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The compressibility of pharmaceutical particulate systems. An illustration of percolation

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Summary

The compaction of particulate materials occurs in stages. This is manifested by a series of linear regions in the plot of the normalized solid fraction, P, as a function of the logarithm of compressive stress, $\ln \sigma$. The slopes of the linear regions represent compressibilities of the particulate system in different states (i.e. powder, flexible compact, rigid compact and continuum) in which the system goes through during compaction. This investigation was conducted to elucidate the mechanical significance of the different slopes of the $P = f(\ln \sigma)$ relationship. To this end, the various slopes of the $P = f(\ln \sigma)$ profiles of various compositions of the binary mixtures of Emcompress^R : Avicel^R and Emcompress^R : lactose were determined. From the results, it can be said that, of all the different slopes of the $P = f(\ln \sigma)$ relationship, only K_{RP} reflects a mechanical property (ductility) of the substance under compression. K_{RP} is the slope in the rigid compact stage, where the substance is undergoing predominantly plastic deformation. K_{RP} is a composite of mechanical properties (elastic, plastic and viscoelastic) and has been shown to be dependent on the speed of compression. It has, therefore, been proposed that it can be used as a discriminating characterization parameter when it is determined at three significantly different speeds, preferably at slow, moderate and fast speeds. Although K_{RP} is influenced by the overall composition of the binary mixture, it is dominated by any material(s) which exist(s) in the particulate system as percolating cluster(s) in accordance to percolation theory.

Introduction

It is undisputable from the numerous studies undertaken in the fields of compaction of powders, reviewed by Donachie and Burr (1963), James (1972) and Shotton et al. (1976), that the compaction of powders comprises processes which occur in stages. The sequence of events is easily recognizable in a semilogarithmic plot of pressure and solid fraction where the different stages are evinced as a series of linear regions.

In a recent article (Holman, 1991), it was shown that the sequence of linear regions of the relationship between the normalized solid fraction, P, and the logarithm of the compressive stress, $\ln \sigma$, is a reflection of the different states which the particulate system goes through during compression. The number of linear regions (and therefore the

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number of states) in the profile of the relationship between the normalized solid fraction, P, and the logarithm of pressure, $\ln \sigma$, is dependent on the hardness or softness of the material on one hand, and the brittleness or ductility on the other. The maximum number of linear regions was exhibited by soft and highly ductile materials which go through the following stages during compaction: powder → flexible compact → rigid compact → a continuum. The slopes in the different regions have been designated K_L (powder region), K_{fl} (flexible compact region), K_R (rigid compact region), K_a (continuum solid region).

Deviations from the above sequence of events were manifested by materials possessing other mechanical properties. Hard materials formed rigid compacts without first forming a flexible compact. They, therefore, did not exhibit K_{fl}. Powders which are not highly ductile did not attain the stage where the compact could be considered a continuum; and moderately brittle materials underwent a brittle-ductile deformation transition within the stage where the compact was rigid. Thus, for moderately brittle materials, the rigid compact stage is made up of two linear regions with slopes K_{RB} and K_{RP} which designate the slopes of the predominantly brittle deformation stage and predominantly ductile deformation stage respectively.

The slopes of these linear regions are in effect measures of the resistance of the particulate system to changes in volume, i.e. compressibility. The different slopes therefore represent compressibilities of the particulate system in the different states in which it occurs in the course of the compaction process. The purpose of this paper is to clarify the significance of the different slopes as to how they reflect the mechanical properties of the materials in an effort to quantify the compression process.

Experimental

Materials

It was rationalized that the objective of this investigation would be best achieved by using materials with contrasting mechanical properties. This will distinctly show any dependence of the slopes on the mechanical properties of the substances. Thus, microcrystalline cellulose (Avicel^R PH102) manufactured by FMC in Philadelphia, PA, U.S.A. a soft, highly ductile and viscoelastic material; and dicalcium dihydrate phosphate (Emcompress^R) manufactured by Edward Mendell Co. in Carmel, NY, U.S.A.; a hard, highly brittle and virtually non-viscoelastic material, were chosen as they represent nearly the endpoints of the wide spectrum of mechanical properties of pharmaceutical materials. β-anhydrous lactose, manufactured by Sheffield in Norwich, NY, U.S.A. was also chosen to serve as an intermediary between the two extremes.

It has been shown (Holman and Leuenberger, 1990) that by continuously varying the relative concentration of the constituents of binary component mixtures the mechanical properties are correspondingly altered in a way that could be predicted by percolation theory. Therefore, in order to cover the whole range of spectrum of mechanical properties, binary component mixtures of Emcompress^R and Avicel^R on one hand and Emcompress^R and β-anhydrous lactose on the other were used. The rationale behind this approach is that, the slopes which are dependent on the mechanical properties of the materials will exhibit a trendwise qualitative change with changing concentration of Emcompress^R in each of the two binary mixtures. For example, the slope reflecting the ductility of a material will decrease with increasing Emcompress^R concentration since Emcompress^R is harder than either Avicel^R or lactose (Jetzer, 1982; Holman and Leuenberger, 1990).

On the other hand, the slope reflecting brittleness will increase with increasing concentration of Emcompress^R, since Emcompress^R is more brittle than Avicel^R or lactose.

