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COMPACTION STUDIES ON BEADS: COMPRESSION AND CONSOLIDATION PARAMETERS

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ABSTRACT

The purpose of this work was to evaluate compaction of the beads containing microcrystalline cellulose (MCC). Although MCC in its powder form is universally recognized as a very compressible material, studies in these laboratories demonstrated that MCC beads prepared by extrusion / spheronization were not. In fact, MCC beads are very hard and not easily deformable or broken. Therefore, the objectives of this work were to modify the bead composition by incorporating materials which might change the bead compactibility and to describe the effects. The dissolution properties of the compacted forms were also evaluated.

To study the compaction behavior of the MCC beads it was necessary to modify the Athy-Heckel equation to describe compression and to combine that analysis with the Leuenberger equation to describe consolidation.

INTRODUCTION

The manufacture of spheres, beads or pellets represents one method of providing a drug entity in a form which can be used for controlled release or for conventional drug delivery. Experimentation has demonstrated that beads or pellets can be prepared in several different types of equipment but that the resulting products are of differing quality, may be formed by different mechanisms and may exhibit different release profiles.

The formulations to be discussed all contain microcrystalline cellulose products at some level and this material appears to impart interesting properties. Immediate release as well as inert matrix and hydrogel types of release can be obtained from uncoated beads. Other materials can be incorporated into the formulations and may also impart desired properties. Drug release can be controlled to a certain extent by appropriate formulation and further control can be obtained by coating and by compaction. In certain cases, a change in release mechanism can be programmed by these operations.

Beads which are coated with a rate controlling membrane and then compacted into a single unit delivery system could conceivably provide either an intact tablet or a multiparticulate system during GI transit, depending on the formulation. The compaction operation, however, could cause damage to the controlling membrane or to the bead cores, and the properties of both must be thoroughly understood. It is the purpose of this work to study the compaction behavior of the core beads and to determine whether it may be controlled.

A capsule dosage form containing spherical beads is an attractive drug delivery system because the beads have the following advantages: high drug loading capacity, an ideal shape for coating or for controlled release of the active drug, good flow, and a high surface area to volume ratio as compared to a tablet (1). The compaction of coated beads is usually of special interest in the pharmaceutical industry, especially beads with a functional or rate controlling coat or membrane. The basic problem is that without sufficient plasticity of the film, the coating could be destroyed under pressure and the rate control would be lost. The coating, however, is not the only part to be considered. The bead within the coating should also exhibit some degree of plasticity, so that it can accommodate a possible change in shape when the coated beads are subjected to tabletting.

This paper addresses the compaction properties of uncoated beads. The beads were prepared by extrusion/marumerization technology. The effect of process variables on the beads has been documented in the literature (2-6) and will not be addressed in this study.

The selection of excipients for the bead matrices is based on well-known differences in deformation behavior in powder form. Microcrystalline cellulose (MCC) is classified as a plastic material (7,8), lactose consolidates primarily by fragmentation first then by plastic deformation (9), and dicalcium phosphate dihydrate (DCP) consolidates primarily by fragmentation (10). Among these excipients only MCC can form beads by itself; neither lactose nor DCP alone could form beads. Thus, MCC must be incorporated into each one of these two materials. All beads formulations contain 10% theophylline as the drug for dissolution evaluation.

Data are presented for the following formulas: MCC (90%), MCC/lactose (22.5%/67.5%), and MCC/DCP (22.5%/67.5%). The results show that the same material in powder form compacts differently than that in bead form. A plot of tablet tensile strength vs. applied pressure (Fig. 1) shows that MCC powder is very compressible and forms hard tablets at very low compaction pressures. Its beads are not compressible and form very soft tablets. These beads, themselves, are very hard; only few bonds are formed between beads as seen physically in the scanning electron micrograph (SEM) (Fig. 2).

THEORETICAL CONSIDERATIONS

Compression:

The compression mechanism in this study is viewed as being similar to the viscous flow of non-Newtonian fluids (11). This mechanism consists of two processes,

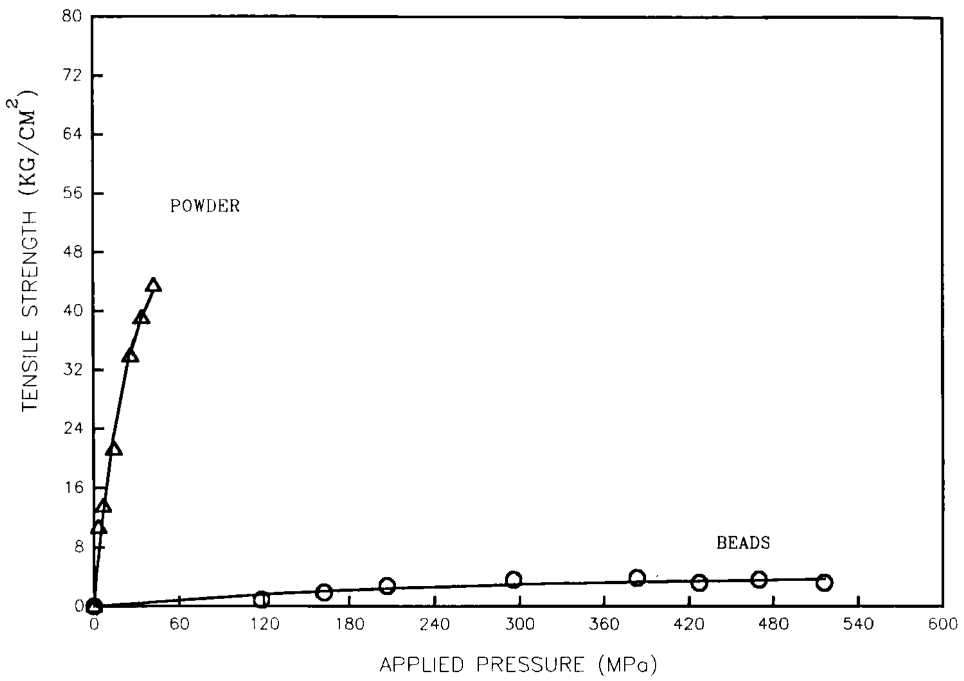

Fig. 1 Compaction profiles for MCC beads and powder

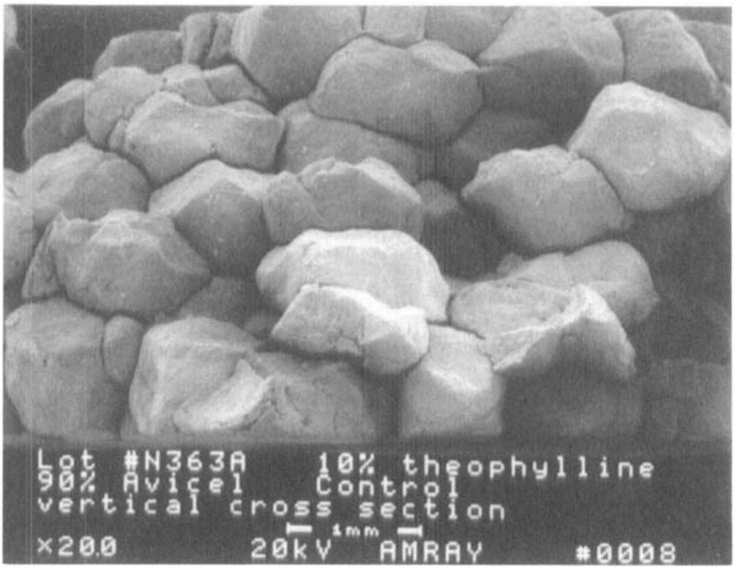

Fig. 2 Micrograph of a broken tablet compressed from MCC beads

namely, the viscoelastic resistance to the plastic flow and the plastic flow after the resistance is overcome.

