DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 19(17&18), 2309-2334 (1993)

A FEASIBILITY STUDY FOR THE DEVELOPMENT OF A PROSPECTIVE COMPACTION FUNCTIONALITY TEST AND THE ESTABLISHMENT OF A COMPACTION DATA BANK

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ABSTRACT

The feasibility for the development of a standard compaction functionality testing method, which is capable of comparing the relative tabletability features of different materials and different lots of the same material with high sensitivity, was tested using an Integrated Compaction Research System. The following factors were optimized: tablet weight, lubrication, tooling, punch displacement profile, pressure range, as well as other pre-, during and post-compaction parameters. The optimized test conditions were found to be as follows: the amount of material to be compacted was calculated to produce a compact with a true volume of 0.25ml; internal lubricant with magnesium stearate at a concentration of 0.5%; standard 10.3mm, flat-faced, round BB tooling; constant punch velocities of 100mm/s and 300mm/s; and a pressure range of 25 to 550MPa. Several model powders which included microcrystalline cellulose, dicalcium phosphate dihydrate, calcium sulfate, dextrates, lactose anhydrous, and spray dried lactose were tested. Using the data generated in this work, the establishment of a compaction data bank that can be utilized as a reference source for tablet formulation studies was also found to be feasible.

INTRODUCTION

An important aspect of tablet product design is the selection of suitable excipients and the assessment of the compactional behavior of the formula ingredients. The monographs of the excipients appeared both in the Unites States Pharmacopeia (USP) and the National Formulary (NF) until they merged in 1970. A decision was then made to include the monographs of the excipients in the NF with the exception of those materials which function as both drug and excipient (such as mannitol, talc, etc.). The latter materials would be placed in the USP and cross-referenced in the NF. In 1974 the Katalog pharmazeutischer Hilfsstoffe (Catalog of Pharmaceutical Excipients), which contained monographs for about 100 Swiss pharmacopeial and non-pharmacopeial excipients, was published (1). Later, the Handbook of Pharmaceutical Excipients (2) was published in 1986 under the direction of the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain with the contribution of 150 scientists representing academic and industrial pharmacy in the U.S.A. and the U.K.

An historical problem encountered by formulation scientists has always been the lack of harmonized standards for excipients. All of the national pharmacopeias contain monographs for specifications and test methods for only a portion of the existing excipients. However, many of these standards are not unified amongst the various pharmacopeias. In 1991 the International Pharmaceutical Excipients Council was formed in order to develop excipient harmonization worldwide. In the same year, the USP/NF formed a special advisory panel in order to develop internationally applicable physical test methods for basic powder properties (such as density, particle size, particle shape, etc.) as well as for applied powder properties (such as fluidity, compactability, etc.).

Early formulators selected mainly either traditionally known excipients or the ones that they were experienced with. The success of the selected material was sometimes just a coincidence. Neither the number of new excipients nor the number of scientists who took the challenge of trying the new excipients was satisfactory. This was partly due to their lack of knowledge about the compaction characteristics, as well as other physico-mechanical properties, of the pharmaceutical powders. Compaction studies have gained increasing importance in tablet formulation development since the introduction of the

instrumented single and multi-station tablet presses and universal testing machines (3-5). More systematic investigations have been facilitated as the integrated compaction research systems, so called 'compaction simulators'(6), have become available. These systems are designed specifically to be capable of mimicking the exact cycle of any tableting process in real time and to record all important parameters during the cycle (4). In a recent study, Çelik and Marshall (6) reported that the latter systems can utilize all of the standard IPT tooling or any kind of specialized tooling. Such systems require a minimum amount of material and provide a maximum amount of information. Although, the phenomena and mechanisms involved during compaction have been the subject of numerous publications, data obtained from two or more studies usually are not comparable, since the equipment (i.e. type of press and tooling), the parameters monitored (i.e. compaction speed, applied force, and punch displacement), or the methods used to manipulate the compaction data (i.e. Heckel equation, work of compaction) vary widely in these studies. The Handbook of Pharmaceutical Excipients (2) is the only reference source presently available that contains compaction information as a library. Since there is no standard test method required by the pharmacopeias, which is capable of comparing the relative tabletability features of different materials and different lots of the same material with high sensitivity, inconsistent techniques were employed to generate data even for this valuable source. Therefore, one of the goals of this study was to conduct feasibility studies for the development of a standard compaction functionality 'tabletability' testing method that can be included in the USP to determine the 'compressibility' and 'compactability' (ability of a material to be reduced in its volume, and to form a coherent compact under an applied pressure, respectively) of pharmaceutical powders. The present work also aimed to generate data for introduction into a compaction data bank that can eventually be utilized as an informative reference source in tablet formulation studies.

MATERIALS AND METHODS

The following commonly used binders and diluents were studied in this part of the work: Calcium phosphate dihydrate (Emcompress Lot# 1037X, E. Mendell), calcium sulfate (Compactrol Lot# 37009NX, E. Mendell), dextrates (Emdex Lot# L-53X, E. Mendell),

microcrystalline cellulose (Emcocel 90M Lot# 1037X, E. Mendell), lactose anhydrous (Lot# RA9301-018, Sheffield Products) and spray dried lactose (Fast-Flo Lot# 3RH210, Foremost Whey Products). Magnesium stearate (Lot# 2256 KCCR, Mallinckrodt) was used for internal and external lubrication purposes throughout the project.

The experimental procedure in this study was followed in two steps:

I. A feasibility study for development of the standard compaction functionality 'tabletability' testing method. This was carried out by the evaluation of the following test factors: tablet weight; compaction equipment; range of compaction pressure; type of punch displacement profile(s); tooling; lubrication; compaction parameters to be monitored; post-compaction tests; data evaluation method(s); and pass-fail vs fingerprinting criteria.

II. A feasibility study for establishing the 'Compaction Data Bank'. This was carried out according to the following methodology:

   i. Using a temperature and humidity controlled oven (Hotpack, PA), each sample was conditioned at 23 ± 1 °C and 52 ± 2 %RH for at least one week prior to the tests.

   ii. Pre-compaction tests included measurements of powder bulk density, tapped density (JEL apparatus, J. Engelsmans, Germany), true density (Quantachrome Multipycnometer, Syosett, N.Y.), moisture content (Computrac Max 50, Arizona Instr. Co., Tempa, AR), flowability (Powder Flow Tester, Type PTG, Pharma-Test, Hainburg, Germany) and particle size (ATM Co., Milwaukee, WI) for each material used.

   iii. During the project, the environmental conditions within the compaction area remained at 22 ± 2 °C and 31 ± 6 %RH. The compaction studies were performed employing an Integrated Compaction Research System (Mand Testing Ltd., Stourbridge, U.K.) (7) fitted with standard 10.3mm round, flat faced BB tooling.

   iv. The true volume of each sample to be compacted was kept constant at

0.25ml throughout the project resulting in the tablet weights varying from 374mg to 579mg depending on the true density of the material. The weight variation allowed in a set of experiments was ±3mg.

