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COMPARATIVE EVALUATION OF A NEW DIRECT COMPRESSION EXCIPIENT, SOLUDEX™ 15

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ABSTRACT

Soludex™ 15, a new corn-based maltodextrin, has been evaluated and compared to nine frequently used commercial excipients for direct compression. The properties of the excipients reported are median size, particle size distribution, bulk density, flow rate, repose angle, moisture content, and hardness and compressibility at several compaction pressures. The influence of concentration of lubricant and mixing time with a lubricant on hardness of Soludex 15 compacts were determined. The effect of 1% magnesium stearate on the hardness of compacts was determined for the ten excipients. Model formulations for direct compression tablets using Soludex 15 are presented, and for a batch of these tablets the weight variation, friability, hardness, disintegration and dissolution are reported. Soludex 15 exhibited excellent flow and compressibility, and model tablets using

Soludex 15 as the direct compression diluent met USP specifications and provided a rapid dissolution of the active ingredient.

INTRODUCTION

Direct compression is widely accepted by the pharmaceutical industry as it is economical because of the reduction of labor cost, time, operational space and machinery utilized. In terms of tablet quality it has the further advantage over wet granulation method that no heat or moisture is used; consequently, thermolabile and moisture-sensitive compounds may be tableted without degradation. Other advantages and limitations of direct compression have been discussed (1).

The currently marketed direct compression excipients may be classified as:

(a) lactose modifications (Fast-Flo lactose, lactose for direct compression)
(b) sucrose modifications (Di-Pac)
(c) starch hydrolyzate (Cantab, Emdex)
(d) cellulose products (Avicel, Emcocel)
(e) inorganic salts (Emcompress, Compactrol)

The properties of an ideal direct compression excipient (2) and those of commercial direct compression excipients (3-5) have been reviewed. No excipient has been found to be ideal. The most significant properties of a direct compression excipient are its flowability and compressibility. This study compares the flowability, compressibility and other characteristics of a new dry corn-based starch hydrolyzate, Soludex 15, to the nine commercial examples cited above.

EXPERIMENTAL

Materials. Avicel™ PH 101, Microcrystalline Cellulose, NF (FMC Corp., Philadelphia, PA. 19103); Cantab™ (Penford Products Co., Cedar Rapids, IA 52406); Compactrol™, Calcium Sulfate Dihydrate, NF (Edward Mendell Co., Inc., Carmel, NY 10512); Di-Pac™, Compressible Sugar, NF (Amstar, New York, NY 10020); Emcocel™, Microcrystalline Cellulose, NF (Edward Mendell Co., Inc., Carmel, NY 10512); Emcompress™, Dibasic Calsium Phosphate, UPS (Edward Mendell Co., Inc., Carmel, NY 10412); Emdex™ (Edward Mendell Co., Inc., Carmel, NY 10512); Fast-Flo™, Lactose #316, Lactose, NF (Foremost, Bloomington, MN 55420); Anhydrous Lactose for Direct Tableting, Lactose NF (Sheffield Products, Norwich, NY 13815); Soludex™ 15 maltodextrin (Penford Products Co., Cedar Rapids, IA 52406); Polyplasdone™ XL, Crospovidone, NF (GAF Chemical Corp., Wayne, NJ 07470); Primojel™, Sodium Starch Glycolate NF (Generichem, Little Falls, NJ 07424); Cab-O-Sil™, Collodial Silicon Dioxide, NF (Cabot Corp., Tuscola, IL 61953); Ac-Di-Sol™ (FMC Corp., Philadelphia, PA 19103).

Moisture Content. The initial moisture content of each excipient was determined using an Ohaus moisture balance. To determine the hygroscopicity tared samples were stored in open containers in desiccators at 47, 70 and 80% relative humidity (6) and room temperature for a 7-day period. Samples were then

weighed to determine the percentage of moisture sorbed. The tabulated values are the average of three determinations.

Size Analysis. Sizing was accomplished by operating for 20 minutes an Allen-Bradley Sonic Sifter fitted with 20- to 325-mesh stainless steel U.S. Standard sieves. A 25 or 50 g sample was used. The median size was determined from a logarithum-probability plot of the size against the cumulative percent equal to or less than a given size.

Flowability. The repose angle was measured by a fixed funnel and free-standing cone method (7). The tabulated repose angle is the average of three measurements. The tabulated rate of flow through a circular orifice 1.905 cm in diameter is the average of five determinations in a flowmeter described in a previous report (8).

