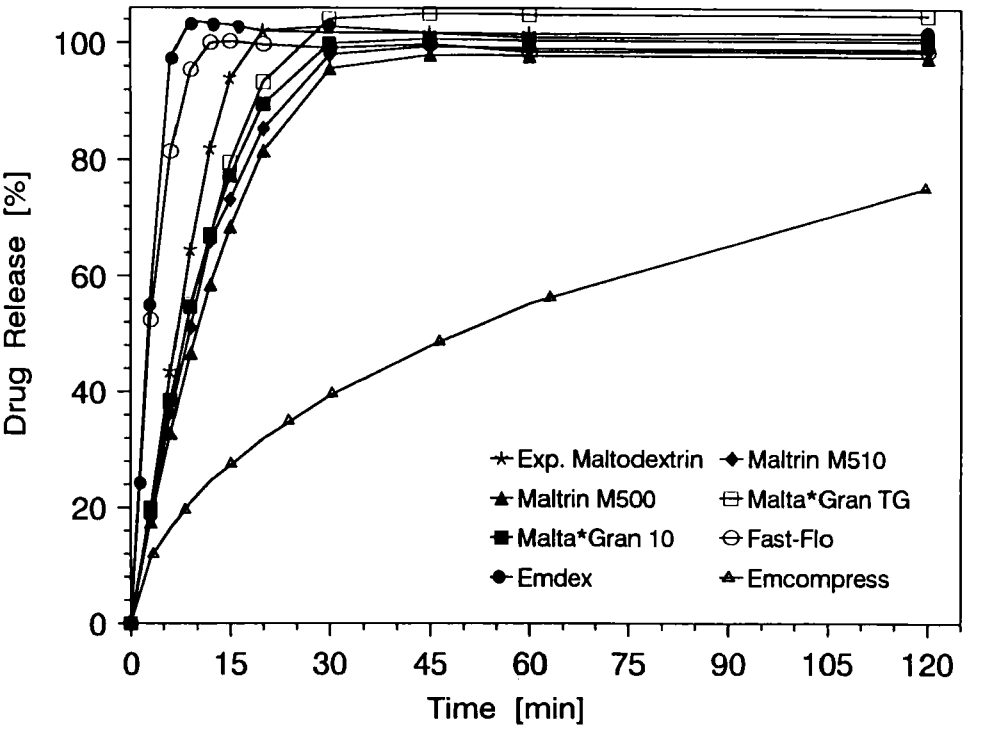

FIGURE 10
Percent Propranolol HCl Release Profiles From the Compacts Made at 50 MPa Pressure

linear equation. Although this method of determining "yield pressure" has drawbacks over what exactly can be considered linear, it does have usefulness in determining a relative number for the degree of plastic/elastic and brittle behavior of materials when used in a comparison study. The yield pressures determined from both methods were in generally good agreement with each other. Fast-Flo lactose is a material with known brittle behavior, and had the highest yield pressure. Experimental maltodextrin is a roller compacted material and this process was expected to give a degree of brittle behavior to the material, which is proven out by its high yield pressure. The other maltodextrins all had similar yield pressures which indicate that they are plastic/elastic deforming types of materials.