The plastic flow or the densification due to the permanent deformation can be expressed in the following equation:

$$\ln \frac{1}{1-D_{DP}} = kP + A \qquad (1)$$

This equation is the same as the original Athy-Heckel equation (12,13). In this equation D_{DP} is the relative density due to the permanent deformation or a ratio of the apparent density of the compact and the true density of the compressed material; k is the material constant and is a measure of the ability of the material to deform plastically; P is the applied pressure; A is a constant.

When the data were plotted according to Equation 1, a curve with continual decrease in slope was obtained as shown in Figs. 3, 4 and 5. These results are consistent with the literature (14). It was, therefore, difficult to calculate the mean yield pressure from the slope and to calculate the density due to plastic flow, D_A, from the y-intercept.

Therefore, a modification to the Athy-Heckel equation (Eq. 1) was developed. In the present study, it was proposed that the densification is a combination of two different events; that is, the densification due to viscoelastic resistance and the densification due to permanent deformation. The second event can be described adequately by the Athy-Heckel equation (Eq. 1). During the early stage of compression, the beads exhibit some degree of resistance to the permanent deformation. The change in density due to this viscoelastic resistance with the change in the applied pressure is proportional to the density left in this viscoelastic region. A rate equation can be written as follows:

$$\frac{d\left\{\ln \dfrac{1}{1-D_{RE}}\right\}}{dP} = -\alpha \left\{\ln \frac{1}{1-D_{RE}}\right\} \qquad (2)$$

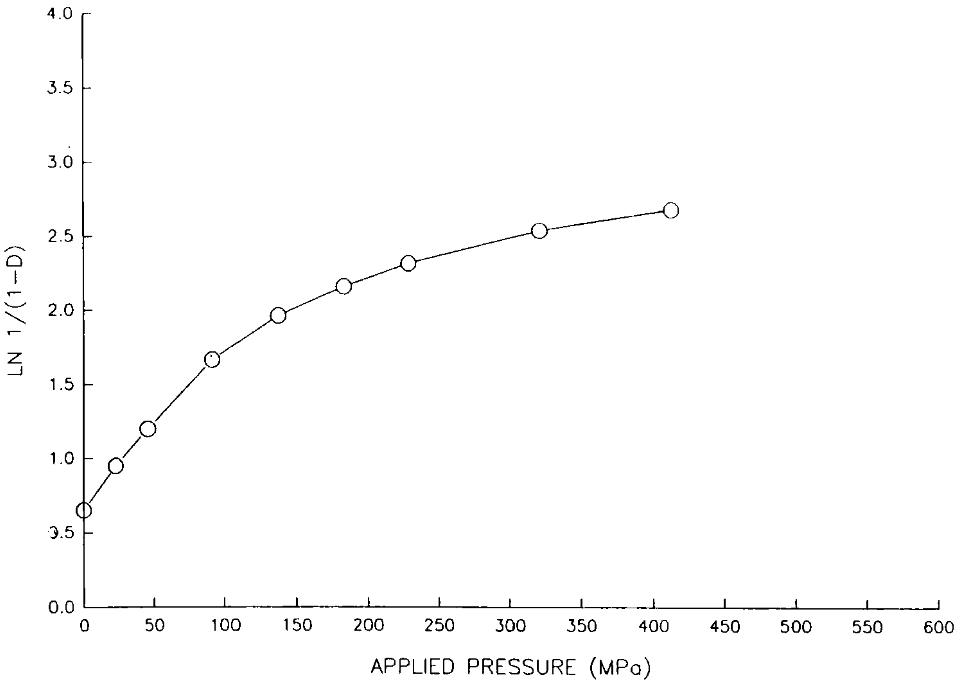

Fig. 3 Heckel plot for MCC beads

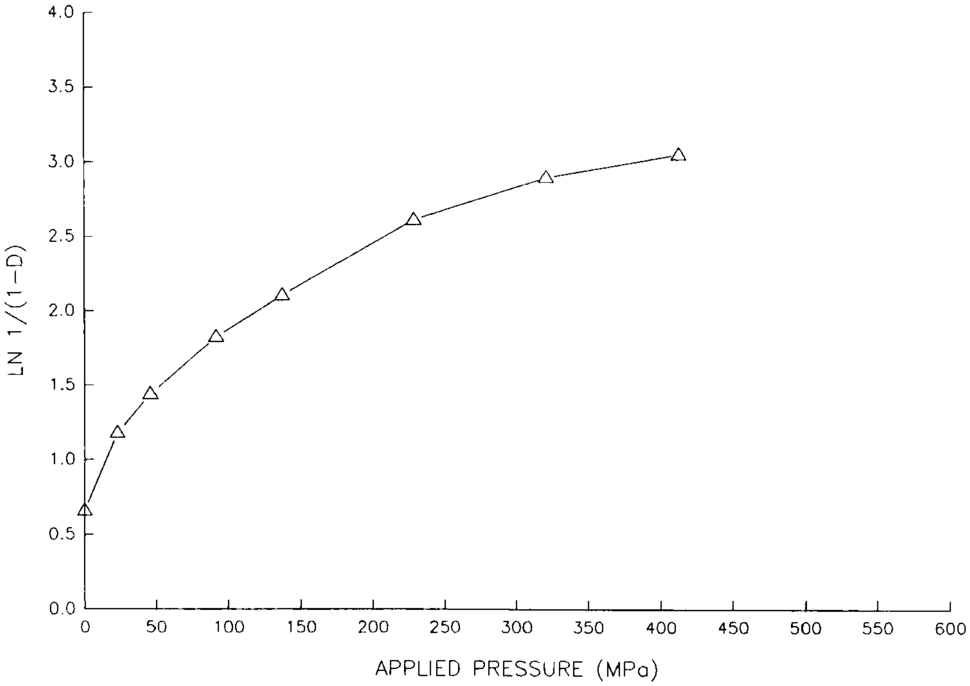

Fig. 4 Heckel plot for MCC:lactose beads (1:3 ratio)