Density. The true density of Soludex 15 was found to be 1.515 g/cm^3 by means of a pycnometer using cyclohexane. The bulk density was determined by pouring a sample into a 100 ml-cylindrical graduate and then measuring the volume occupied by the weight of the sample. Tablet density is the quotient of the weight of the tablet to its volume, which was calculated from the dimensions measured by a Starrett thickness gauge.

Compression, Friability and Hardness. A Carver hydraulic press fitted with a guage was used to compress 1.2 g samples of the excipients. Model tablet formulations were compressed using a Stokes Model E press. After allowing 24 hours for elastic

recovery, the hardness was measured by means of a Schleuniger-2E hardness tester. The tabulated value is the average of five determinations. Friability was determined by the Roche friabilator method (9).

Disintegration and Dissolution. Disintegration time was determined using the standard USP method. The dissolution tests for haloperidol, maprotiline hydrochloride and propranolol hydrochloride tablets are specified in the monographs of the USP (10). The dissolution test for clorazepate dipotassium tablets was conducted using USP apparatus 1 operating at 50 rpm with 900 ml of distilled water at 37°C. The pH of a 10% solution of Soludex 15 was 4.

RESULTS AND DISCUSSION

Soludex is a specially processed maltodextrin made from commercial spray-dried materials obtained by the hydrolysis of starch. The morphology of Soludex is shown in Figure 1 and may be compared to that of other excipients (11,12). Some of the physical characteristics of ten direct compression excipients are summarized in Table 1. The flow rate represents the flowability of a material better than the static repose angle; however, as four excipients blocked the flowometer, the angles of repose are reported as a comparative parameter of the ten excipients. The flowability of Avicel, Compactrol, Emcocel and anhydrous lactose for direct compression is unsatisfactory. Since tablet presses function on the volumetric fill of the die cavi-

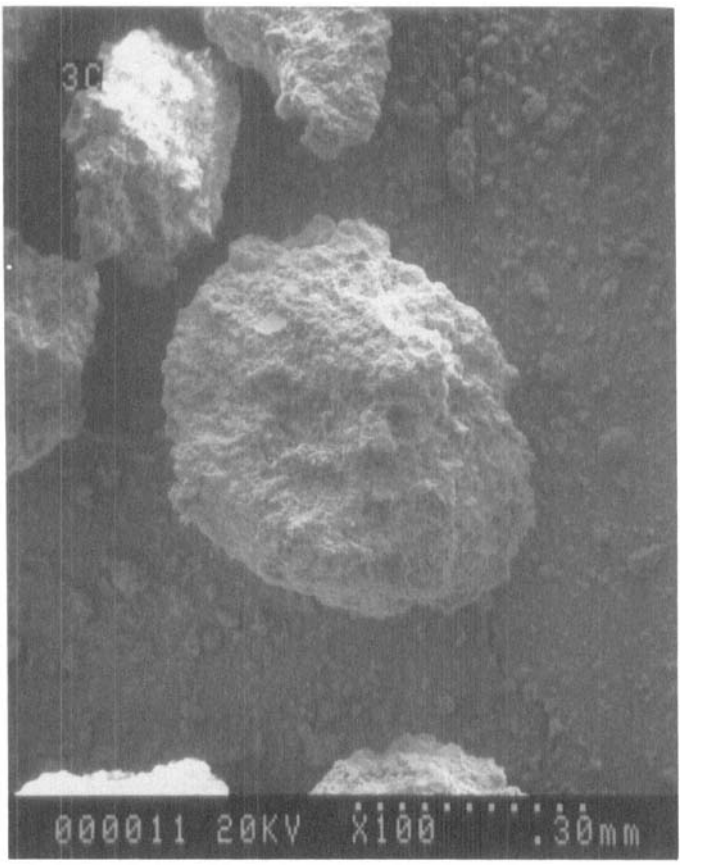

FIGURE 1

Scanning Electron Micrograph of Soludex 15.

ties, the volume flowing per second may be useful information. By using the bulk densities, the volumetric flow rates in terms of cm^3/s were calculated for Cantab, Emdex, Emcompress, Soludex 15, Di-Pac and Fast-Flo lactose to be 91.4, 90.5, 87.7, 83.4, 82.3 and 73.5 cm^3/s, respectively.