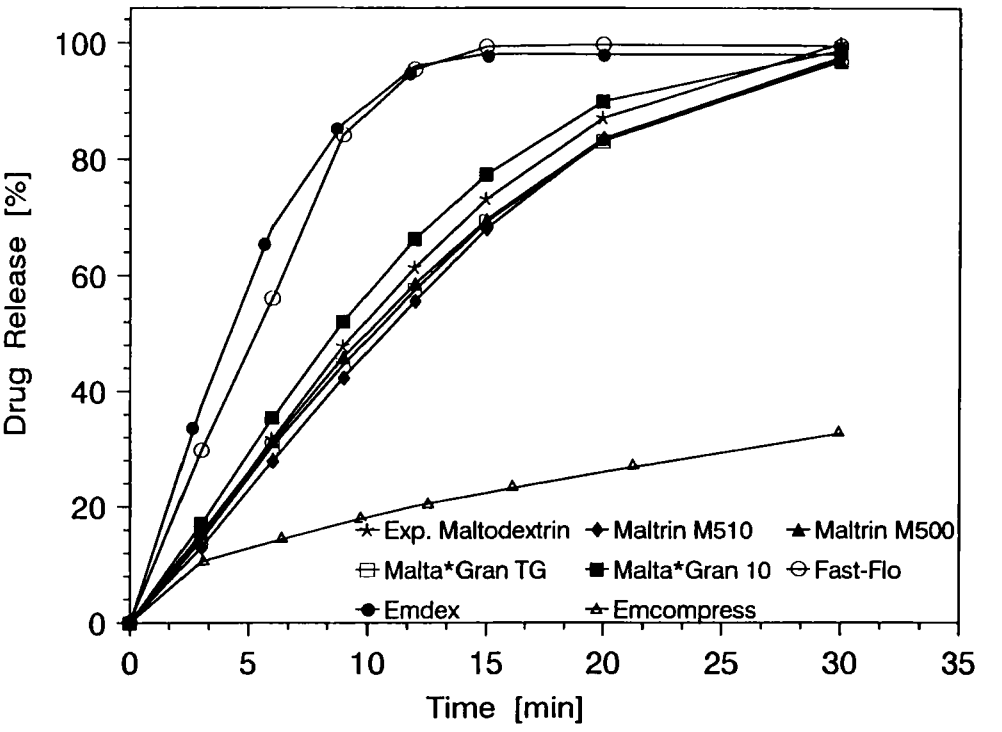

FIGURE 11
Expanded Initial Portion of the Percent Propranolol HCl Release Profiles From the Compacts Made at 50 MPa Pressure

Figure 10 is a graph of all the excipient formulations at 50 MPa, and shows the percent drug release profiles in a rank order of; Emdex, Fast-Flo lactose, Experimental Maltodextrin, then the other maltodextrins, and finally Emcompress, from fast to slow, respectively. All of the excipient formulations, with the exception of Emcompress, passed USP requirements for dissolution testing. Figure 11 is an expanded section of the initial region of Figure 10, and better illustrates the differences between the dissolution behavior of the materials. Figure 12 is a graph of all the excipients at 150 MPa mean compaction pressure. The same general trend as was observed at 50 MPa was seen, with the major exception occurring with the Experimental Maltodextrin which now shows indistinguishable behavior to the other maltodextrins. Figure 13 is an expanded initial portion of Figure 12, and better illustrates the significant differences seen between the soluble excipients, Fast-Flo lactose and Emdex, with the maltodextrins which all

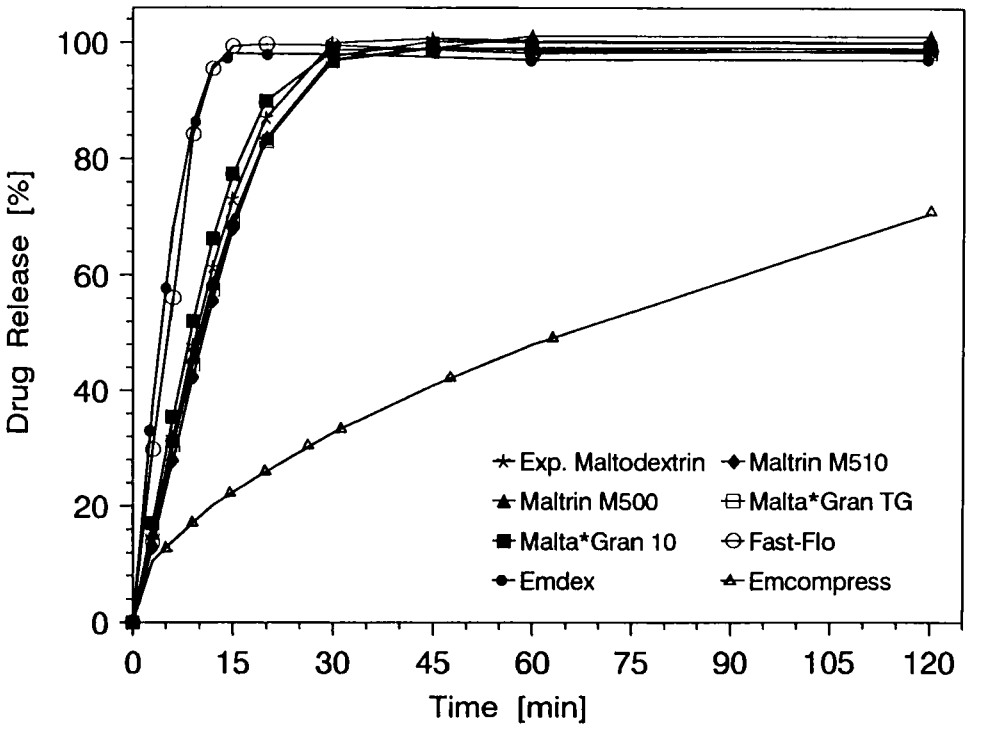

FIGURE 12
Percent Propranolol HCl Release Profiles From the Compacts Made at 150 MPa Pressure

exhibited similar dissolution behavior, as well as compared to the insoluble excipient, Emcompress.