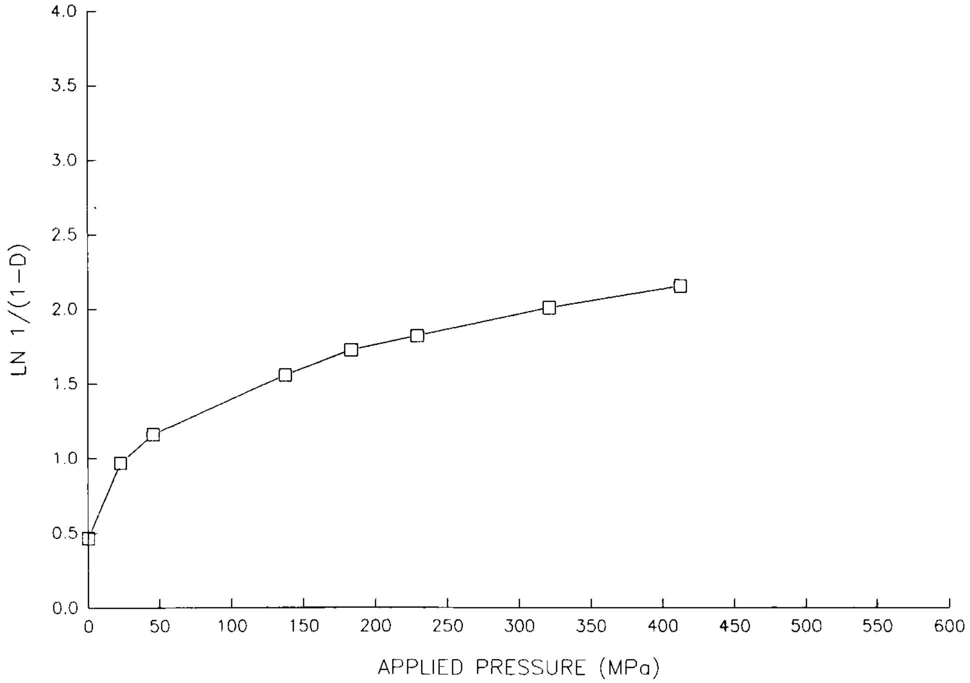

Fig. 5 Heckel plot for MCC:DCP beads (1:3 ratio)

where D_{RE} is the density due to viscoelastic resistance, P is the applied pressure, α is a proportionality constant or the coefficient of compressibility. If we let

$$V = \ln \frac{1}{1-D_{RE}}$$

then, Equation 2 can be rewritten as:

$$\frac{dV}{dP} = -\alpha V$$

Upon rearranging and integrating, one arrives at Eq. 3:

$$\int_{V_0}^{V} \frac{dV}{V} = -\alpha \int_{0}^{P} dP$$

$$\ln V - \ln V_0 = -\alpha\ P$$

$$V = V_0 \exp -(\alpha\ P)$$

$$\ln \frac{1}{1-D_{RE}} = B \exp - (\alpha\ P) \qquad (3)$$

The compression mechanism of the bead is described by the combination of Equation 1 and Equation 3, which results in the following equation:

$$\ln \frac{1}{1-D} = kP + A - B exp\text{-}(\alpha P) \qquad (4)$$

Equation 4 is the authors' modification of the Heckel Equation and it describes a visco-elastic flow. The exponential term is the change in density due to the viscoelastic resistance; the linear term is the ultimate plastic flow after the effect of the viscoelastic resistance vanishes. Therefore, the more compressible the bead; the greater the exponential term, so that the visco-elastic resistance vanishes faster with pressure.

In this equation D, k, P, A, α have the same definitions as mentioned earlier.

The constants in Eq. 4 can be converted to density by the following equation:

$$D_{(A)} = 1 - \exp\text{-}(A) \qquad (5)$$

The density of the beads at zero pressure or initial packing density, is designated as D_O and can be obtained experimentally.

The 3-stage densification can be quantitatively calculated as follows:

1. Densification by bead rearrangement, D_R:

$$D_{(R)} = D_{(B)} - D_{(O)} \tag{6}$$

2. Densification by initial deformation or fracture, D_F, prior to plastic deformation:

$$D_{(F)} = D_{(A)} - D_{(B)} \tag{7}$$

3. Densification by plastic deformation, D_A, or the density contribution from the constant A of Eq. 4.

Consolidation:

The Heckel analysis and the modified Heckel analysis only describe the compression (densification or volume reduction). The other component of compaction, namely, consolidation (tablet strength) is analyzed using the Leuenberger relationship (15), which was derived for the deformation hardness and is written here in terms of tensile strength:

$$T = T_{\max} \{1 - \exp(-\gamma DP)\} \tag{8}$$

where T is the tensile strength (kg/cm^2), T_{max} is the maximum tensile strength obtained when $\rho_r \to \infty$, D is the relative density, P is the applied pressure (MPa), γ(MPa^{-1}) is defined as compression susceptibility. The T_{max} parameter indicates the compactibility of the compressed material. According to the author, γ and T_{max} can be used together to categorize a material as either plastic deformation or fragmentation; $1/\gamma$ is related to the activation energy required to induce plastic deformation or brittle fracture (16); the physical significance of γ , however, requires further study.

MATERIALS AND METHODS

Materials:

The materials used to prepare beads were as follows: microcrystalline cellulose (MCC), NF (Avicel®, FMC Corporation, Philadelphia, PA), lactose, NF (Sheffield Products, Norwich, NY), dicalcium phosphate dihydrate (DCP), NF (Emcompress, Edward Mendell, Inc. Carmel, NY). All beads contain anhydrous theophylline USP (Knoll Fine Chemicals, New York) as the active drug model.

Methods:

Bead Preparation

The beads were prepared by the normal steps, i.e., blending, granulation, extrusion, spheronization and drying. The starting materials were dry blended for 5 minutes and granulated in a planetary mixer (Hobart Model A-200, Hobart Corp., Hobart, NY). The batch size was held constant at 1.0 kg of dry powders. The granulating liquid used was water which was added over the dry powder mixture for 3 minutes; mixing was continued for an additional 2 minutes. The wet granulation was passed through an extruder (Model EXDS-60, LUWA Corp., Charlotte, NC), which was fitted with 1.5 mm screens and operated at 50 rpm. The extrudate was then placed in a marumerizer (Model Q-230, LUWA Corp., Charlotte, NC), which was fitted with a 2.0 mm scored friction plate, and operated at 1000 rpm; after a 1 minute residence time, the wet beads were removed, placed on a tray and dried in a hot air oven (Stokes Model 38C, Pennwalt Corp., Warminster, PA) overnight at 42° C.