Table 1
Physical Characteristics of Excipients

Excipient	Flow Rate, g/s	Repose Angle, ^{o}	Density, g/cm^{3}	Median Size, μm	Moisture, %
Avicel PH 101	blocked	33.1	0.304	47	3.2
Cantab	65.8	27.8	0.720	200	8.7
Compactrol	blcoked	32.2	1.053	70	5.8
Di-Pac	57.4	29.4	0.697	250	2.1
Emcocel	blocked	33.1	0.330	50	2.6
Emcompress	67.1	30.6	0.765	130	3.7
Emdex	58.8	29.3	0.650	170	8.6
Fast-Flo Lactose	48.5	26.5	0.660	100	2.0
Anhydrous Lactose	blocked	36.5	0.580	130	1.0
Soludex 15	47.4	31.9	0.568	290	3.6

As shown in Table 1 the median size of the excipients varied 6-fold. In comparing materials a more useful expression of the size of a material is its particle size distribution as shown for the excipients in the histograms of Figure 2 and 3.

The moisture content of the batches of excipient reflects the affinity of the material for moisture (see Table 1). The hygoscopicity of Soludex 15 was determined by placing samples dried for 24 hours at 52°C in constant humidity chambers at

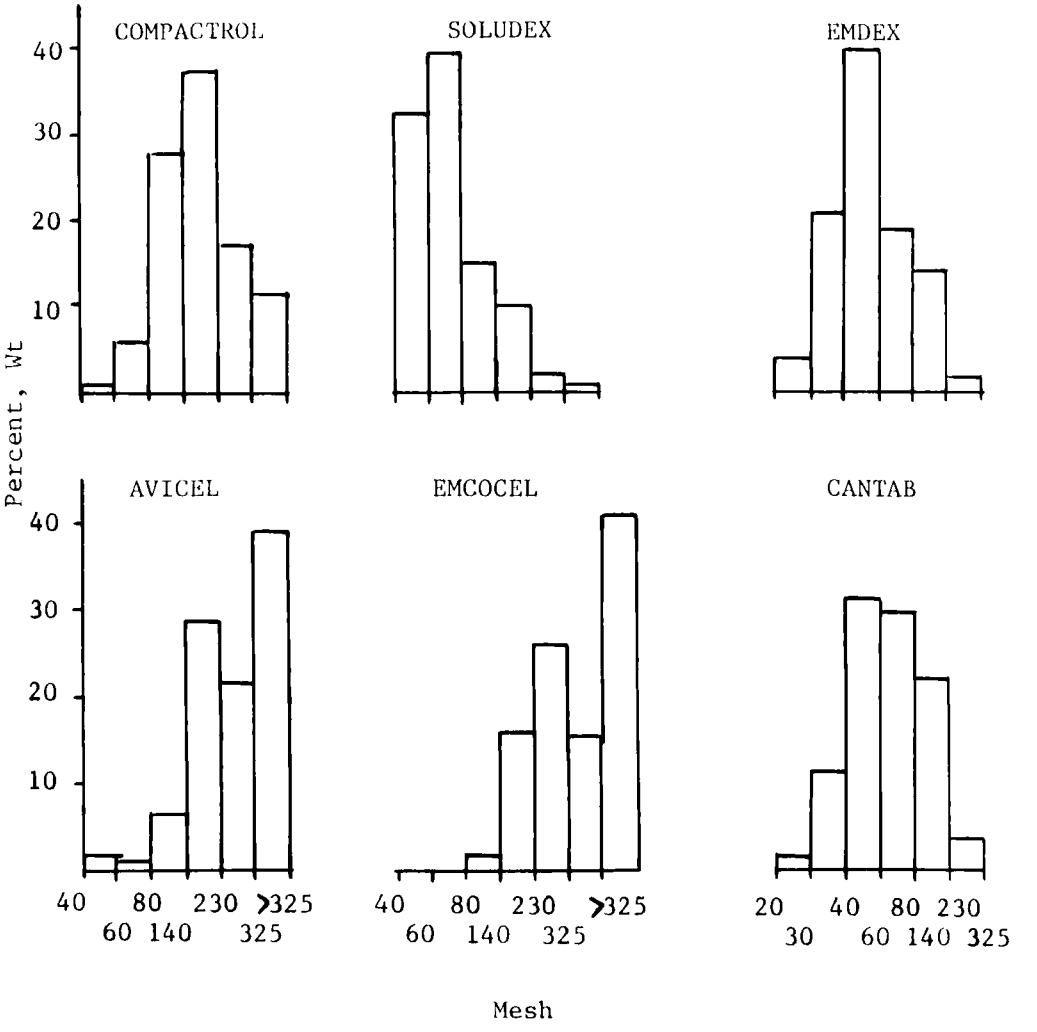

FIGURE 2

Size-frequency Histograms of Compactrol, Soludex, Emdex, Avicel, Emcocel and Cantab.

room temperature for one week. The moisture sorption is shown in Table 2. Soludex 15 has a surface area of 1.248 m^2/g and an average pore size of 628 A (13). The large surface area and pore accessibility make Soludex hygroscopic at high relative