The materials were conditioned at a relative humidity of 45% by placing them over saturated potassium carbonate solution for a minimum period of 7 days before being used.

Method

The binary mixtures of Emcompress^R : Avicel^R and Emcompress^R : lactose were prepared for compression by deagglomerating through sieving and mixing as previously described (Holman, 1991). Avicel^R, lactose and Emcompress^R and the various compositions of the binary mixtures were then compressed on a compaction simulator (Mand Testing Machines Ltd, Stourbridge, U.K.) operated to mimic a 16 stationary 'D' press as described elsewhere (Holman, 1991). Unless otherwise stated, the compaction simulator was run to mimic a 'D' press running at a speed of 15 rpm. The experiments were carried out in an environment with a relative humidity of 40 ± 10%.

Results and Discussion

The data obtained from the compression of the single substances and binary mixtures were plotted as normalized solid fraction, P, as a function of the natural logarithm of the compressive pressure, ln σ, as described in Holman (1991). All the substances exhibited one of the six different profiles presented in Holman (1991) representing different mechanical classes. Some of the plots are shown in Figs 1–3 and 6 to illustrate the different slopes. Only a fraction of the data points obtained (and used to determine the slopes) are depicted in the graphs to ensure clarity.

The various slopes K_L, K_{fl}, K_R (K_{RB} and K_{RP}) and K_a were determined for the $P = f(\ln \sigma)$ relationship and are listed in Tables 1 and 2.

The slope, K_L

The slope, K_L, represents $dP/d(\ln \sigma)$ in that stage of compaction just after the transitional

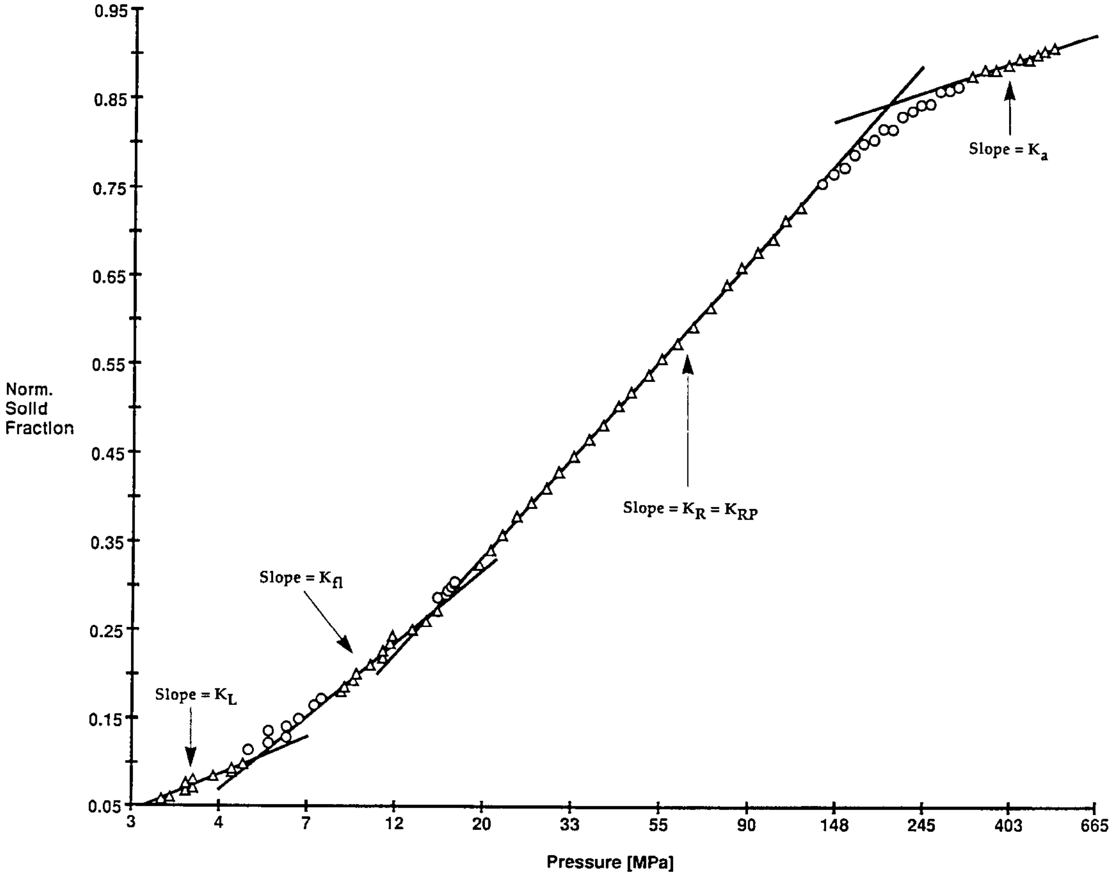

Fig. 1. Typical relationship between the normalized solid fraction, P, and the logarithm of applied pressure, ln σ, for Emcompress^R : Avicel^R 3.1 : 6.9 v/v (4 : 6 w/w) illustrating the various slopes.

restacking (initial extensive rearrangement) has taken place but before the bond particulate threshold, P_{cs}, where a three-dimensional network of bonds is formed (Holman, 1991). Thus, the particulate system consists of single and agglomerated particles (isolated clusters) in this region. This part of the $P = f(\ln \sigma)$ relationship is shown in Figs 1–3 and 6.