Tablet Preparation

The dried beads were compacted into tablets via a laboratory hydraulic press (Carver) using 1.11 cm (7/16") diameter round, flat faced punches and a die, which were lubricated with magnesium stearate prior to tabletting. The tablet mass was held constant at 500 mg/tablet. The tablet was held under the maximum compression force for 3 seconds; the force was then removed and the tablet was ejected.

Test Methods

The size distribution for the beads was determined by sieve analysis. The true bead density is a ratio of the bead weight and the true volume of the bead composition.

The relative density of the tablet is a ratio of the apparent density of the tablet at a given pressure and the true density of the bead. The tablet thickness and hardness were measured on the ejected tablet.

The tensile strength of the bead compact is calculated according to the equation given by Fell and Newton (17):

$$T = \frac{2F}{\pi\, d\, h} \qquad (9)$$

where, F is the tablet crushing force (kg), d is the tablet diameter (cm), and h is the tablet thickness (cm).

Dissolution testing was performed on the beads and on the tablets using the USP basket method in 900 ml of distilled water at 37° C. The basket rotational speed was 50 rpm. The samples were analyzed for theophylline by UV spectrophotometry at a wavelength of 272 nm.

RESULTS AND DISCUSION

The beads were satisfactorily prepared from the three formulations as mentioned earlier. It was found that formulations containing 80% of lactose or DCP do not form beads without further formula modification. This may be due to the lack of sufficient plasticity needed for spheronization. The beads prepared by the above method exhibit a narrow size distribution as shown in Fig. 6; the addition of DCP or lactose slightly widens the size distribution compared to the MCC beads. However, a significant amount of the 16/20 mesh fraction beads was collected from all the formulations, and this size fraction was specifically selected for the compaction studies.

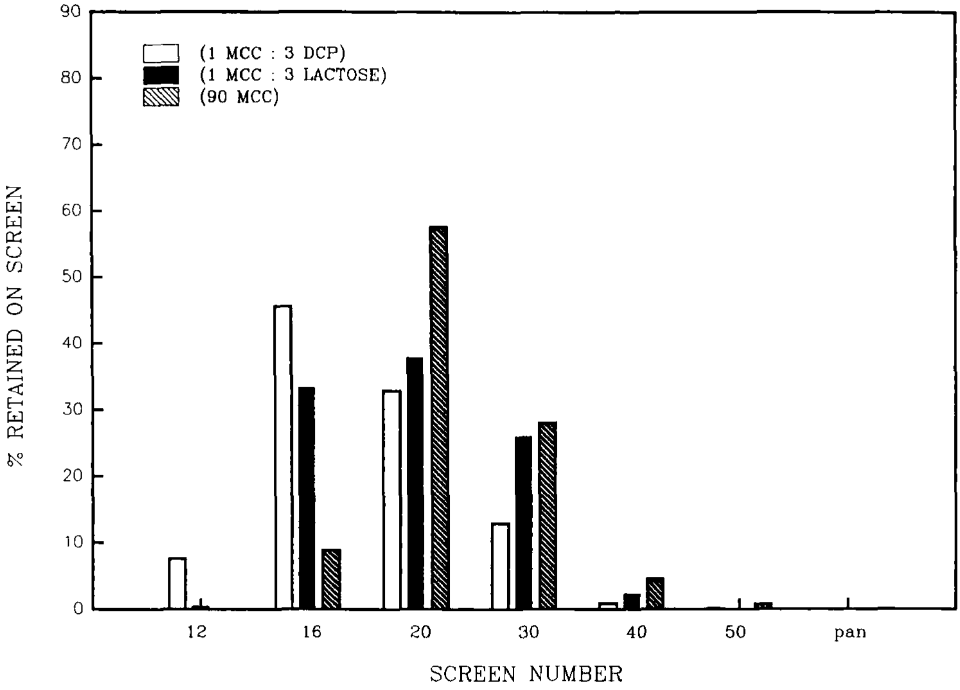

Fig. 6 Effect of Excipients on bead size distribution

COMPRESSION:

In the present study, the relative densities of the tablets were measured by the out-of-die method. The data were plotted as if one were going to plot the Heckel plot. The data analysis however, was fitted according to the new proposed equation (Eq. 4). The results for this equation were computed by using the nonlinear regression program PCNONLIN.

The densification profile for MCC beads is shown in Fig. 7. In this graph the solid line is the regression line, for the modified equation. The long dashed line is viscoelastic resistance; and the end of the dotted line indicates the onset of plastic flow, or the lower linearity limit, which is used to determine the fracturability of the beads. This graph is consistent with the physical observation that MCC beads are not compressible (Fig. 2). Thus, viscoelastic resistance exists in the entire normal range

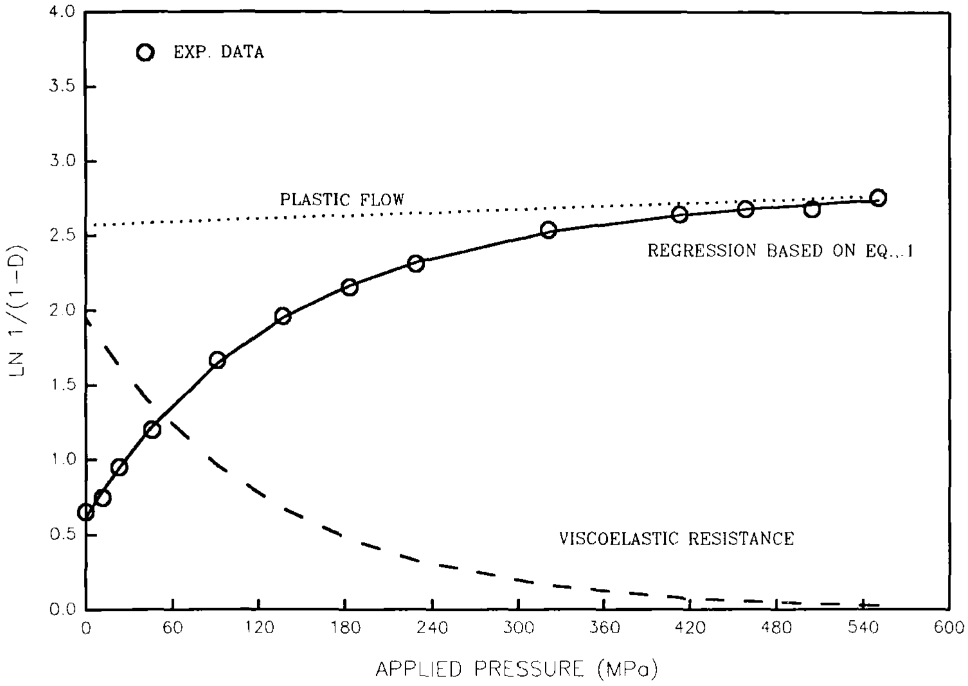

Fig. 7 **Densification profile for MCC beads [By modified Heckel Eqn.]**

$$* \ln \frac{1}{1 - D} = k P + A - B \exp - (\alpha P)$$

of compression pressure range (curve coming down); plastic flow does not occur until unrealistically high pressures are applied.