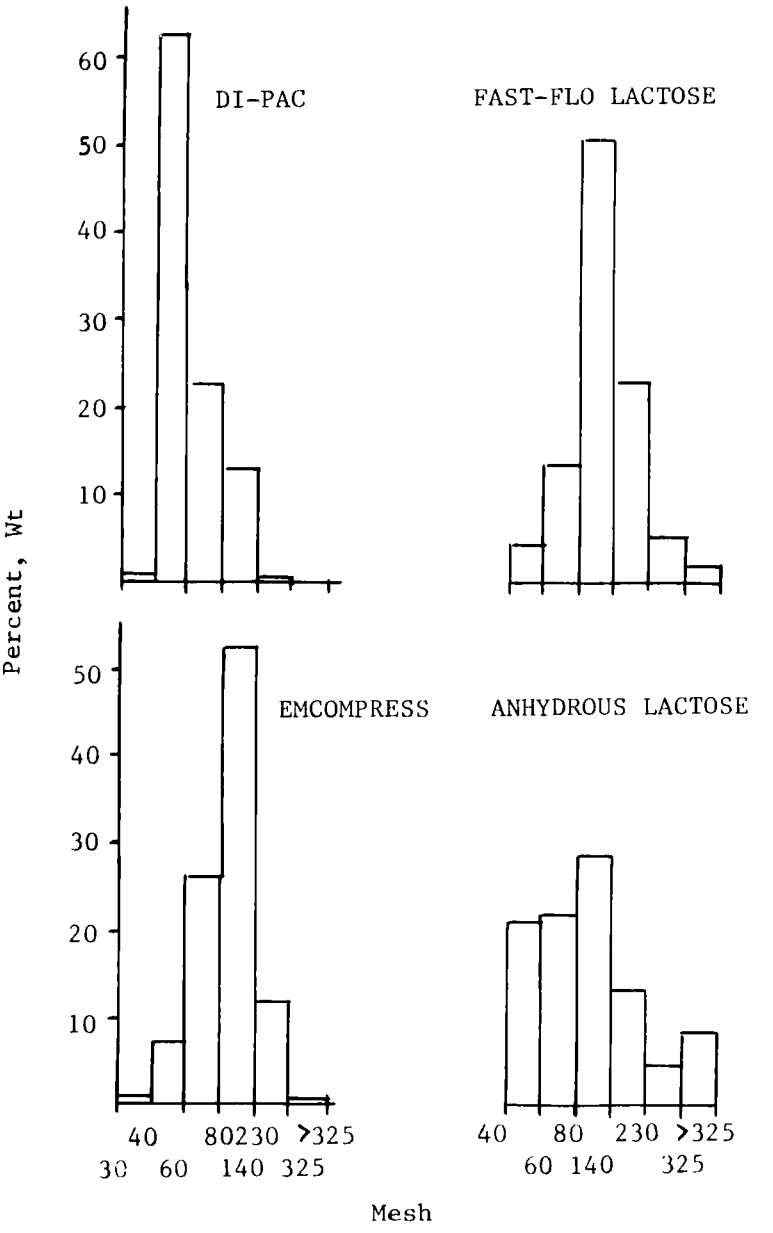

FIGURE 3

Size-frequency Histograms of Di-Pac, Fast-Flo Lactose Emcompress and Anhydrous Lactose.

TABLE 2

Moisture Sorption and Hardness of Tablets After One Week at 47, 70 or 80% Relative Humidity

Excipient or Tablet	Relative Humidity 47%		70%		80%	
	Moisture Sorped,%	Hardness, kp	Moisture Sorbed,%	Hardness, kp	Moisture Sorbed,%	Hardness kp
Soludex 15[a]	4.15		8.27		15.20[b]	
Clorazepate dipotassium	2.46	5.1(6.7)[c]	6.13	3.5	10.94	4.8
Haloperidol	1.81	6.1(6.2)	3.70	5.2	8.00	4.8
Maprotline hydrochloride	1.86	4.7(5.4)	3.81	2.7	10.00	1.4
Propranolol hydrochloride	1.28	4.9(4.5)	4.11	3.2	9.34	1.3

[a]Unprocessed excipient. [b]Pliable, nonsticky mass. [c]Initial hardness.

humidity, and it formed a pliable, nonsticky mass at 80% relative humidity.