v. The samples which contained an internal lubricant were prepared by mixing 0.5% of previously sifted (through #50 mesh size) magnesium stearate with the excipient for three minutes using a mixer (Turbula Type T2C, Glen Mills Inc., N.J.) at 42rpm. During mixing, the containers were filled to a maximum of two-thirds of their capacity. Prior to lubrication, Fast-Flo and Emdex were also sieved through #40 and #25 mesh size sieves, respectively, to break any agglomerates. When external lubrication was used, this was carried out by applying a 2% magnesium stearate suspension in acetone onto the die wall and the punch faces with a cotton applicator following the compaction of each replicate.

vi. The compacts were made using two double ended sawtooth profiles at punch velocities of 100mm/s and 300mm/s. The compaction parameters collected were the forces exerted by the upper and lower punches and their displacements. All of the displacement data obtained were corrected for the deformation of the system (consisting of the punches and other machine components associated with the punches). This was repeated five times throughout this project.

vii. For each set of conditions, experiments were repeated until ten satisfactory replicates were obtained. Post-compaction properties of five compacts were measured immediately after ejection while the remaining compacts were stored in sealed plastic bags for testing 24 hours later. These post-compaction tests included measurements of the dimensions, crushing force, and appearance of the compacts. Following the completion of each set of experiments, the die wall and the punch faces were cleaned with alcohol.

TABLE 1
Summary of Compaction Test Conditions for Mannitol
(Data 'Extracted' from the Handbook of Pharmaceutical Excipients (2))

Parameter	Method #1	Method #2	Method #3
Supplier	Triangle Import & Export	Triangle Import & Export	Atlas
Lot#	N/A	1233R8060791	2022BO
Press	Manesty E2	Carver Press	Stokes B2-16
Tooling Diameter (inches)	1/2	1/2	7/16
Tooling Concavity	N/A	Flat-faced	Standard Concave
Lubrication	External	External	Internal
Speed	50 tpm	N/A	N/A
Tablet Weight (mg)	600	500	500
True Volume (cc)	0.43	0.33	0.33
Data Presentation	Crushing Strength (N) vs Compression Pressure (MPa)	Breaking Strength (N) vs Compression Pressure (MPa)	Breaking Strength (N) vs Compression Force (kN)

RESULTS AND DISCUSSION

FEASIBILITY STUDY FOR THE COMPACTION FUNCTIONALITY TESTING:
The phenomena and mechanisms involved during compaction have been the subject of numerous publications (8,9). However, data obtained from such studies are not directly comparable, if, even one compaction parameter (such as equipment, methods, monitored parameters, data evaluation techniques) varies amongst the studies. The utilization of existing information in the literature is also limited because of the lack of a standard comparison method. As mentioned earlier, even the Handbook of Pharmaceutical Excipients (2) contains some data generated using inconsistent techniques. An example is given in Table 1 which presents the 'extracted' compaction test conditions for the three

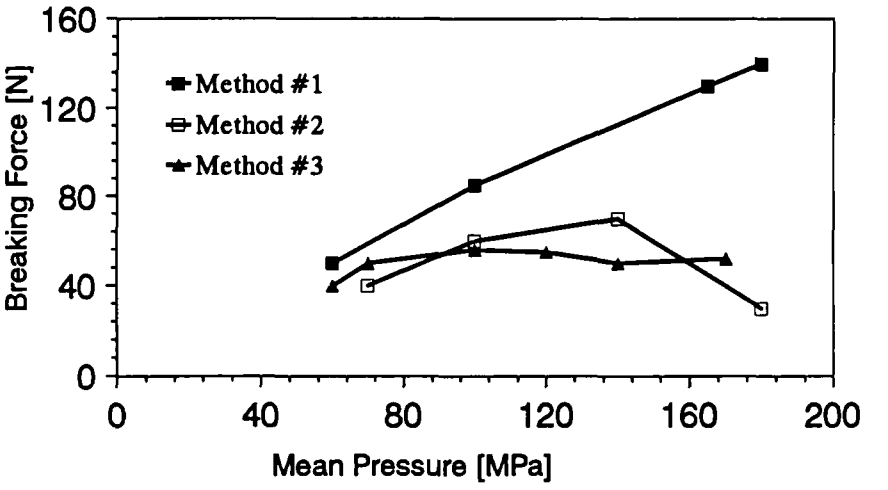

FIGURE 1

Breaking Force vs Mean Applied Pressure Plots for Mannitol

(Data 'Extracted' from the Handbook of Pharmaceutical Excipients (2))

different methods that were used to assess the compaction properties of Mannitol. Figure 1 shows the crushing force vs applied pressure profiles obtained from these methods. Significant 'batch to batch' and 'supplier to supplier' variations are observed. However, it is possible that these differences could also be due to the inconsistency of the compaction test conditions rather than the properties of the material. Whether the differences are due to the material or due to variations in the test conditions, the need for the development of a standard compaction functionality testing method is obvious in order to obtain a sound comparison of tableting excipients. The determination of the test conditions for this method is also vitally important since such a method is expected to be simple, reproducible, universally applicable, informative, and cost effective. Therefore, in the present study, an attempt was made to address some of these test parameters.

Monitored Parameters: A simple and universally applicable compaction functionality test should not require measurements of parameters that are complicated in terms of instrumentation and validation such as the measurement of the force transmitted to the die-wall. Therefore, measurements of the forces on and displacements of the upper and

TABLE 2
Comparison of Equipment for Tableting Studies
(After Çelik & Marshall (6))

Feature	single-station press	multi-station press	Isolated punch and die set	ICRS
mimic production conditions	NO	YES	MAYBE	YES
mimic cycles of many presses	NO	NO	MAYBE	YES
require small amount of material	YES	NO	YES	YES
easy to instrument	YES	NO	YES	YES
easy to set up	YES	NO	MAYBE	MAYBE
data base in literature	YES	YES	SOME	SOME
used for stress strain studies	NO	NO	YES	YES
equipment inexpensive	YES	NO	MAYBE	NO

lower punches, and ejection force are recommended to be used in the functionality testing.

Type of Press: This is probably the most critical parameter since the information obtained from such a machine will be expected to apply to other types of presses. As can be seen from Table 2, which compares the equipment on which tableting studies can be performed, Integrated Compaction Research Systems (ICRS) have many advantages over the others. Because of these advantages, the ICRS at Rutgers was selected for the feasibility study. However, once the method is developed, a simplified version of the ICRS can be suggested due to concerns about cost effectiveness.