The densification profile for the MCC/lactose beads is shown in Fig. 8. The MCC/lactose beads are primarily lactose. This bead system shows a reduction in viscoelastic resistance, i.e., the exponential term vanishes at lower pressureS. The linearity becomes more apparent and starts at lower pressure indicating that the beads undergo plastic flow more easily and, thus, exhibit a greater degree of deformation or fracture. This change corresponds with the physical observation in Fig. 9. This photomicrograph shows that the MCC/lactose beads are more compressible and exhibit more fracture than the MCC beads.

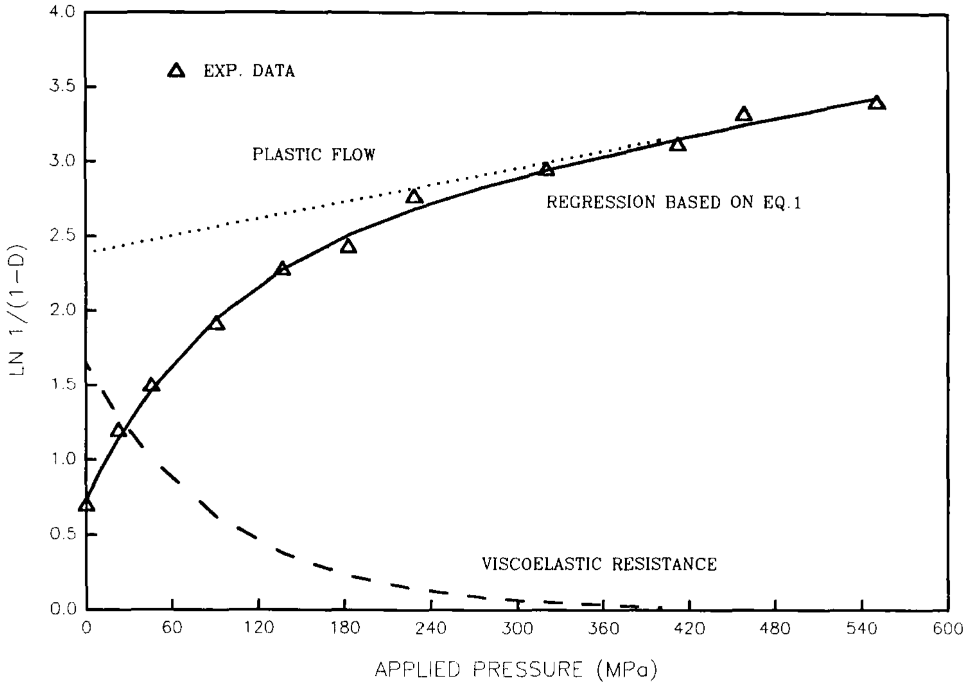

Fig. 8 Densification profile for MCC:lactose beads (1:3 ratio)
[By modified Heckel Eqn.]

$$* \ \ln \frac{1}{1 - D} = k P + A - B \exp - (\alpha P)$$

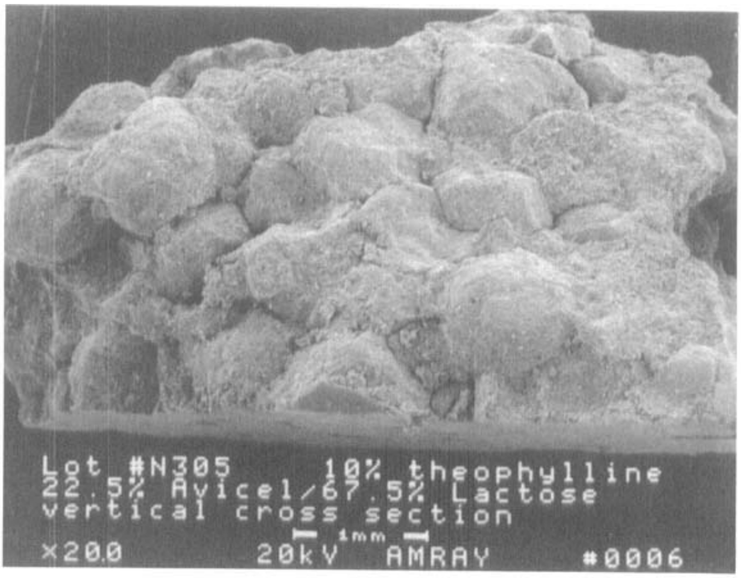

Fig. 9 Micrograph of a broken tablet compressed from MCC:lactose beads (1:3 ratio)

The MCC/DCP beads are primarily calcium phosphate. These beads are even more compressible and exhibit the smallest viscoelastic resistance as shown by a quick drop of the exponential function at very low pressure (see Fig. 10.) Plastic flow starts at very low pressures, indicating that these beads undergo plastic flow more easily than the MCC and MCC/lactose beads. A greater slope indicates a greater amount of deformation or fracture. The photomicrograph, Fig. 11, clearly shows that these beads fracture more and are even more compressible, as expected.

Several parameters can be obtained from this analysis, and are listed in Table I.

Numerically, the reduction in the effect of viscoelastic resistance is shown by an increase in the coefficient of compressibility, α. A large value of α causes the exponential term to vanish faster and to disappear at the lower pressure. This pressure is defined here as the lower linearity limit because it also marks the onset of plastic flow.

The results show that α increases in this order:
MCC < lactose < DCP beads. The deformation starts earlier in the following order: 100 MPa for DCP, 400 MPa for lactose, and 550 MPa for the MCC beads.

The beads undergo plastic flow more easily with a smaller value of 1/k, and deform more with a larger value of k. The k value increases and 1/k decreases from MCC to lactose to DCP beads.

The density contribution to the compression stages is listed in Table II. These densities are defined in the theoretical section. The most important densities are D_R (density due to rearrangement) and D_F (density due to initial fracture prior to plastic flow). The less resistant beads should exhibit less rearrangement and more fracture before yielding to the plastic flow; a lower D_R value and higher D_F value reflect this observation, respectively. In addition to the lower linearity parameter, D_F is also used to determine the fracturability of the bead. The D_F value for the MCC beads is lowest, while the D_F value for MCC/DCP beads is highest.