Compressibility. The excipients were compressed into 15.875 mm flat-faced compacts using several compaction pressures. After 24 hours the hardness at each compaction pressure was measured and is given in Table 3, 4 and 5. A visual comparison of the hardness-pressure profiles of the excipients is shown in Figure 4. Microcrystalline cellulose and Cantab are extremely compressible. Soludex 15 and Emdex are highly compressible.

TABLE 3

Hardness of Unlubricated Excipients and Excipients Lubricated with 1% Magnesium Stearate at Several Compaction Pressures

Pressure, kg/cm^2	Hardness, kp					
	Fast-Flo Lactose		Anhydrous Lactose		Soludex 15	
	Unlub[a]	Lub[b]	Unlub	Lub	Unlub	Lub
57					7.8	
115	2.6	2.2	4.7	5.0	9.1	2.2
173					10.0	2.9
229	4.2	3.4	5.3	5.9	12.1	3.8
287					13.4	4.3
345					15.4	5.9
402					18.2	6.4
459	6.9	6.7	8.6	9.5	19.9	7.0
574						
690	9.3	8.6	13.3	13.4		
919		11.2	16.6	19.1		
1149	13.4	15.4	18.4	18.0		
1608						

[a]Unlubricated excipient only. [b]Lubricated with 1% magnesium sterate.

TABLE 4

Pressure, kg/cm^2	Hardness, Kp							
	Compactrol		Di-Pac		Emcompress		Emdex	
	Unlub[a]	Lub[b]	Unlub	Lub	Unlub	Lub	Unlub	Lub
57							6.5	2.9
115			2.9	2.5			7.2	3.7
173							7.9	4.6
229			4.2	2.7	3.6	2.4	10.0	5.3
287							10.5	6.0
345							12.1	7.2
402							13.8	8.0
459	2.2		6.6	6.5	5.4	4.6	15.6	9.2
574							16.6	10.2
690	4.1	1.6	9.7	8.3	6.3	6.8		
919			12.4	12.0				
1149	6.5	4.8	16.6	15.4	9.8	10.6		
1608	8.5	6.2			12.9	13.2		
2297	12.5	8.3			17.1	17.2		
2756	14.2	10.0			17.5			

[a]Unlubricated excipient only. [b]Lubricated with 1% magnesium sterate.

TABLE 5

Hardness of Unlubricated Excipients and Excipients Lubricated with 1% Magnesium Stearate at Several Compaction Pressures

Pressure, kg/cm^2	Hardness, kp					
	Avicel PH 101		Emcocel		Cantab	
	Unlub[a]	Lub[b]	Unlub	Lub	Unlub	Lub
14	13.3	7.7	10.3	6.4	2.9	
29	16.1	9.7	12.3	7.7	5.4	
43	16.4	11.2	13.2	9.4	5.6	2.2
57	>20	11.7	16.5	10.2	8.0	2.4
72			18.6	11.4	9.4	4.4
86					12.5	6.5
115					18.3	9.7

[a]Unlubricated excipient only. [b]Lubricated with 1% magnesium sterate.

A linear relationship exists between the densities of the tablets and the logarithm of compaction pressures except at high-force levels where the density of the tablet approches the true density of the excipient (14). The rate of increase in tablet density with increasing compaction pressure may be considered as an expression of compressibility (15). The values of the slopes of the plot in Figure 5 of tablet density against logarithm of pressure are given in Table 6. The excellent com-