Tablet Weight: Constant weight has been used in many compaction studies while constant true volume has been employed in others. However, the use of constant true volume is particularly important when comparing materials since the response to punch movement (i.e. punch force) is a function of the volume of solid in the die and not its weight (10). Since the bulk densities of pharmaceutical powders exhibit a wide range,

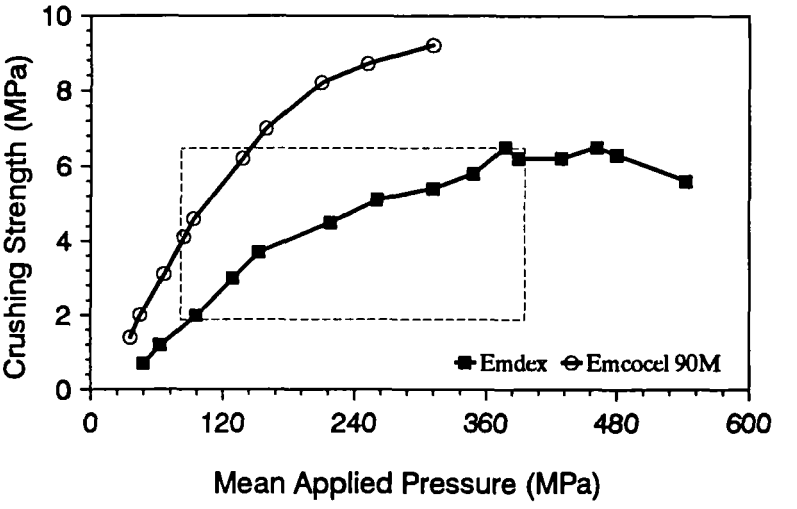

FIGURE 2

Compaction Pressure Range Studied

(The 'Box' Denotes a Common Pharmaceutical Range)

it is suggested that prospective functionality testing should be based on the use of a constant true volume value that can accommodate as many powders as possible, and yet can results in compacts with a thickness to diameter ratio of 0.25-0.33 at zero porosity.

Load Range: For every material tested, application of a pressure range from fairly low levels (approx. 25MPa) to very high levels (approx. 550MPa) is suggested since, for example, the rank order of the crushing strength values for a number of materials may change when the spectrum of applied pressure is changed. Also there is usually no 'linear' relationship between the strength of the compacts and the applied pressure. An example is given in Figure 2 which shows the crushing strength vs mean pressure for the compacts of Emdex that does not exhibit a linearity. The 'box' in this figure and in the forthcoming figures denotes a common 'pharmaceutical' range.

Tooling: A set of 10.3mm, flat-faced, round, standard IPT tooling is suggested as the standard test tooling for the compaction functionality testing.

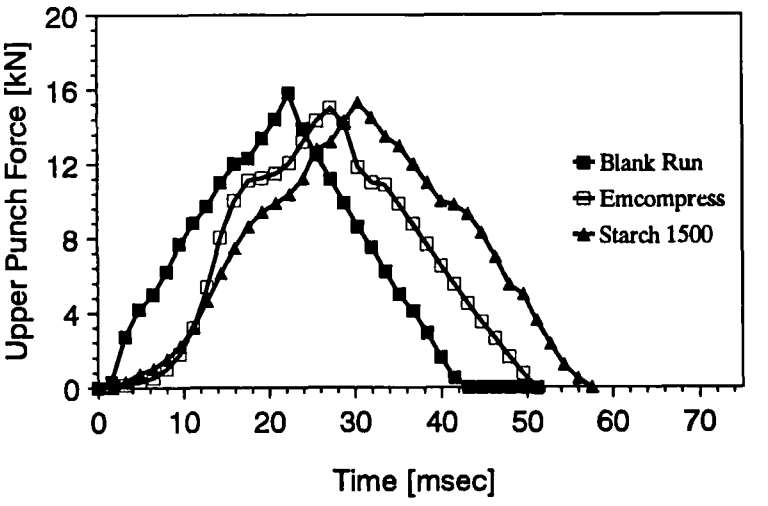

FIGURE 3

ICRS Upper Punch Force vs Time Profiles (Loading Rate: 15kN/sec)

Type of Punch Profile: The existing single- and multi-station tablet presses operate under displacement 'strain' control, i.e., the punches travel certain paths, producing a sine-wave punch displacement profile. The universal testing machines (fitted with an isolated punch and die set) and the Integrated Compaction Research Systems can be programmed to operate under load control, i.e., the punches produce pressures following a given load profile, as well as under displacement control. The profiles of load or displacement can be customized. Figure 3 shows the force vs time profiles obtained when the ICRS was operated under load control. Figure 4 contains punch position vs time profiles obtained when the system was programmed to follow a triangle, i.e. 'sawtooth', profile. As can be seen from these figures, the system can follow a displacement profile more accurately. The sawtooth profile, instead of sine-wave profile, is suggested for use in the functionality testing since this type of profile produces a constant velocity regardless of the type or thickness of the material compacted. However, the results obtained from a sawtooth profile should be comparable with those obtained from sin-wave profiles at least in terms of a time parameter, such as the contact time (during which the powder is in contact with the punches) or the t-max (time to attain maximum pressure), etc. Figure 5 gives t-max vs mean pressure profiles for the compacts of excipients made at a punch

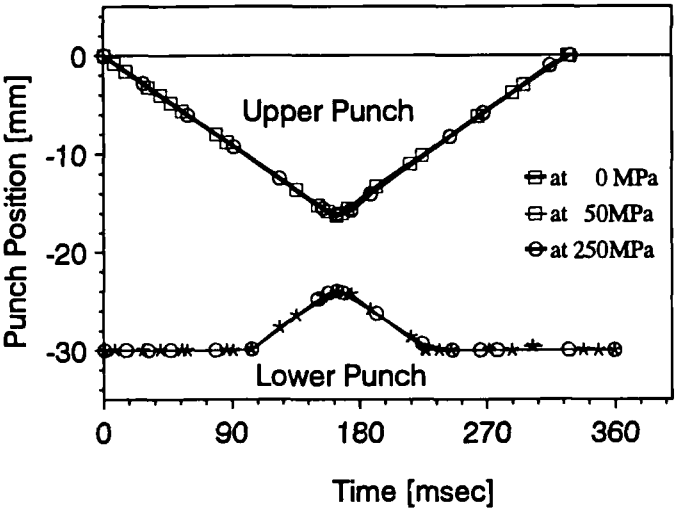

FIGURE 4

ICRS Upper Punch Position vs Time Profiles

(Emcocel 90M Compacts Made at 100mm/sec)

velocity of 100mm/sec. When the t-max values of the compacts (except Emcocel 90M) are compared for a given pressure the variation was ±5msec (again with the exception of Emcocel 90M). When the whole pressure range is examined, it can be seen that the t-max values of the compacts varied from 12msec to 40msec, which were within the range encountered in high speed multi-station press operations, with the exception of microcrystalline cellulose compacts for which the t-max values was as high as 100msec. In order to test the 'robustness' of the materials in terms of time-dependency, a sawtooth profile of 300mm/sec was also employed in this study. This waveform reduced the contact time by an average of three fold. The studies for the feasibility of using other profiles (in terms of type and speed) are still in progress.