CONCLUSIONS

The roller compacted maltodextrin, experimental maltodextrin, had a much denser structure than the spray dried and fluidized bed agglomerated maltodextrins as illustrated by the scanning electron photomicrographs. The roller compacted powder had a larger surface area than the other maltodextrins, which had small surface areas due to their method of processing. Intrinsic compaction testing found that all the maltodextrins formed stronger compacts than Fast-Flo lactose, and limiting tablet strength generally

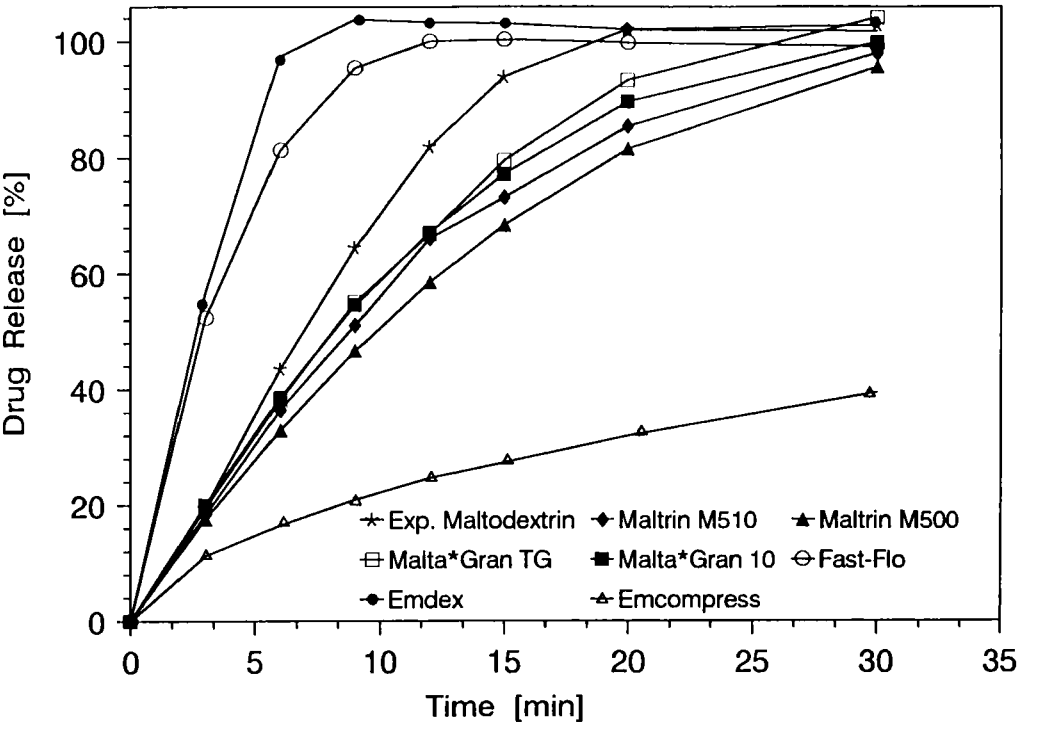

FIGURE 13
Expanded Initial Portion of the Percent Propranolol HCl Release Profiles From the Compacts Made at 150 MPa Pressure

occurred around 300 MPa pressure. The disintegration times of the maltodextrins were all generally long, with the formation of a rate limiting "gel" layer around the tablets. The disintegration times were insensitive to the maximum applied pressure. Heckel plotting of "in-die" and "out-of-die" data was useful in determining relative degrees of brittle to plastic behavior. The roller compacted maltodextrin was the must fragmentary of the maltodextrins tested, while the other maltodextrins exhibited more plastic/elastic deformation behavior.

The results of dissolution testing showed no significant difference in release pattern as a result of compaction pressure for the maltodextrins as well as for the other soluble excipients. Emcompress, an insoluble material, was sensitive to compaction pressure for its release pattern. The maltodextrins all had drug release rates which were indistinguishable from each other, however they all had longer release rates than the

other soluble filler/binders tested, Emdex and Fast-Flo lactose. The maltodextrins all were able to have 80% released in 30 minutes as per USP and passed the test, in spite of their long disintegration times which were seen in previous chapters.

ACKNOWLEDGEMENTS

The authors would like to thank Edward Mendell Co., Zumbro/IFP Inc., Grain Processing Co., and Foremost Whey Products for the supply of materials. The authors would also acknowledge Edward Mendell Co. for financial support of the project.

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