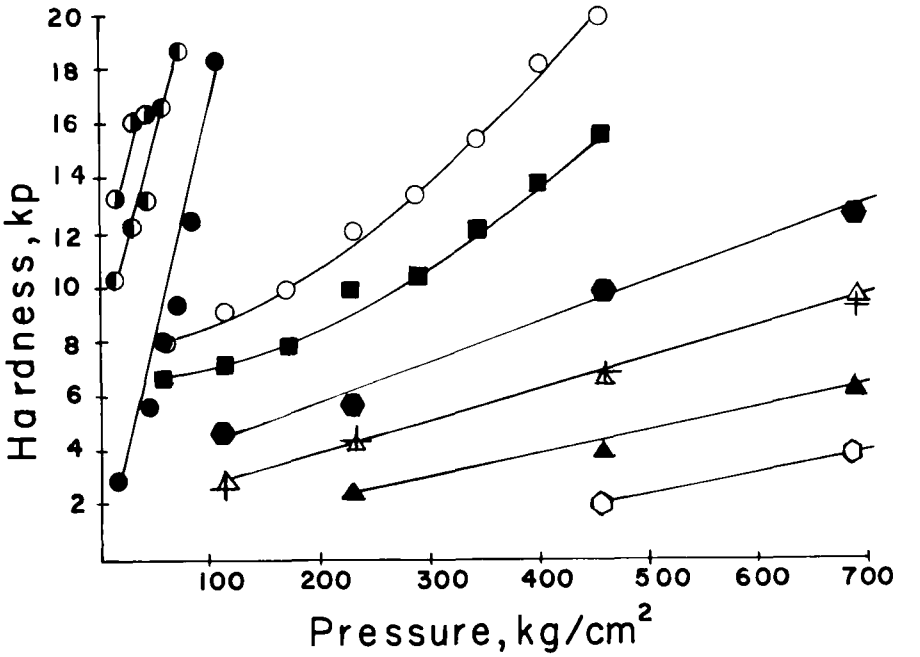

FIGURE 4

Hardness-pressure Profiles. Key: (○) Soludex; (●) Cantab; (■) Emdex (◑) Avicel; (◐) Emcocel; (+) Fast-Flo Lactose; (▲) Emcompress; (⬡) Compactrol; (△) Di-Pac; and (⬢) Anhydrous Lactose for Direct Compression.

pressibility of Soludex 15 is reflected in the comparatively high rate of increase of density with increased compaction pressure.

In general a solid lubricant decreases the mechanical strength of a tablet, because it acts as a physical barrier between the particles that undergo deformation and interferes with bonding during compression (16,17). Magnesium stearate is an excellent lubricant; however, it has been shown that as lit-

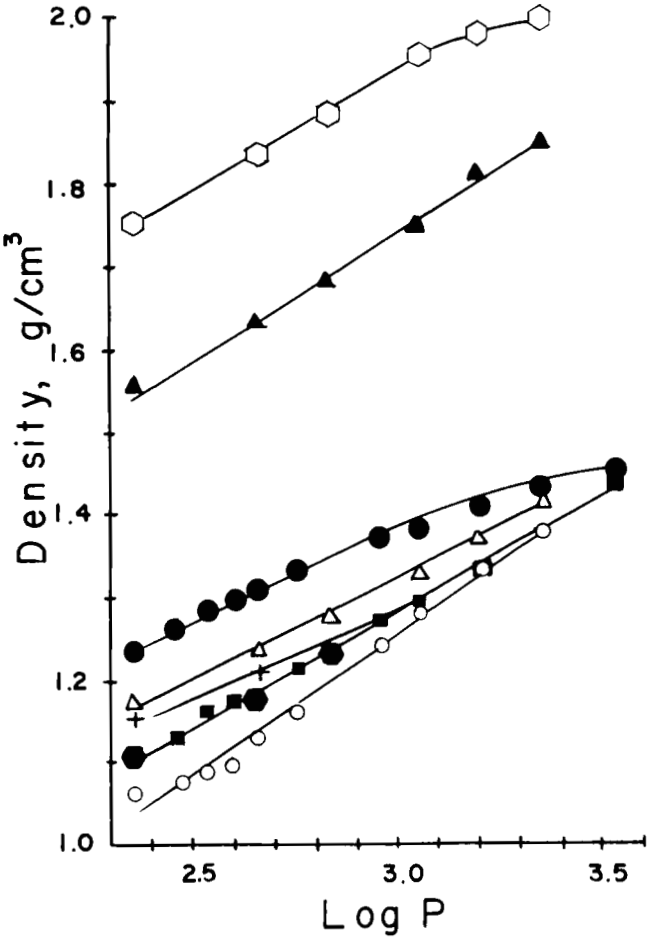

FIGURE 5

Influence of Compaction of Pressure on Tablet Density (Symbols same as in Figure 4).

tle as 0.25% magnesium stearate will reduce the work of axial failure of microcrystalline cellulose tablets from 866 g cm for a tablet of pure microcrystalline cellulose to 28 g cm (18). The influence of 1% magnesium stearate on the hardness of compacts of the ten excipients is given in Table 3, 4 and 5.

TABLE 6

Compressibility

Excipient	Slope
Soludex 15	0.340
Emcompress	0.310
Emdex	0.275
Di-Pac	0.250
Cantab	0.246
Compactrol	0.226
Fast-Flo Lactose	0.217
Anhydrous Lactose	0.214
Emcocel	0.175

The concentration of a lubricant may effect the hardness of a tablet (19). Soludex 15 was blended for 5 minutes with various concentrations of magnesium stearate in a V-blender. The blend was compressed in a hydraulic press at 460 kg/cm^2, and the hardness of the compact was measured. As shown in Figure 6 an increase in the concentration of magnesium stearate decreases the hardness; however, a tablet of acceptable strength was produced with 0.5% magnesium stearate.