The slopes, K_L, determined for the $P = f(\ln \sigma)$ relationship for the substances tested in this work are illustrated in Figs 4 and 5 listed in Tables 1 and 2. It is seen that, in spite of the differences in the mechanical properties of the substances, the K_L values are approximately the same. This implies that although some interparticulate bonds (mostly localised at the surface asperites) are formed at this stage, K_L is not dependent on the mechanical properties of the materials being compressed. This is probably because, in this region, the clusters of bonded particles are in effect isolated (Holman, 1991). Consequently, they do not offer resistance to changes in volume to the particulate system as a whole. The forces responsible for K_L are probably frictional in nature which are dependent on the physical properties of the particles like particle shape and surface roughness.

The slope, K_{fl}

The slope, K_{fl}, as illustrated in Fig. 1, represents the slope in that part of the graph of the

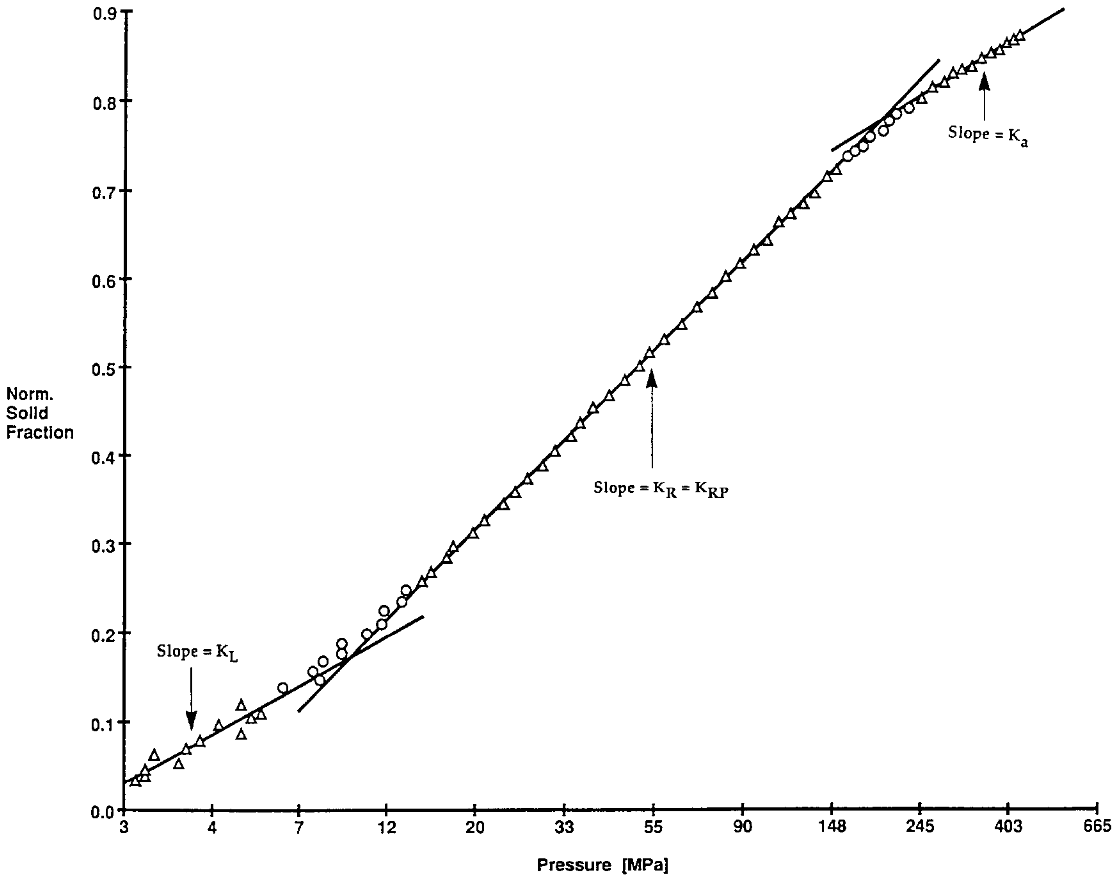

Fig. 2. Typical relationship between the normalized solid fraction, P, and the logarithm of applied pressure, $\ln \sigma$, for Emcompress^R : Avicel^R 6.11 : 3.89 v/v (7 : 3 w/w) illustrating the various slopes.

$P = f(\ln \sigma)$ relationship where the incipient percolating cluster formed is not rigid but flexible, i.e. between the bond percolation threshold, P_{cs}, and the rigidity threshold, P_R (Holman, 1991). Flexible incipient percolating clusters are typically formed by polymers and tenous materials (Alexander, 1984). As such, they are exhibited only in the plots of the binary mixtures of Emcompress^R : Avicel^R in the ratios of 5.03 : 4.97 v/v (6 : 4 w/w) to 0 : 10 v/v and Emcompress^R : lactose in the ratios 4.98 : 5.02 v/v (6 : 4 w/w) to 0 : 10 v/v. As a sequel, K_{fl} values could be determined for only these mixtures. The results are presented in Tables 1 and 2 and in Figs 4 and 5.