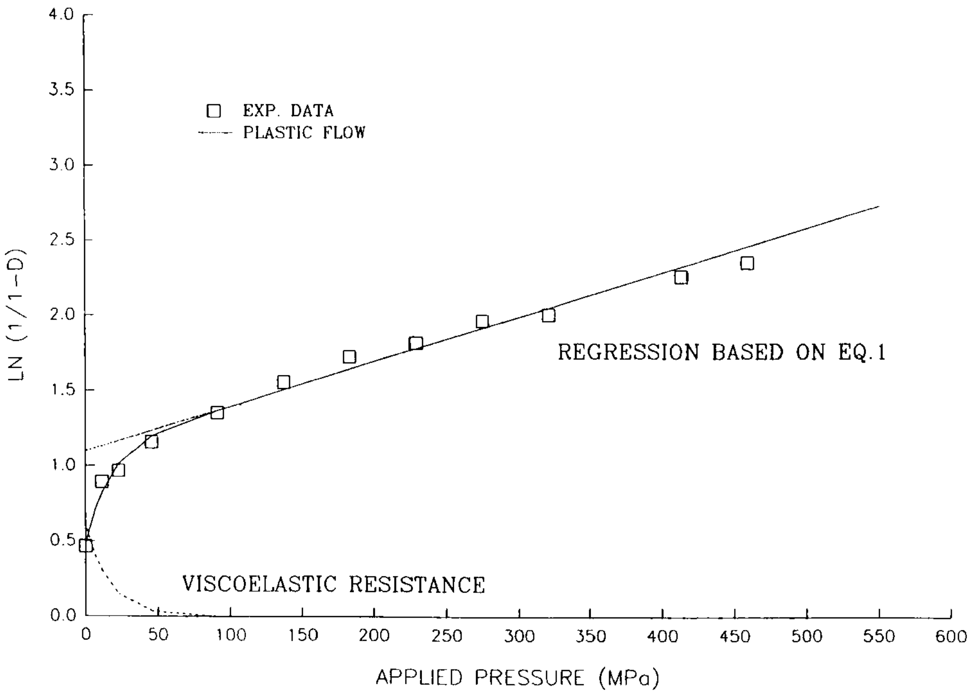

Fig. 10 Densification profile for MCC:DCP beads (1:3 ratio)
[By modified Heckel Eqn.]

$$* \ln \frac{1}{1 - D} = k P + A - B \exp - (\alpha P)$$

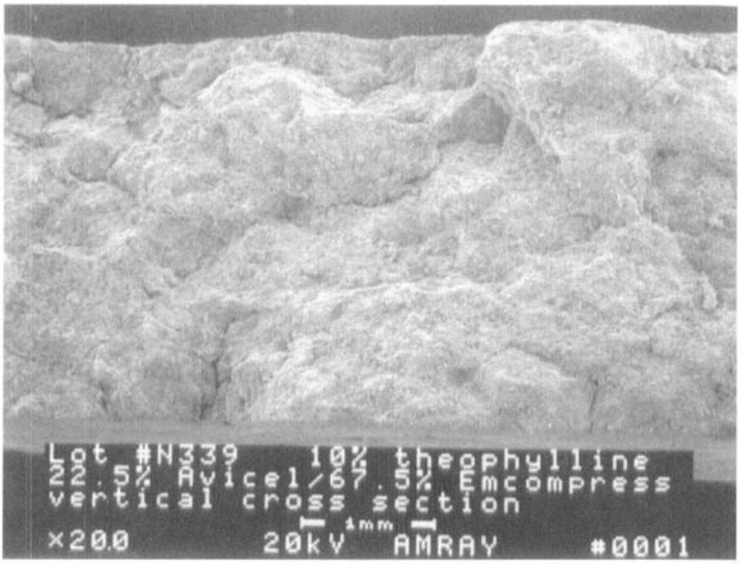

Fig. 11 Micrograph of a broken tablet compressed from MCC:DCP beads (1:3 ratio)

TABLE I

Effect of Excipients on the Densification Parameters

Compression Parameters	Excipient Ratio		
	MCC (90%)	MCC/lactose (22.5%/67.5%)	MCC/DCP (22.5%/67.5%)
α (MPa^{-1})	7.8×10^{-3}	1.1×10^{-2}	6.2×10^{-2}
Lower linearity (MPa)	> 550	400	100
k (MPa^{-1})	3.6×10^{-4}	1.9×10^{-3}	3.0×10^{-3}
1/k (MPa)	2.8×10^{3}	5.2×10^{2}	3.3×10^{2}

TABLE II

Effect of Excipients on Densities Before and During Tabletting

Densities	Excipient Ratio		
	MCC (90%)	MCC/lactose (22.5%/67.5%)	MCC/DCP (22.5%/67.5%)
D_{True} (g/cc)	1.552	1.534	2.005
D_{App} (g/cc)	0.742	0.739	0.746
D_O	0.478	0.501	0.372
D_A	0.923	0.908	0.665
D_B	0.858	0.808	0.458
D_R	0.380	0.307	0.086
D_F	0.065	0.100	0.207

CONSOLIDATION:

Although the modified Heckel analysis (Eqn. 4) does show differences in densification or plasticity; it is not designed to address the consolidation, or tablet strength. Therefore, the Leuenberger equation was selected for this purpose.

The tensile strength data for the beads were plotted according to Equation 8. The parameters T_{max} and γ were obtained from this equation and were defined in the theoretical section.

The results were computed using the Guggenheim technique (14) and the PCNONLIN program. As shown in Fig. 12, the consolidation properties of the beads are in a rank order. The non-compressible MCC beads form soft tablets, MCC/lactose beads form hard tablets, and MCC/DCP beads form hardest tablets.

The increase in tablet tensile strength can be expressed quantitatively by the T_{max} parameter as tabulated in Table III. The T_{max} of this analysis was found to be correlated with the constant k of equation 4 or the degree of plastic deformation. The shape of the compaction curves in Fig. 12 can be described by the value of γ. That is, the MCC/lactose and MCC/DCP beads fragment and bond concurrently in the process of tablet formation. Thus, the change in tablet strength is gradual as shown by decreasing γ. For the non-compressible MCC beads, the value of γ is higher because T_{max} is reached rather rapidly. The combination of T_{max} and γ parameters does not seem useful in classifying the beads into either the plastic or the brittle fracture catergory as specified by Leuenberger.

DISSOLUTION:

It was hypothesized that the fractured bead in the form of a compact would dissolve faster than the non-fractured beads. Therefore, the compaction mechanism of the beads should be further supported by the dissolution data. The dissolution results for tablets of comparable hardness prepared from beads of MCC, MCC/lactose and MCC/DCP are shown in Fig. 13.