Lubrication: The intrinsic compaction properties of pharmaceutical powders should ideally be studied by performing compaction tests using a thoroughly cleaned punch and die set without any type of lubrication. However, this can be a tedious and impractical process when the material exhibits serious sticking and picking problems. External

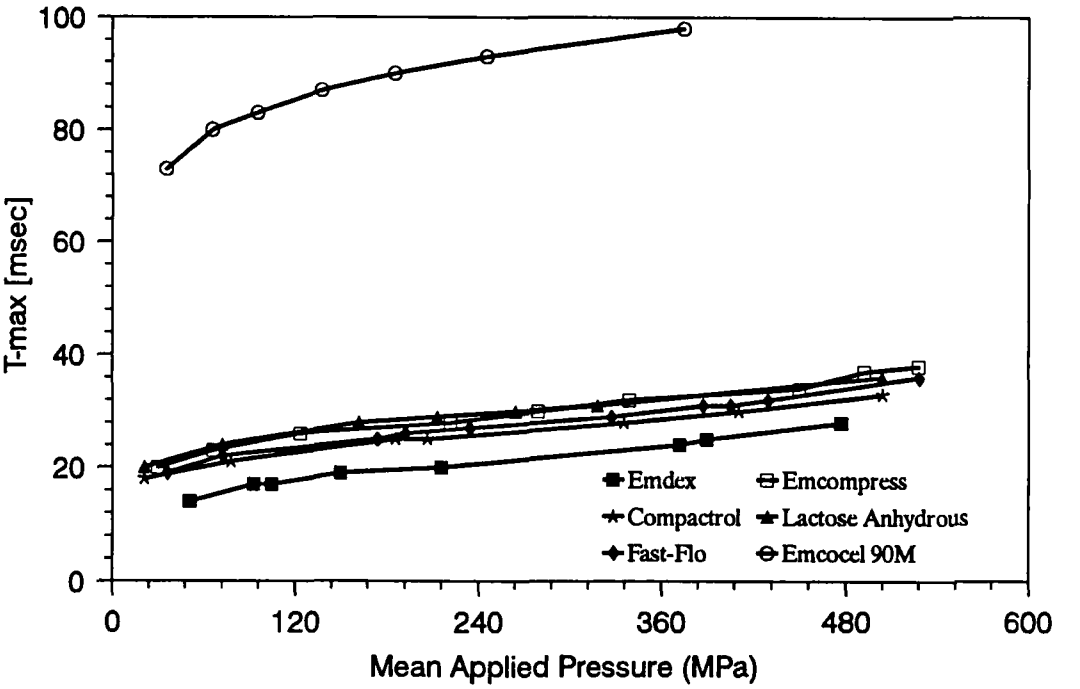

FIGURE 5

T-max (Time to Attain Maximum Pressure) vs Max Applied Pressure Plots (Punch Velocity: 100mm/sec)

lubrication can cause complications during application of the lubricant. For example, it is difficult to achieve a uniform distribution of lubricant on the die wall. Internal lubrication has drawbacks in terms of the optimum type and amount of lubricant, as well as the mixing time of the lubricant.

Figure 6 compares the crushing strength vs mean pressure profiles for the compacts of microcrystalline cellulose and lactose anhydrous which were made using both external and internal lubricants. It is obvious from the data that the lubrication method affects the compactional behavior of the materials and this may be a concern when a selection is made for the optimum lubrication method for the functionality testing.

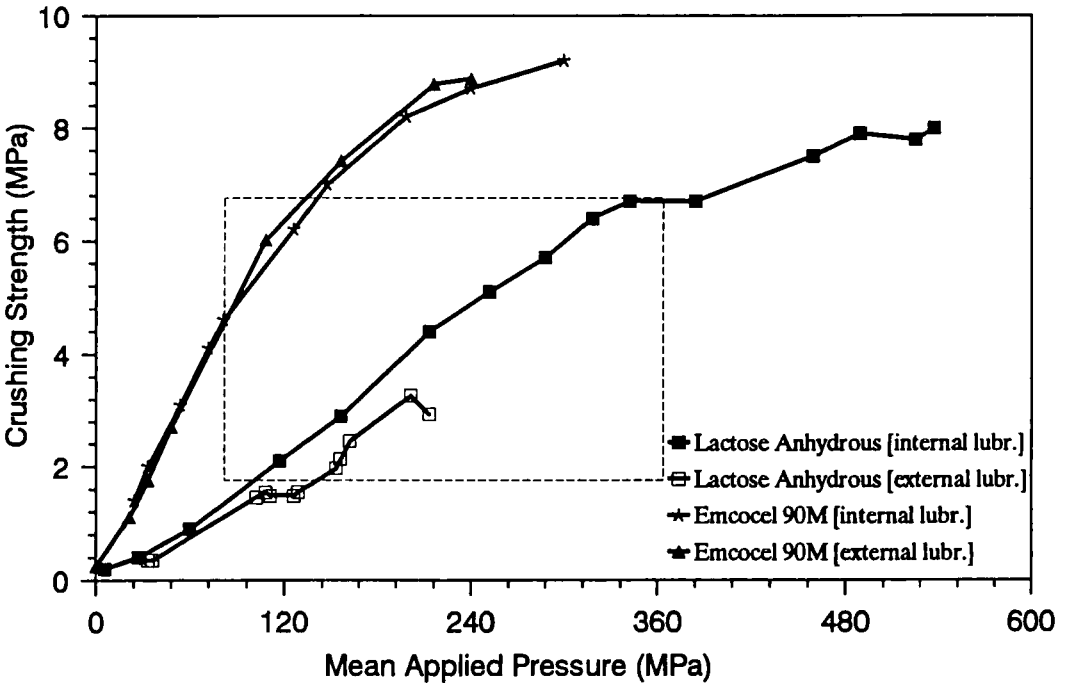

FIGURE 6

The Effects of Internal and External Lubrication on the Crushing Strength of the Compacts of the Excipients Used (Punch Velocity: 100mm/sec)

Despite the above mentioned concerns, the internal lubrication method is suggested for use in compaction functionality testing due to the practicality of this method. However, the lubrication issue should and will be addressed in future communications.

Post-Compaction tests: These tests must include at least measurements of the dimensions and the crushing force of the tablets. It is also recommended that these tests be performed following a pre-determined storage period as well as immediately after ejection on a replicate number of tablets.