As is evident in the plots (Figs 4 and 5), the values of the slope, K_{fl}, are approximately the same for the various compositions of the binary mixtures, indicating the independency of K_{fl} on the mechanical properties of the substance under compression. This is because, although there is a continuous percolating network of bonds traversing the whole system in three dimensions, the bonds are not strong enough to render rigidity to the incipient percolating cluster of particles (Holman, 1991). The forces responsible for the mechanical properties of the incipient percolating cluster for these soft materials are scalar (entropic) in nature (Alexander, 1984). The interparticulate bonds (which are vectoral in nature) play a less

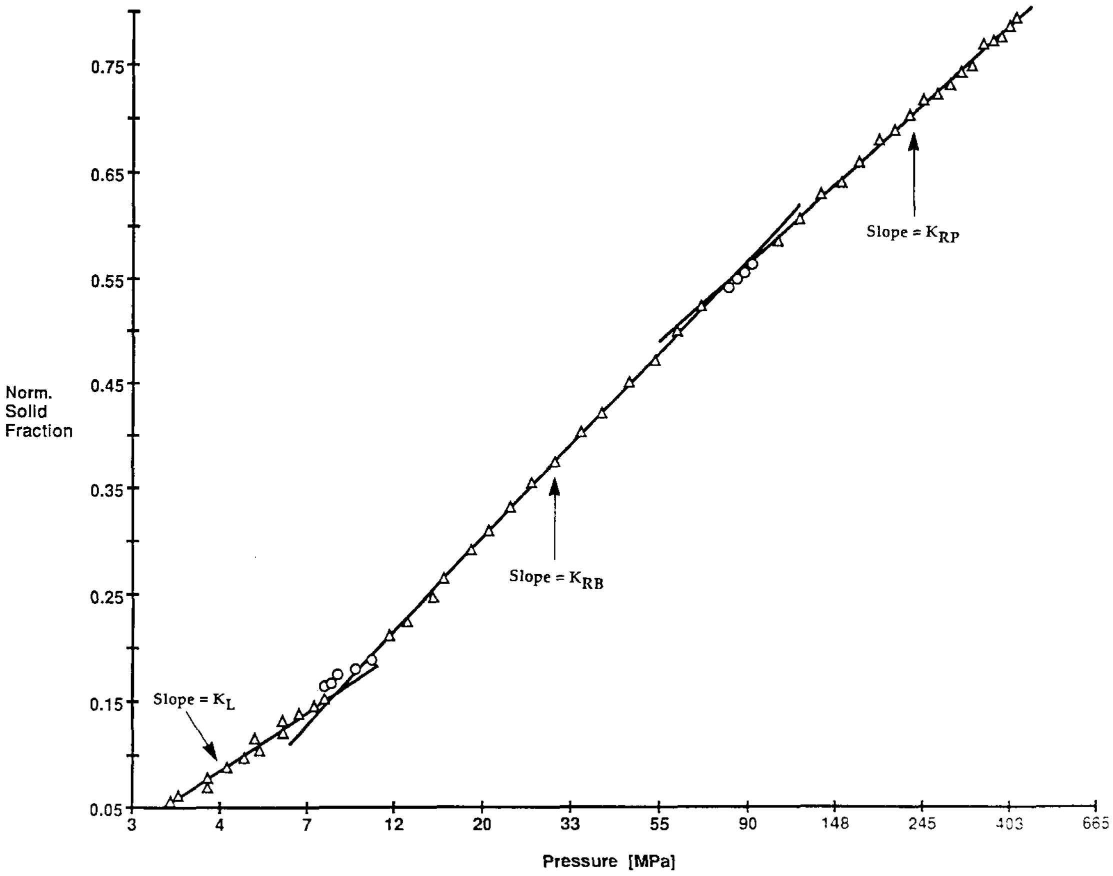

Fig. 3. Typical relationship between the normalized solid fraction, P, and the logarithm of applied pressure, $\ln \sigma$, for Emcompress^R : lactose 8.56 : 14.4 v/v (9 : 1 w/w) illustrating the various slopes.

dominant role. As such, it is not surprising that K_{fl} shows no dependency on the mechanical properties of the substances.

The slope, K_R

The slope, K_R, represents the slope in the stage of the compaction process where the compact is rigid (Holman, 1991). Thus, it represents that part of the $P = f(\ln \sigma)$ graph between the rigidity threshold, P_R, and the pore percolation threshold, P_{ca}, in the case of tenous materials (see Fig. 1). For hard materials $P_R = P_{cs}$, since the incipient percolating cluster is rigid; thus, K_R, represents the slope in the region $P_{cs} < P < P_{ca}$ (see Figs 2, 3 and 6).