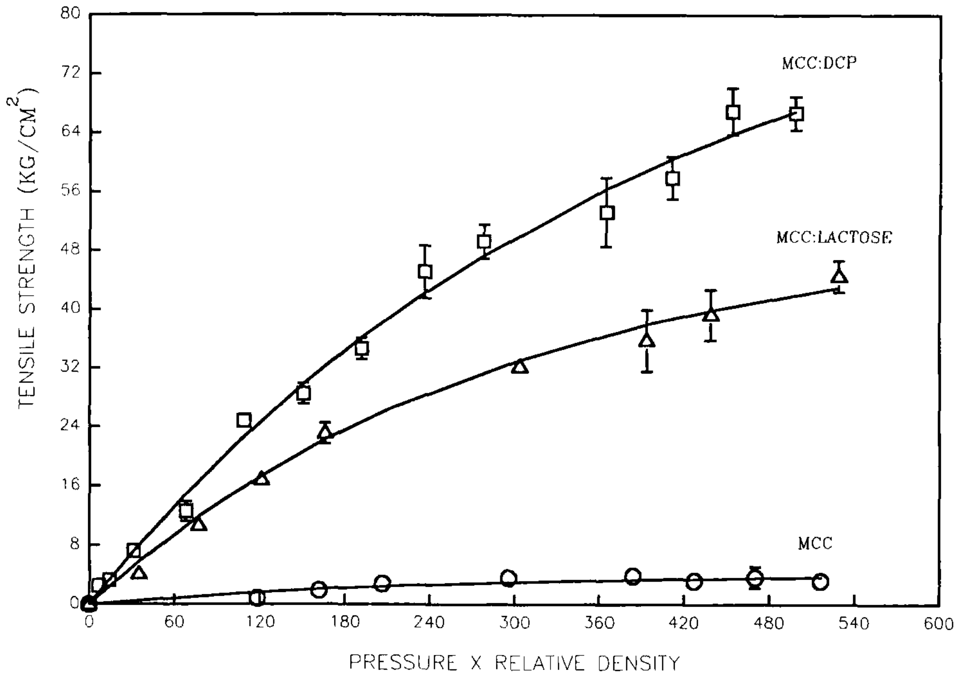

Fig. 12 Effect of excipients on the compaction profile: Leuenberger model [Eq. 8]

TABLE III

Effect of Excipients on Leuenberger Parameters

Leuenberger	Excipient Ratio		
Parameter	MCC (90%)	MCC/lactose (22.5%/67.5%)	MCC/DCP (22.5%/67.5%)
T_{max} (kg/cm^2)	4.14	51.5	92.8
γ (MPa)	4.4×10^{-3}	3.4×10^{-3}	2.6×10^{-3}

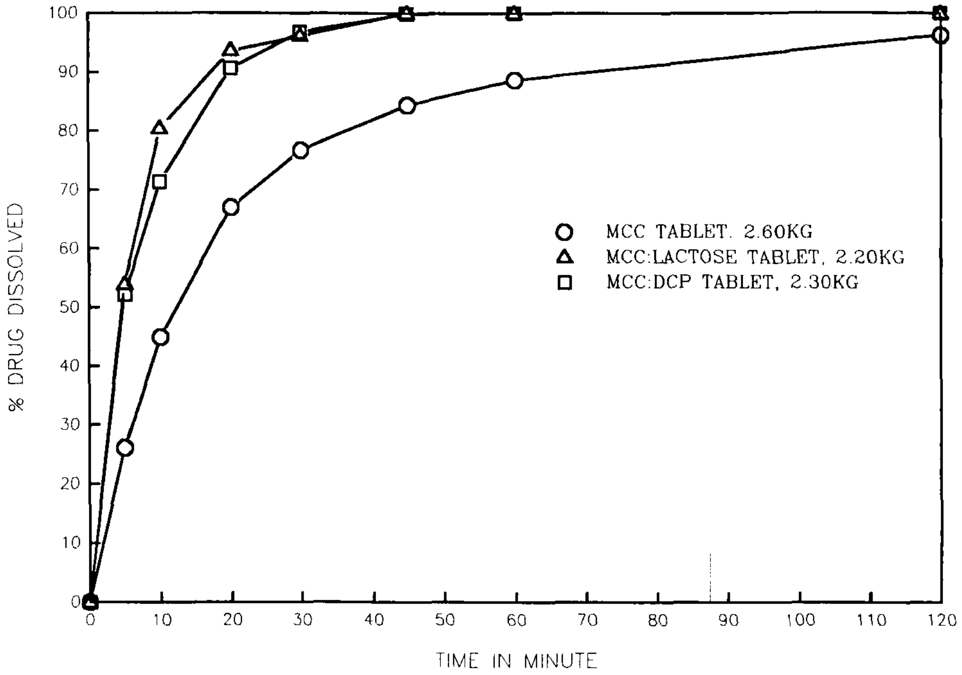

Fig. 13 **Effect of excipients on the dissolution of tabletted beads: MCC, MCC:lactose (1:3 ratio), and MCC:DCP (1:3 ratio)**

At very low tablet hardness (the only place that tablets of comparable hardness could be obtained), the tablet immediately disintegrates into its component beads. The MCC compacted beads exhibit a slower dissolution profile which seems to follow the matrix type. The MCC/lactose and MCC/DCP compacted beads exhibit a faster dissolution, which may be due to two factors: the beads may have slightly fractured at this low compressional pressure, and the presence of lactose or DCP in the MCC bead certainly disrupted the bead matrix.

The dissolution behavior of MCC non-compacted beads and their tablets are illustrated in Fig. 14. These data show that at very high compressional force the MCC beads exhibit some slight amount of fracture and dissolve a little faster than the non-compacted beads.

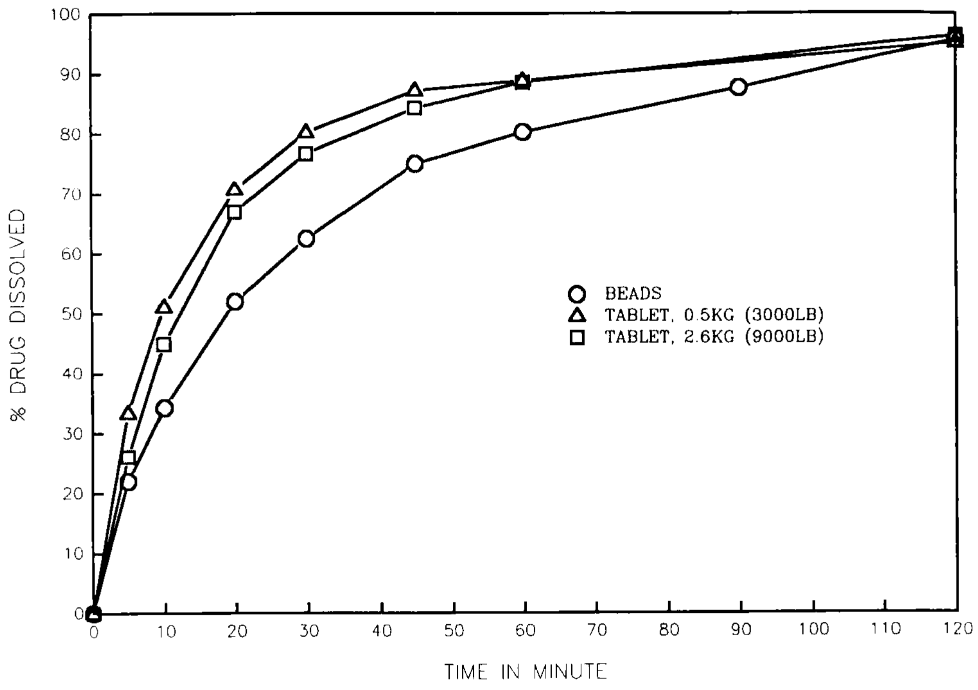

Fig. 14 **Effect of compressional force on the dissolution of MCC beads and tablets**

The dissolution of MCC/lactose bead system is presented in Fig. 15. The tablet and the non-compacted beads exhibit the same dissolution behavior due to the water solubility of lactose. Therefore, the dissolution behavior of this bead system does not support its compaction mechanism.