Mixing time may effect the hardness of a tablet. Soludex 15 containing 1% magnesium stearate was blended in a V-blender

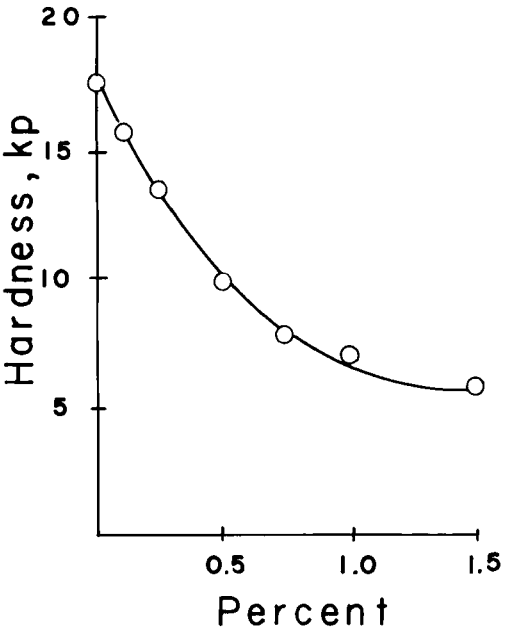

FIGURE 6

Influence of Concentration of Magnesium Stearate on Hardness of Soludex Compressed at 460 kg/cm^2.

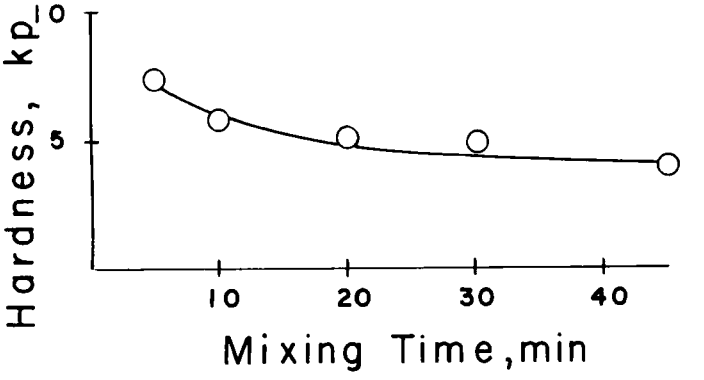

FIGURE 7

Influence of Mixing Time on Hardness of Soludex Containing 1% Magnesium Stearate Compressed at 460 kg/cm^2

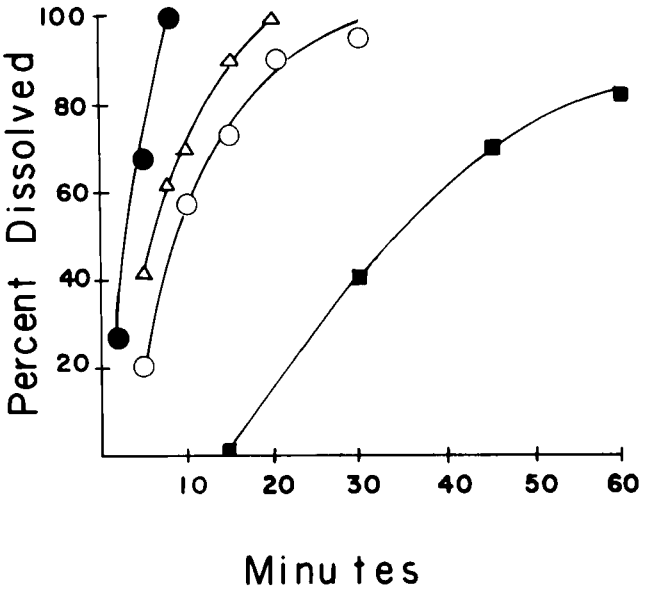

FIGURE 8

Dissolution Profiles from Model Tablets. Key: (●) Propranolol Hydrochloride; (△) Clorazepate Dipotassium; (○) Maprotiline Hydrochloride; and (■) Haloperidol.

for various times. As shown in Figure 7 extended mixing times produce a softer tablet.

Model Tablet Formulations. The flowability and compressibility of Soludex 15 suggested that it would be an excellent direct compression excipient. Thus, model tablet formulations were designed to evaluate the properties of tablets containing medicinal compounds. The characteristics of each batch of tablets were determined and are presented with the individual formula in the Appendix. The batches of haloperidol, maprotiline

hydrochloride and propranolol hydrochloride tablets met the specifications of the USP monographs.