The distortion of a particle and its subsequent fragmentation, which marks the end of plastic deformation, are inherent processes in compaction for both ductile and brittle materials. These processes occur simultaneously in the compaction of particulate materials because of the heterogeneity of the stress distribution in a powder system on one hand, and the heterogeneity of the particulate system (different particle geometries and mechanical properties) on the other. For some materials, either of the two processes, distortion or fragmentation dominates. To distinguish between the slopes of the two forms of consolidation in the rigid compact region, K_{RP} and K_{RB} will be used to designate the slopes for the materials which

TABLE 1

Slopes of the $P = f(\ln \sigma)$ relationship for various compositions of Emcompress^R : lactose mixture ($n = 3$)

Volume fraction of constituents (in percent) in mixture Emcompress^R : lactose		Slopes (mean ± S.D.)			
		K_L[a]	K_{fl}[b]	K_R[c]	
				K_{RB}[d]	K_{RP}[e]
0	100	0.076 ±0.003	0.163 ±0.003	e[f]	0.261 ±0.003
6.8	93.2	0.090 ±0.015	0.155 ±0.001	e	0.245 ±0.002
14.2	85.8	0.081 ±0.008	0.144 ±0.004	e	0.219 ±0.001
22.1	77.9	0.090 ±0.010	0.150 ±0.005	e	0.208 ±0.003
30.6	69.4	0.071 ±0.010	0.145 ±0.004	e	0.192 ±0.001
39.8	60.2	0.095 ±0.013	0.146 ±0.002	e	0.183 ±0.001
49.8	50.2	0.100 ±0.011	0.153 ±0.003	e	0.172 ±0.001
60.7	39.3	0.116 ±0.001	e	e	0.160 ±0.001
72.6	27.4	0.111 ±0.007	e	0.164 ±0.002	0.151 ±0.001
85.6	14.4	0.103 ±0.009	e	0.171 ±0.002	0.146 ±0.001
100	0	0.083 ±0.009	e	0.184 ±0.002	0.143 ±0.000

[a] K_L = slope of the particulate system in the powder state.
[b] K_{fl} = slope of the particulate system in the flexible compact state.
[c] K_R = slope of the particulate system in the rigid compact state.
[d] K_{RB} = slope of the particulate system in the rigid compact state where fragmentation is the dominant form of deformation.
[e] K_{RP} = slope of the particulate system in the rigid compact state where plastic flow is the dominant form of deformation.
[f] e = not exhibited in the $P = f(\ln \sigma)$ plot for this composition.

deform predominantly by distortion and fragmentation, respectively (see Figs 1 and 2). A crossover from a predominantly fragmentation deformation stage to a predominantly plastic flowing stage also occurs for other materials (Carless and Sheak, 1976; Kendall, 1978; Holman, 1991). This has been attributed to the fact that below a certain critical particle size even the most brittle material undergoes plastic deformation (Carless and Sheak, 1976; Kendall, 1978; Sikong et al., 1990), especially when they are confined in a closed space (Von Karman, 1911). Such a phenomenon termed brittle-ductile transition was exhibited by the mixtures in the ratios of Emcompress^R : lactose 8.56 : 1.44 v/v (9 : 1 w/w) and 7.26 : 2.74 v/v (8 : 2 w/w) and Emcompress^R : Avicel^R 8.58 v/v (9 : 1 w/w) (see Holman, 1991; and Fig. 3). For such materials, K_{RB} is used to designate the slope in the predominantly brittle stage and K_{RP} to designate the slope in the predominantly ductile stage as illustrated Fig. 3.

For the highly brittle materials used in this study, i.e. Emcompress^R and Emcompress^R/Avicel^R mixtures in the ratios of 9.28 : 0.72 v/v (9.5 : 0.5 w/w) and 8.93 : 1.07 v/v (9.25 : 0.75 w/w), the $P = f(\ln \sigma)$ relationship at $P > P_{cs}$ is

TABLE 2

Slopes of the $P = f(\ln \sigma)$ relationship of various compositions of Emcompress^R : Avicel^R mixture (n = 3–6)

Volume fraction of constituents (in percent) in mixture Emcompress^R : Avicel^R		Slopes (mean ± S.D.)				
		K_L	K_{fl}	K_R		K_a[a]
				K_{RB}	K_{RP}	
0	100	0.079 ±0.018	0.185 ±0.003	e	0.265 ±0.002	0.104 ±0.007
7.0	93.0	0.071 ±0.008	0.136 ±0.004	e	0.253 ±0.001	0.072 ±0.000
14.4	85.6	0.063 ±0.006	0.175 ±0.005	e	0.233 ±0.002	0.073 ±0.001
22.4	77.6	0.085 ±0.008	0.173 ±0.002	e	0.224 ±0.001	0.082 ±0.005
31.0	69.0	0.104 ±0.004	0.168 ±0.003	e	0.220 ±0.001	0.075 ±0.002
40.3	59.7	0.088 ±0.008	0.147 ±0.005	e	0.213 ±0.001	0.106 ±0.004
50.3	49.7	0.087 ±0.013	0.150 ±0.005	e	0.209 ±0.002	0.107 ±0.005
61.1	38.9	0.097 ±0.008	e	e	0.205 ±0.001	0.125 ±0.003
72.9	27.1	0.101 ±0.009	e	e	0.194 ±0.001	0.138 ±0.005
79.3	20.7	0.098 ±0.009	e	e	0.186 ±0.001	0.138 ±0.001
82.5	17.5	0.096 ±0.008	e	e	0.174 ±0.002	0.142 ±0.001
85.8	14.2	0.103 ±0.003	e	0.191 ±0.001	0.153 ±0.002	e
89.3	10.7	0.086 ±0.005	e	0.197 ±0.008	0.150 ±0.000	e
92.8	7.2	0.092 ±0.006	e	0.180 ±0.001	0.144 ±0.000	e
100	0	0.083 ±0.009	e	0.184 ±0.002	0.143 ±0.000	e