Evaluation of data: There are numerous methods used to evaluate the data obtained from monitoring the displacement of and forces on the upper and lower punches, and the

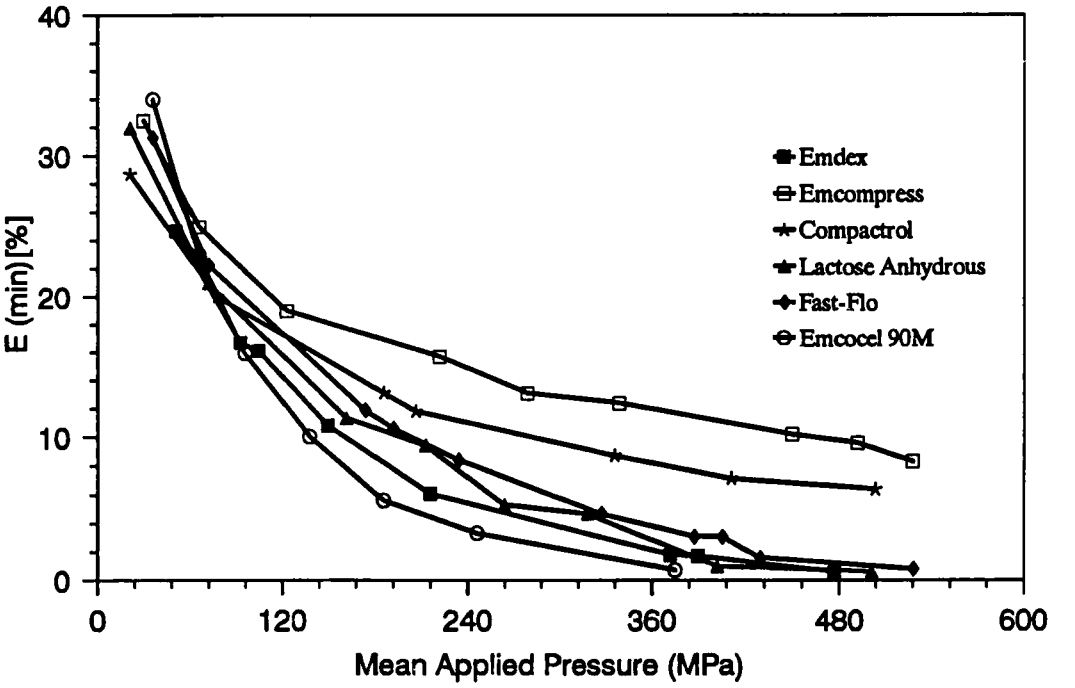

FIGURE 7

The Percent Porosity (Minimum) vs Mean Applied Pressure for the Compacts of the Excipients Used (Punch Velocity: 100mm/sec)

ejection force. However, many of these methods have been shown to have applicability over only a limited range of force and for only a few types of materials (9). Certainly, no universal method has yet emerged, and is unlikely to do so, due to the difficulty involved in the comprehensive analysis of the systems being compacted. Future studies are needed to determine which of the existing methods must be employed, or whether new methods must be attempted, for use in compaction functionality testing. At present, the functionality assessment is suggested to be based at least on the following parameters: porosity, energy, time, and crushing strength.

Pass/Fail vs Fingerprinting: No criteria to pass or to fail a material for the compaction functionality testing is suggested. Instead, fingerprinting of data analysis profiles is

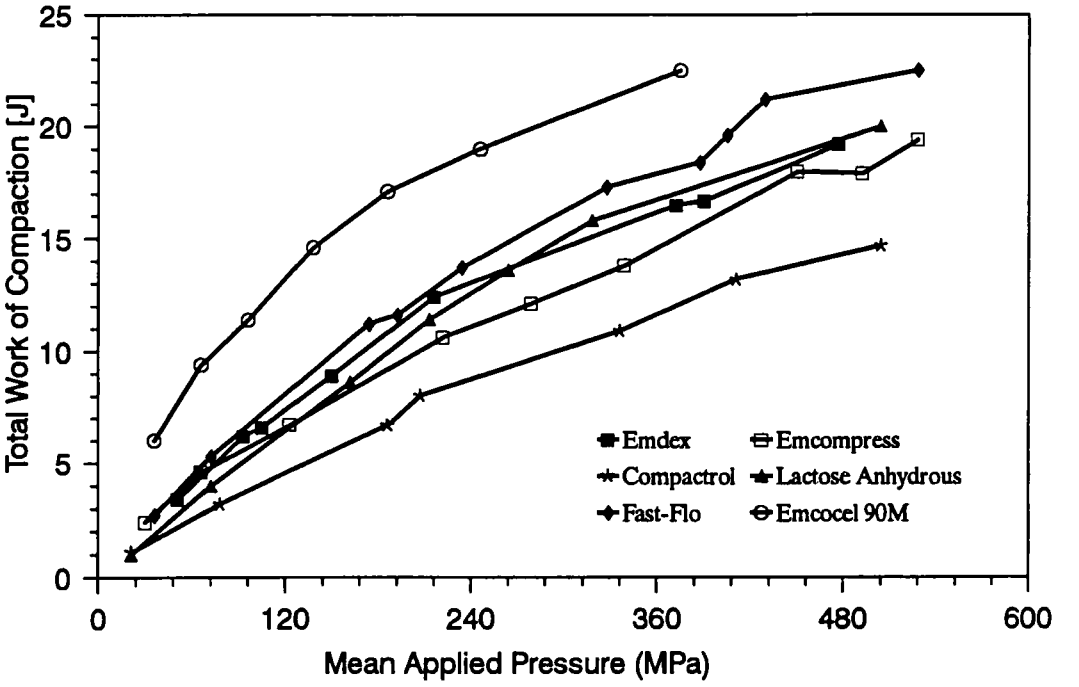

FIGURE 8

The Total Work of Compaction vs Mean Applied Pressure for the Compacts of the Excipients Used (Punch Velocity: 100mm/sec)

recommended. However, the determination of the optimum criteria necessary for the fingerprinting of the methods that can successfully identify a material amongst others requires the examination of many more materials. Here, only a suggestion is made that the minimum porosity vs applied pressure profiles can be used for fingerprinting for the 'compressibility' of the materials (Figure 7), while the total work of compaction (Figure 8) and the crushing strength profiles (Figure 2) as a function of pressure can be used for fingerprinting of the 'compactability' of the material. In these figures, the porosity and total work of compaction were calculated using the methods described by Çelik and Marshall (6).

TABLE 3
Particle Diameter of the Excipients Used

Excipient	Lot#	Particle Diameter (μ)		
		median	arithmetic	geometric
Compactrol	37009NX	267 sd=2.209	265 sd=90	237 sd=1.56
	83309NX	255 sd=4.619	250 sd=99	230 sd=1.65
Emcocel 90M	2075X	124 sd=5.859	128 sd=66	110 sd=1.90
	1037X	119 sd=12.050	118 sd=67	102 sd=1.85
Emcompress	3144X	177 sd=2.082	180 sd=54	172 sd=1.34
	3119X	176 sd=2.646	173 sd=59	162 sd=1.31
Emdex	H-16X	271 sd=18.583	293 sd=114	272 sd=1.56
	L-53X	251 sd=12.767	280 sd=103	258 sd=1.53
Fast-Flo Lactose	2RH210	99 sd=2.517	104 sd=36	96 sd=1.44

FEASIBILITY STUDY FOR THE COMPACTION DATA BANK:

Basic Powder Properties:

Table 3 presents the results of the particle size analysis of the excipients tested. Other powder properties of these materials are given in Table 4 in terms of their powder bulk density, tapped density, true density, moisture content, and flowability measurements.