The dissolution of the MCC/DCP bead system is shown in Fig. 16. It is apparent that these beads fracture, but those nice clean surfaces form a hard, stable tablet. The tablet must disintegrate before dissolving, thus, exhibiting a slower dissolution profile than that for the non-compacted beads.

SUMMARY AND CONCLUSIONS

The traditional Athy-Heckel equation has been modified to provide a measure of the densification due to the viscoelastic resistance of materials under compression.

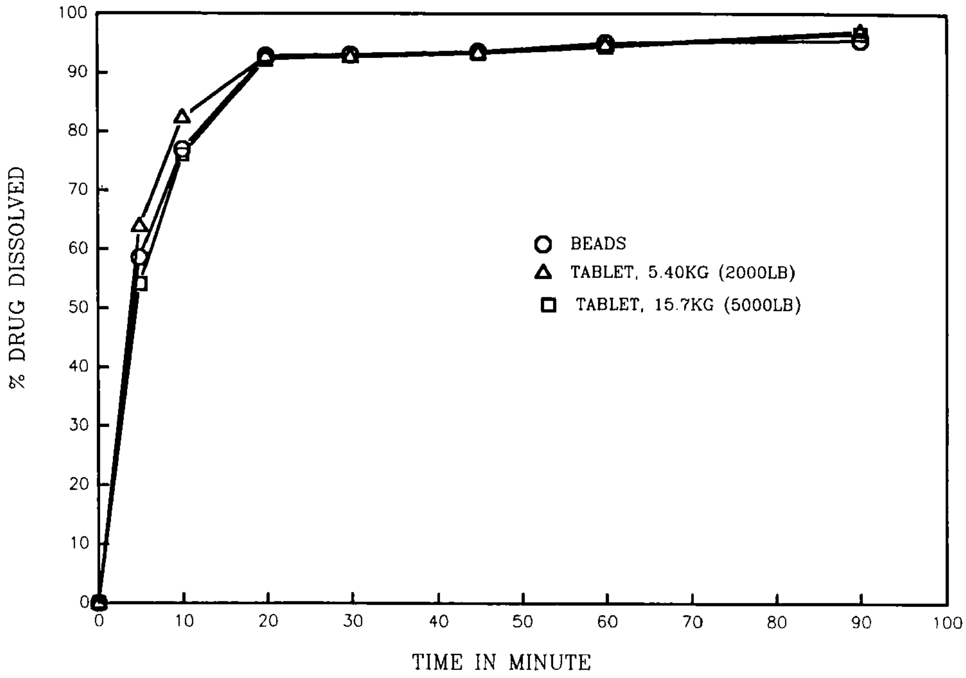

Fig. 15 Effect of compressional force on the dissolution of the MCC:lactose bead system (1:3 ratio)

The modified equation still includes the Athy-Heckel term to describe the densification due to permanent deformation. The compaction behavior of beads can be adequately described by combining this modified Heckel equation for compression and the Leuenberger equation for consolidation.

Scanning electron micrographs (SEMs) are shown to be very valuable in elucidating the compression mechanism of the beads in this study. The micrographs show that the beads do not deform all at once; the fracturing and the bonding occur simultaneously. Therefore, it is not theoretically feasible to separate out the fragmentation and the plastic deformation components. The results and the numerical constants obtained in these studies are consistent with physical observations based on SEMs.

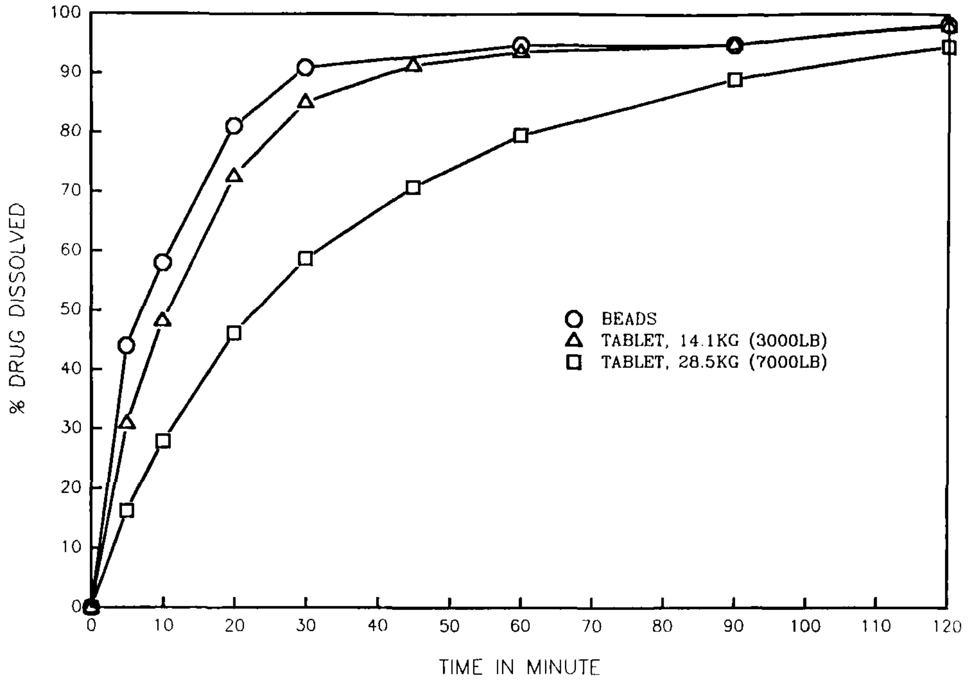

Fig. 16 **Effect of compressional force on the dissolution of the MCC:DCP bead system (1:3 ratio)**

Based on the formulation changes in this study, it is clear that one could have any desired compaction profile by changing the bead components; or that bead components will have a profound effect on the compaction behavior of uncoated beads, and therefore, on coated beads as well.

The dissolution data do not appear to support the compaction mechanisms in a predictable manner, since the dissolution properties are also influenced by the nature of the excipients and the hardness of the compact. However, the explanations do fit the observations.

ACKNOWLEDGEMENTS

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