[a] K_a = slope of the system as a continuum solid body. Other symbols are the same as in Table 1.

nonlinear as evident in Fig. 6. The nonlinear relationship, attributable to the brittle nature of the substances, is due to the continuously increasing ductility and decreasing brittleness of the particles with increasing compressive stress (Holman, 1991). However, at low P values, just after the crossover region in which the compact is just formed (Holman, 1991), the $P = f(\ln \sigma)$ relationship is linear over approx. 0.2 units of P (see Fig. 6). This slope may be used as an estimate of K_{RB}. Similarly, at high P values (at approx. $P > 0.65$), the $P = f(\ln \sigma)$ relationship is linear (see Fig. 6). The slope of this linear region at approx. $P > 0.65$ was thus used as a measure of K_{RP}. The residual plots of the linear relationships at the low and high P values were satisfactory, thus confirming linearity. The linearity in the $P = f(\ln \sigma)$ relationship at high P values is probably because at high P values (at high pressures) no appreciable change in the degree of fragmentation occurs. A similar situation where no appreciable change in communition occurs at high pressures has been reported by Turba (1965) for glass (a highly brittle material).

Thus, for ductile materials, K_{RP} is the slope of the linear region at P values just after the rigidity threshold, P_R, in the case where the material is soft, or just after the particulate bond percolation threshold, P_{cs}, if the material is hard. For moderately brittle substances which undergo brittle-ductile transition, K_{RP} is the slope of the linear region at P values just above the brittle-ductile transition point. For highly brittle materials which do not exhibit a clear transition but a very gradual crossover as exhibited by Emcompress^R, an estimate of K_{RP} is obtained from the slope of the linear section of the $P = f(\ln \sigma)$ relationship which occurs at high P values.

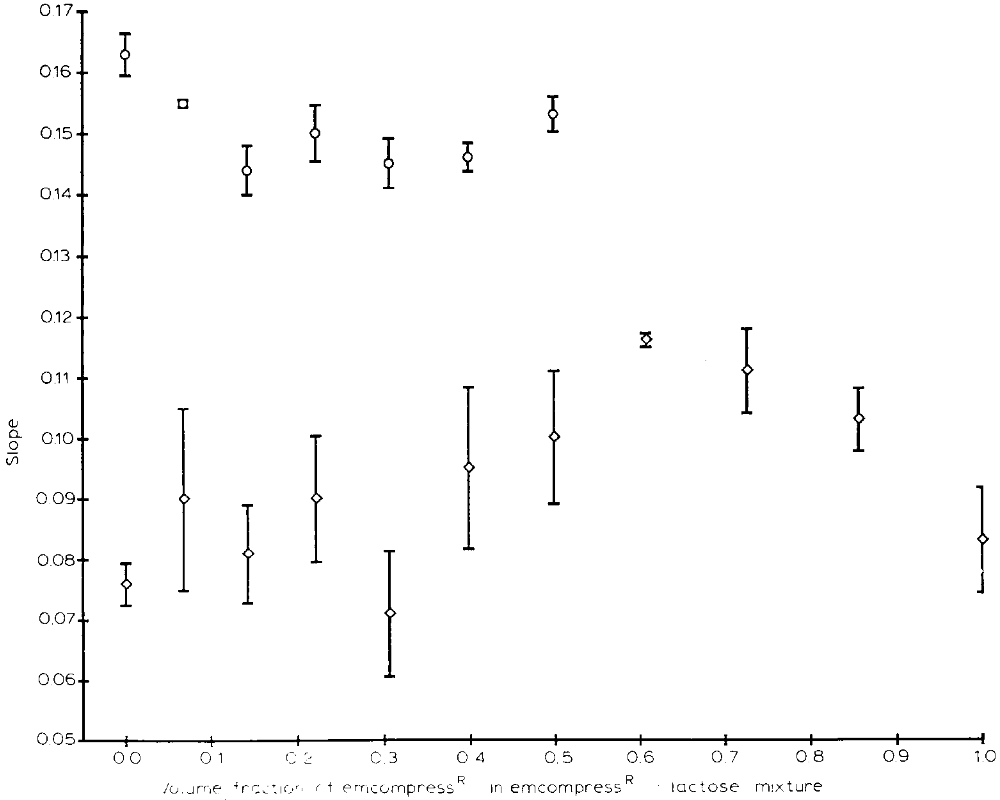

Fig. 4. The slopes K_L and K_{fl} (mean ± S.D.), as functions of the composition of Emcompress^R : lactose mixture ($n = 3$). (◇) K_L, (○) K_{fl}.

The K_{RB} values are listed in Tables 1 and 2. K_{RB} shows a dependency on the composition of the Emcompress^R : lactose binary mixtures, increasing with increasing concentration of Emcompress^R. However, this dependency is not apparent in the Emcompress^R : Avicel^R binary mixture system. It, therefore, appears that the dependency of K_{RB} on the relative concentrations of the components in the binary mixture is dependent on the type of ingredients in the binary mixture. However, the limited number of composition ratios for which K_{RB} was obtained for the Emcompress^R : lactose mixture system does not allow a definite conclusion to be made.