TABLE 4

The Measurements of Basic Powder Properties of the Excipients Used

Excipient	Lot#	Density Measurements (g/cc)			Moisture Content(%)	Gravimetric (g/sec) and True Volumetric (cc/sec) Flow		
		ρ_{bulk}	ρ_{tapped}	ρ_{true}		repose angle (°)	(g/sec)	(cc/sec)
Compactrol	37009NX	0.938 sd=0.011	1.103 sd=0.004	2.309 sd=0.010	19.73 sd=0.035	37.6 sd=0.200	5.20 sd=0.365	2.252
	83309NX	0.946 sd=0.005	1.109 sd=0.002	2.334 sd=0.010	18.97 sd=0.144	38.3 sd=0.378	4.72 sd=0.074	2.022
Emcocel 90M	2075X	0.291 sd=0.003	0.351 sd=0.001	1.552 sd=0.010	4.91 sd=0.277	34.4 sd=0.764	1.41 sd=0.036	0.908
	1037X	0.269 sd=0.001	0.334 sd=0.001	1.552 sd=0.015	5.00 sd=0.047	37.3 sd=0.611	1.35 sd=0.063	0.869
Emcompress	3144X	0.886 sd=0.020	0.950 sd=0.008	2.335 sd=0.011	3.65 sd=0.300	28.3 sd=0.862	11.63 sd=0.006	4.980
	3119X	0.863 sd=0.004	0.933 sd=0.005	2.329 sd=0.010	3.60 sd=0.435	28.3 sd=0.360	11.35 sd=0.040	4.873
Emdex	H-16X	0.682 sd=0.006	0.718 sd=0.003	1.517 sd=0.006	8.93 sd=0.017	26.4 sd=0.503	9.16 sd=0.098	6.038
	L-53X	0.679 sd=0.005	0.719 sd=0.005	1.513 sd=0.006	8.86 sd=0.011	24.7 sd=0.305	9.51 sd=0.195	6.286
Fast-Flo Lactose	2RH210	0.570 sd=0.002	0.642 sd=0.001	1.537 sd=0.005	2.39 sd=0.105	29.5 sd=2.343	3.28 sd=1.186	2.134

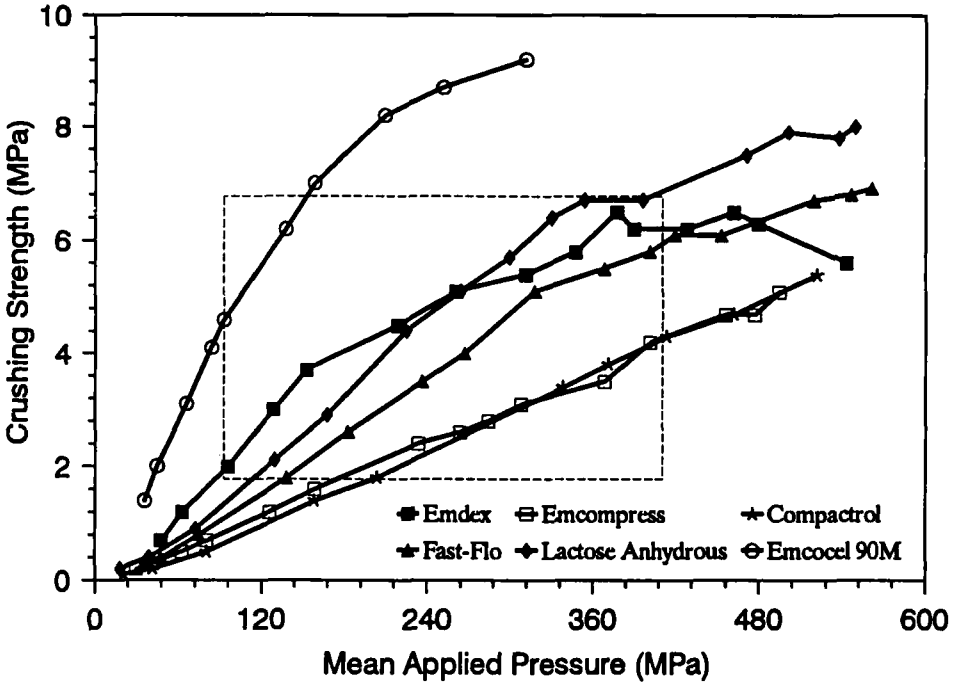

FIGURE 9

The Crushing Strength vs Mean Applied Pressure for the Compacts of the Excipients Used (Punch Velocity: 100mm/sec)

Crushing Strength of the Compacts:

The tablet crushing strength (T_s) was calculated from the thickness (H_e), diameter (D_e) and crushing force (F_c) measurements for each replicate using the following equation:

$$T_s = 2 F_c / \pi D_e H_e \quad (1)$$

Figure 9 contains the crushing strength vs applied pressure plots for the compacts which were made at a speed of 100mm/sec and tested immediately after ejection. As can be seen from this figure, the results show that Emcocel 90M clearly exhibited the greatest rate of strength increase with increasing applied pressure. This material produced crushing strength values of as high as 1.2MPa at compaction pressures as low as 30-40MPa, and the crushing force values were already out of the range of the hardness tester

(50kp) at pressures of 300-320MPa. Its compacts exhibited no sign of capping or lamination at pressures as high as 560MPa. Amongst the other excipients studied, Emcompress and Compactrol exhibited the lowest rate of strength increase with increasing pressure. Their crushing strength profiles kept their linearity up to high pressures (550MPa). The remaining materials, lactose anhydrous, Fast-Flo, and Emdex were between the two extremes. The rank order for crushing strength increase of tablets of these excipients was somewhat dependant on the pressure range studied. Despite the greater strength of compacts of lactose anhydrous compared to Fast-Flo, the visual examination of these compacts showed that the former was significantly more prone to chipping at high pressures than the latter.

The compacts of Emcocel and Compactrol did not exhibit any difference in strength values after a 24 hour storage period. However, a reduction in strength values was observed for the compacts of lactose anhydrous, Fast-Flo, and Emdex within the same storage period after application of 160MPa, 280MPa and 320MPa, respectively. The compacts of Emcompress exhibited a slight, but consistent, increase in strength during storage.

When the crushing strength profiles of the compacts, which were made at 300mm/s punch velocity and tested immediately after ejection, were compared, it was observed that the overall rank order for the strength increase with applied pressure did not change (Figure 10). However, a critical change occurred in the performance of the time dependant microcrystalline cellulose as the crushing strength value of its compacts began to decrease after reaching 8.3MPa at a pressure of 200MPa and the compacts began to cap and laminate severely beyond 240MPa pressure applications. Not allowing enough time for plastic deformation to take place and the overpowering effect of elasticity may be the mechanism responsible for the failure of this material at high speeds of compaction.