The flow, compression and ejection of the model formulations were excellent. The weight variation from the average weight was 4.7% for the clorazepate dipotassium tablet, 0.8% for the haloperidol tablet, 1.7% for the maprotline hydrochloride tablet and 1.5% for the propranolol hydrochloride tablet. This weight variation is within tolerances of USP XX Weight Variation (20). The friability of the clorazepate dipotassium tablet, haloperidol tablet, maprotiline hydrochloride tablet and the propranolol hydrochloride tablet was 0.042, 0.05, 0.34, and 0.21%, respectively. Conventional compressed tablets that lose less than 0.5 to 1.0% of their weight are generally acceptable (21).

The rate of absorption of a medicinal compound may be determined by the rate of release of the medicinal compound from an ingested tablet. The disintegration test indicates the time required for a tablet to break into many small particles having a greater total surface than the intact tablet. The model tablets using Soludex 15 as the direct compression excipient disintegrated within 11 minutes. If the rapid attainment of a high serum concentration is an objective of the therapy, rapid dissolution of the medicinal compound from a tablet is essential to the efficacy of a product. The dissolution profiles of the model formulations are given in Figure 8. For clorazepate dipo-

tassium tablet, maprotiline hydrochloride tablet and proporanolol tablet not less than 90% of the medicinal compound was dissolved within 20 minutes. The haloperidol tablet met the USP specification of not less than 80% dissolved in 60 minutes.

The affect of moisture and storage on a tablet are considered in the selection of an excipient. The model tablets were stored in an open glass container for one week at room temperature in 47, 70 and 80% relative humidity, and the quantity of moisture sorbed is shown in Table 2. Moisture content may affect the hardness of a tablet. The initial hardness of the tablet and the hardness after exposure to high humidity are given in Table 2. At 47% relative humidity the hardness of the tablets remained essentially unchanged. The properties of the medicinal compound may influence the sorption of moisture and subsequently the hardness. At 70% relative humidity the hardness of the haloperidol tablet and the propranolol hydrochloride tablet was decreased 16 and 29%, respectively. At 70% relative humidity the hardness of the clorazepate dipotassium tablet and the maprotiline hydrochloride tablet was decreased 48 and 50%, respectively.

CONCLUSION

Soludex 15 has been evaluated and compared to nine commercial direct compression excipients. It exhibited excellent flow properties as evidenced by a rapid flow rate and by meeting the USP XX and USP XXI Weight Variation criteria. The compressibili-

ty of Soludex 15 is comparable to that of Cantab, microcrystalline cellulose and Emdex and superior to that of lactose, Compactrol, Di-Pac and Emcompress. Dissolution of four medicinal compounds from model tablets was rapid. It is felt that Soludex 15 possesses many of the desired properties of an ideal direct compression excipient and that Soludex 15 warrants serious consideration in the selection of a direct compression diluent.

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APPENDIX

The formulas for model tablets are given in Table 7. The correct weights of all ingredients except the magnesium stearate were placed in a V-blender and blended for 10 minutes. The correct weight of magnesium stearate was then added to the mixture in the V-blender and blended for 10 minutes. A standard concave punch and die set was used to compress the tablets. The characteristics of a batch of the model tablets are given in Table 8.

TABLE 7

Model Tablet Formulas

Ingredients	Milligrams/Tablet			
	Clorazepate	Haloperidol	Maprotiline	Propranolol
Medicinal compound	15.00	20.00	75.00	90.00
Soludex	79.30	215.65	115.60	277.00
Ac-Di-Sol	5.00	-	-	-
Corn starch	-	12.50	-	-
Primojel	-	-	33.00	-
Polyplasdone XL	-	-	-	50.00
Cab-O-Sil	0.2	0.60	0.40	0.90
Magnesium stearate	0.5	1.25	1.00	2.10

TABLE 8

Characteristics of Model Tablets

	Clorazepate	Haloperidol	Maprotiline	Propranolol
Diameter, mm	6.35	9.00	9.00	10.32
Thickness, mm	2.79	4.05	3.94	5.43
Hardness, kp	6.75	6.20	5.40	4.50
Friability, %	0.042	0.05	0.34	0.21
Assay, mg/tablet	14.325	19.20	85.10	92.09
Weight variation:				
within 85-115%	yes	yes	yes	yes
average, % label	90.32	95.86	89.65	102.30
standard deviation	2.439	1.261	1.899	3.993
R.S.D.	2.700	1.315	2.118	3.892
meets USP criteria	yes	yes	yes	yes
USP Disintegration, min	5.60	10.80	6.20	4.60
USP Dissolution:				
criteria, %	-	80	75	75
with in, min	-	60	60	30
Batch Dissolution:				
%	90.1	82.3	91.3	103
min	15	60	20	8