The K_{RP} values are listed in Tables 1 and 2 and graphically represented as a function of the composition of the binary mixtures in Figs 7 and 8. Evidently, K_{RP} shows a clear dependency on the composition of the binary mixtures. Since Emcompress^R is hard and less compressible than either lactose or Avicel^R, K_{RP} expectedly decreases with increasing concentration of Emcompress^R in both binary mixture systems. This indicates the dependency of K_{RP} on the mechanical properties of the substance under compression. The profiles of the relationship of K_{RP} as a function of the composition of the binary mixtures, however, differ for the two binary mixture systems; they are discussed below.

Emcompress^R / lactose

The profile of the relationship of K_{RP} as a function of the concentration of Emcompress^R, V_L, in the Emcompress^R : lactose binary mixture consists of three linear regions (see Fig. 7). The initial linear region at low Emcompress^R concentration deviates to a second linear region with a less steep slope at an Emcompress^R concentra-

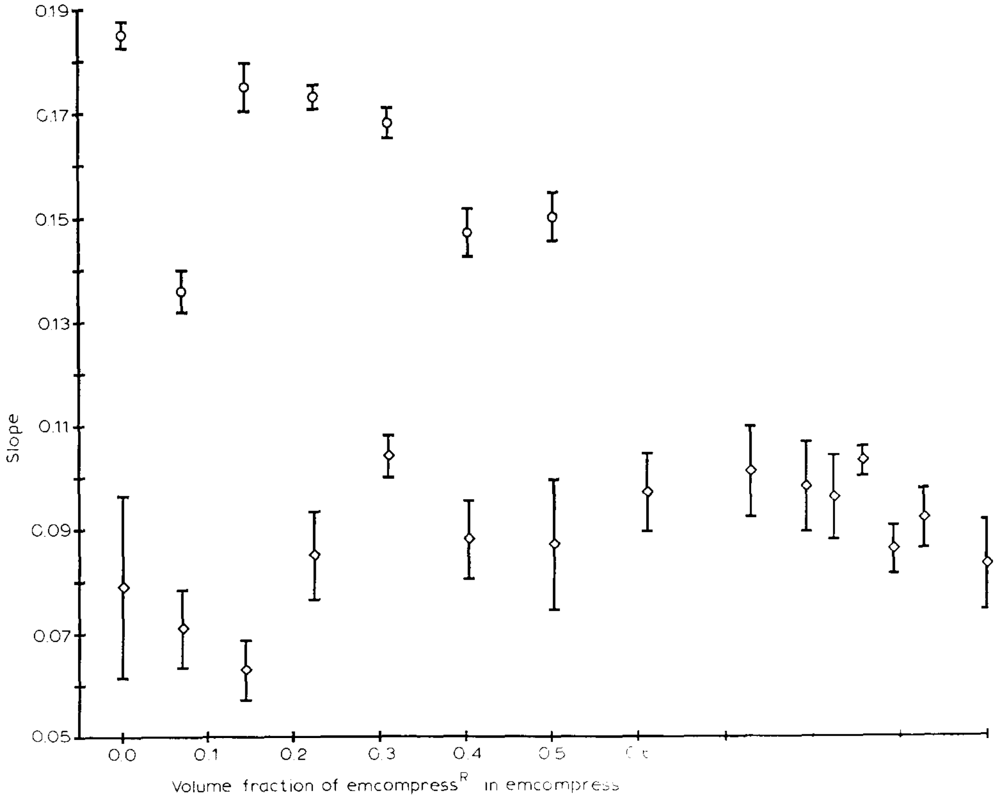

Fig. 5. The slopes K_L and K_{fl} (mean ± S.D.), as functions of the composition of Emcompress^R : Avicel^R mixture (n = 3–6). (◇) K_L, (○) K_{fl}.

tion of 0.245. This second linear region also deviates to a third linear region, exhibiting the least steep slope, at $V_L = 0.687$. Thus the slope of $K_{RP} = f(V_L)$ decreases successively from one linear region to another with increasing concentration of Emcompress^R. The two inflexion points at $V_L = 0.245$ and $V_L = 0.687$ signify percolation thresholds of Emcompress^R and lactose, respectively. Emcompress^R exists as finite isolated clusters in the continuous percolating cluster of lactose at $V_L < 0.245$ and as a continuous percolating cluster at $V_L > 0.245$. The second inflexion point at $V_L = 0.687$, i.e. at lactose concentration of $0.313 = 1 - V_L$, signifies the percolation threshold of lactose. At $V_L > 0.687$ or $1 - V_L < 0.313$, lactose occurs as finite clusters in the continuous matrix of Emcompress^R, and as a percolating cluster at $V_L < 0.687$ or $1 - V_L > 0.313$. At $0.245 < V_L < 0.687$, both lactose and Emcompress^R occur as percolating clusters side by side. The concurrence of the two percolating clusters simultaneously is exhibited by three-dimensional systems as opposed to two-dimensional systems (Holman and Leuenberger, 1990).

The K_R (V_L) relationship shows that, although the compressibility is influenced by the overall density of the compact, the percolating cluster plays a more dominant role.