Compactrol also appeared to have some time dependant properties as its compacts possessed slightly greater strength values at the slower compaction speed (Figures 9 and 10). The crushing strength profiles for Emdex, Emcompress and Fast-Flo were

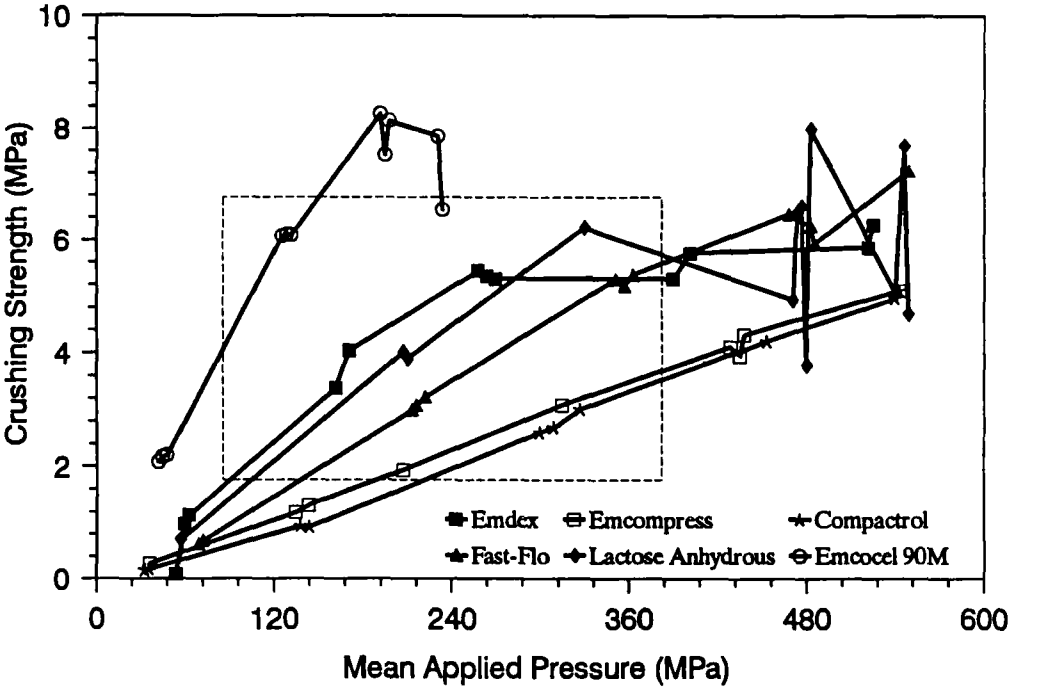

FIGURE 10

The Crushing Strength vs Mean Applied Pressure for the Compacts of the Excipients Used (Punch Velocity: 300mm/sec)

unaffected by the punch velocity. Lactose anhydrous was also completely insensitive to the increased compaction speed up to pressures of 340MPa after which a rapid decrease and a wide variability in crushing strength values was evident. Chipping was also observed during the visual examination of these compacts.

When the crushing strength of the compacts, which were made at a speed of 300mm/sec, were tested after a storage period of 24 hours, a reduction in the strength of compacts of Emcocel was observed only at high compaction pressures. These compacts were close to the capping point. The strength of Compactrol, Emdex and Emcompress compacts were unaffected over time. However, there was a slight decrease in the strength of both lactose anhydrous and Fast-Flo compacts made at 300mm/s punch velocity.

Percent Volumetric Strain Recovery of the Compacts:

The percent volumetric strain recovery (VSR) was calculated according to the method of Maganti and Çelik (11) by taking not only the change in thickness (H) of the compacts over time, but also the change in their diameter (D), into account as shown below:

$$VSR(\%) = [(D_e^2 H_e - D_u^2 Hu) / (D_u^2 H_u)] * 100 \quad (2)$$

where D_u and H_u , and D_e and H_e are the diameters and thickness of the compacts, respectively.

In the equation, the "u" denotes the end of unloading (i.e., where the upper punch is just loosing contact with the compact), and the "e" stands for ejection. Measuring the dimensions both immediately after the ejection of the compacts and at the end of the 24 hour storage period, the time dependant strain relaxation behavior of the compacts of several materials were examined. Although this phenomenon is commonly referred to as 'elastic recovery', it is known that the majority of actual elastic recovery is completed by the time the tablet is ejected from the die and that the recovery taking place beyond that point is viscoelastic in nature (12).

When immediate VSR% vs mean pressure plots were compared for compacts made at 100mm/s, the difference in consolidation behavior of Emcocel 90M from the others can be seen clearly (Figure 11). The extensive expansion of compacts of this material at low pressures rapidly diminished as the pressure was increased to 250MPa where it reached a minimum. This decrease in elasticity is due to the increasing contribution from the plasticity of microcrystalline cellulose at higher pressures. The rest of the excipients studied are usually regarded as brittle materials which undergo fragmentation under high compaction pressures. Hence, the compacts of Emdex, Emcompress, Fast-Flo and Compactrol did not exhibit this type of time dependant behavior. However, no material can be solely elastic or brittle and even these materials possessed some elasticity when the applied pressure was beyond 480MPa. Although Emdex, Emcompress, Compactrol and Fast-Flo exhibited a distinct brittle behavior with very insignificant tablet strain recovery, lactose anhydrous clearly exhibited some elastic component in its consolidation

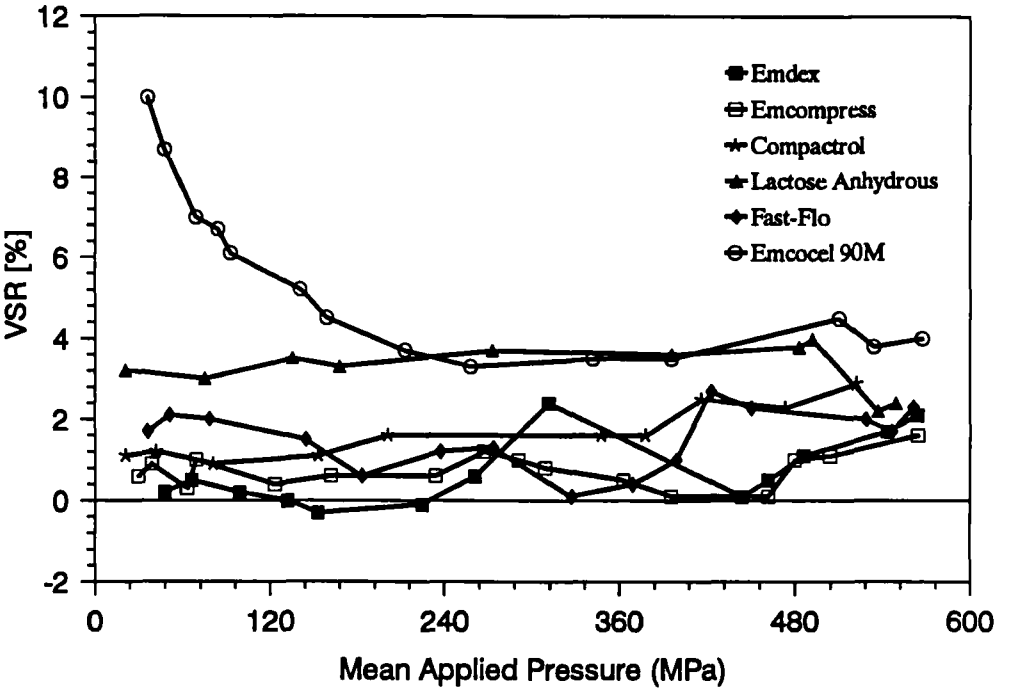

FIGURE 11

The Viscoelastic Strain Recovery (%) vs Mean Applied Pressure for the Compacts of the Excipients Used (Punch Velocity: 100mm/sec)

mechanism amongst its brittleness. This elasticity remained the same throughout the pressure range studied. The decrease in VSR% at pressures above 500MPa for this material may also be due to observed chipping of the compacts resulting in false readings of tablet thickness. During the 24 hour storage period, the magnitude of VSR% did not change for the brittle materials compacted at 100mm/s punch velocity, but increased slightly for the time-dependant microcrystalline cellulose at a given pressure.

When a 300mm/s punch velocity was applied, the overall results for immediate VSR% vs mean pressure plots (Figure 12) were almost the same as for 100mm/s. The comparison of the magnitude of VSR% results obtained at the two different compaction speeds at the given pressure did not indicate any significant dissimilarity for brittle

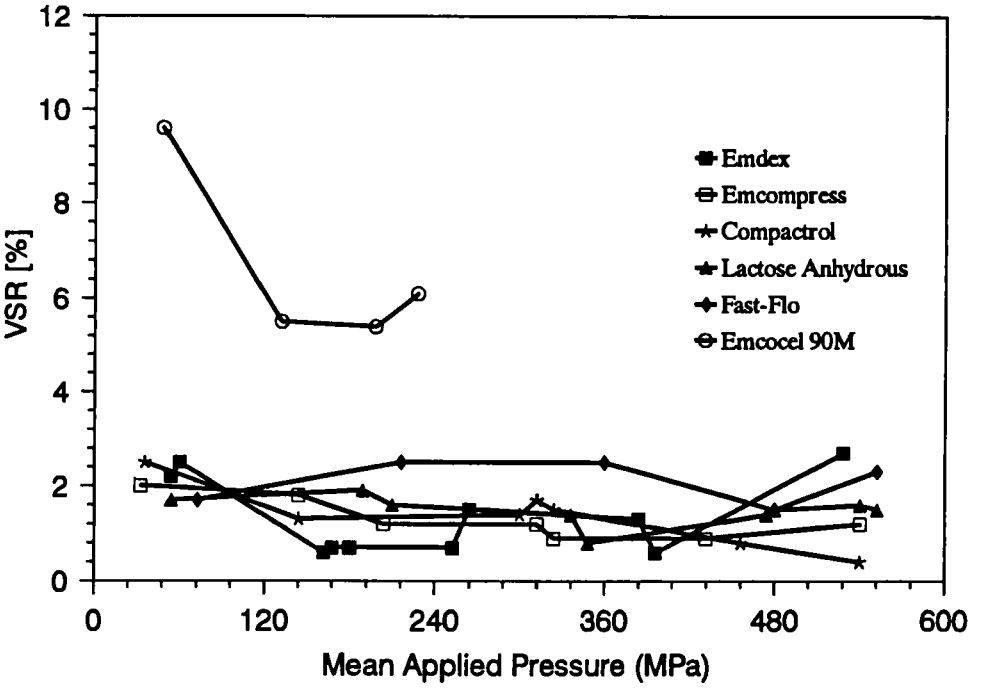

FIGURE 12

The Viscoelastic Strain Recovery (%) vs Mean Applied Pressure for the Compacts of the Excipients Used (Punch Velocity: 300mm/sec)

materials. On the other hand, Emcocel 90M presented an increased elasticity at the faster compaction speed which became more distinct closer to the pressures where capping and lamination occurred. This also is a result of the time-dependant nature of this material as it needs more time to deform plastically. At 300mm/sec punch velocity, lactose anhydrous exhibited only brittle consolidation. At the end of the 24 hour storage period, microcrystalline cellulose underwent some further viscoelastic expansion whereas there was no underlying trend for the other materials that were compared.

CONCLUSIONS

It can be concluded from the findings of this work that the development of a standard compaction method as a prospective functionality test for pharmaceutical powders is

feasible. At present, the following suggestions can be made for the standardization of the critical test conditions:

- employ an Integrated Compaction Research System or its simplified version fitted with standard flat-faced, round BB tooling,
- calculate the amount of material to be tested according to a constant true volume,
- use internal lubrication,
- operate the machine with constant punch velocities that can produce 'realistic' contact times,
- repeat the compaction tests for a wide range of applied pressure,
- monitor the forces on and displacements of the upper and lower punches, and ejection force,
- measure at least the dimensions and the crushing force of the compacts, and repeat the tests following a pre-determined storage period as well as immediately after ejection on a replicate number of tablets,
- evaluate the test performance of a material, at least, using the parameters of porosity, energy, time, and crushing strength,
- obtain fingerprints of data analysis profiles related to the 'compressibility' and 'compactability' of the test material.

Using the data generated in this work, the establishment of a compaction data bank that can be utilized as a reference source for tablet formulation studies was also found to be feasible. The initial compaction studies on a number of excipients demonstrated that, when Emcocel 90M was compacted at a punch velocity of 100mm/sec, it yielded the most outstanding quality compacts at all force ranges. However, due to its time dependant nature, this material should be used with caution at high speed compaction (i.e. 300mm/sec), since capping may occur even at moderate pressures. Within the range of pharmaceutical applications, the rank order for compact strength amongst the materials used was: Emcocel 90M > Emdex > lactose anhydrous > Fast-Flo > Emcompress $\geq$ Compactrol. Although, lactose anhydrous produced stronger tablets than Fast-Flo, their physical quality was poorer. The speed of compaction did not influence the performance of brittle excipients.

Further studies on the compaction functionality testing must include the tests on numerous powders in order to finalize the optimization of the critical parameters and to develop 'fingerprint' values of the materials for a number of data analysis methods. The future studies for the prospective Compaction Data Bank should include the following information and/or profiles for individual materials:

- basic pre-compaction powder properties, such as density, moisture content, particle size analysis, and scanning electron micrographs,
- the results of 'in-die' compaction data analysis methods including, but not limited to, compaction time, porosity (%), Heckel plots, energy involved in compaction, and ejection force, etc.,
- post-compaction properties, such as crushing strength and compact expansion,
- Wherever it is possible, the above information must be obtained for three lots and two suppliers of each material to be studied.

ACKNOWLEDGEMENTS

The authors would like the acknowledge the following companies for their financial support of this study: Hoffmann La-Roche, Johnson & Johnson Corporation, McNeil Consumer Products Company, Mendell, and RWJ-Pharmaceutical Research Institute. They are also thankful to Mendell, Foremost Whey Products and Berlex Laboratories Inc. for providing the excipients studied in this portion of the work, and Colleen E. Driscoll for her invaluable assistance during the preparation of this manuscript.

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