Emcompress^R : Avicel^R

The profile of the relationship between K_{RP} and the concentration of Emcompress^R in the

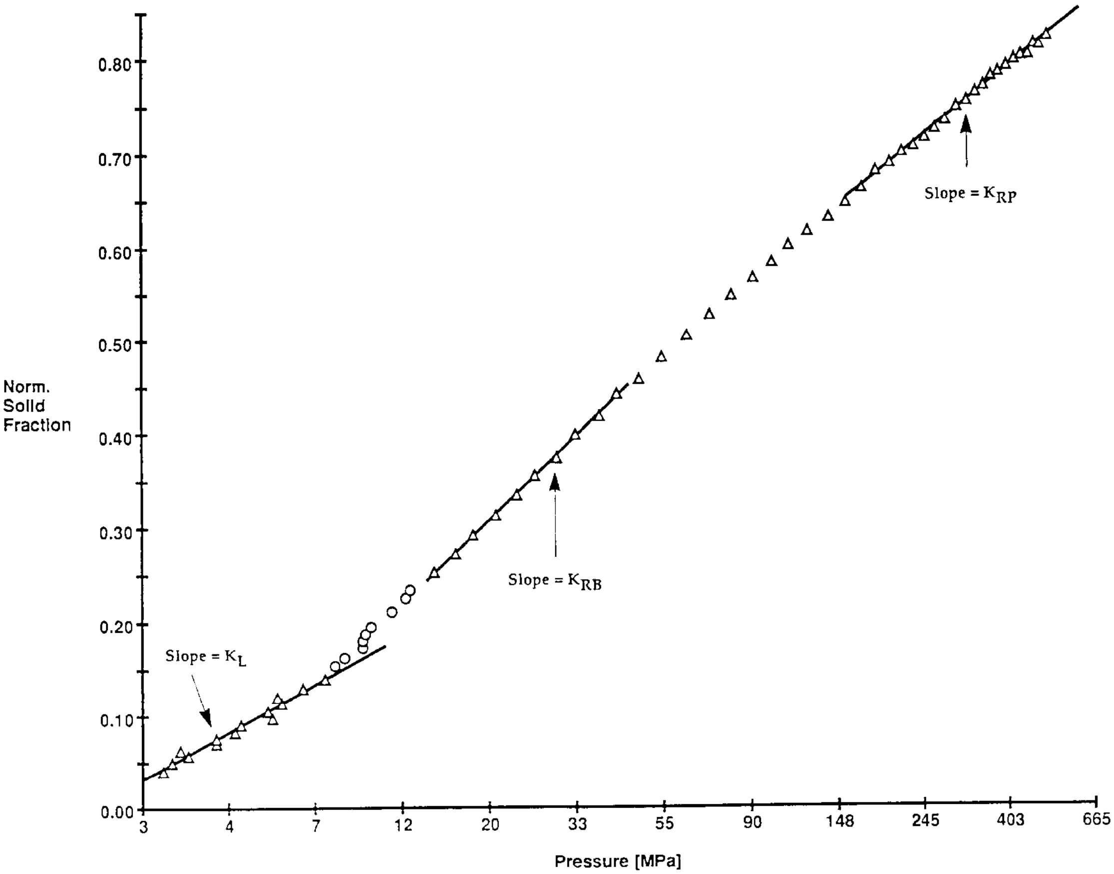

Fig. 6. Typical relationship between the normalized solid fraction, P, and the logarithm of applied pressure, ln σ, for Emcompress^R : Avicel^R 9.28 : 0.72 v/v (9.5 : 0.5 w/w) illustrating the different slopes.

binary mixture of Emcompress^R : Avicel^R, V_A, depicted in Fig. 8 shows four linear regions. The inflexion points at $V_A = 0.205$ and $V_A = 0.864$ are the percolation thresholds of Emcompress^R and Avicel^R, respectively. The inflexion point at $V_A = 0.783$ (or at an Avicel^R concentration of $1 - V_A = 0.217$) signifies the rigidity threshold of the percolating cluster of Avicel^R.

The percolating cluster of Avicel^R at $V_A = 0.864$ or $1 - V_A = 0.136$ is not rigid because the concentration of Avicel^R in the mixture is too low for an appreciable number of cohesive Avicel^R-Avicel^R bonds to be formed. It attains rigidity at $V_A = 0.783$ or $1 - V_A = 0.217$ as more Avicel^R-Avicel^R bonds are formed. The percolating Avicel^R cluster is therefore rigid at $V_A < 0.783$ or $1 - V_A > 0.217$ and flexible at $0.783 < V_A \leq 0.864$ or $0.136 \leq 1 - V_{AE} < 0.217$. Such a phenomenon has been reported by Travers et al. (1986) for another binary mixture.

The concentration at which Avicel^R forms a percolating cluster in the Emcompress^R : Avicel^R mixture is rather low. This is a typical site-bond percolation problem (Stauffer et al., 1982; Holman and Leuenberger, 1990). The great difference in the yield stresses of Avicel^R and Emcompress^R and the extensive flow properties of Avicel^R, lead to a situation where the Avicel^R particles flow extensively through the voids between the Emcompress^R particles to form bonds with each other before Emcompress^R deforms appreciably.

The profile of $K_{RP} = f(V_A)$ for the Emcompress^R : Avicel^R mixture system is different from that of the relationship between the indentation hardness at zero porosity, H_0, as a function of the composition of Emcompress^R : Avicel^R mixture system as reported in Holman and Leuenberger (1990), which showed only the percolation threshold of Emcompress^R. This is because any existing percolating cluster plays a significant role

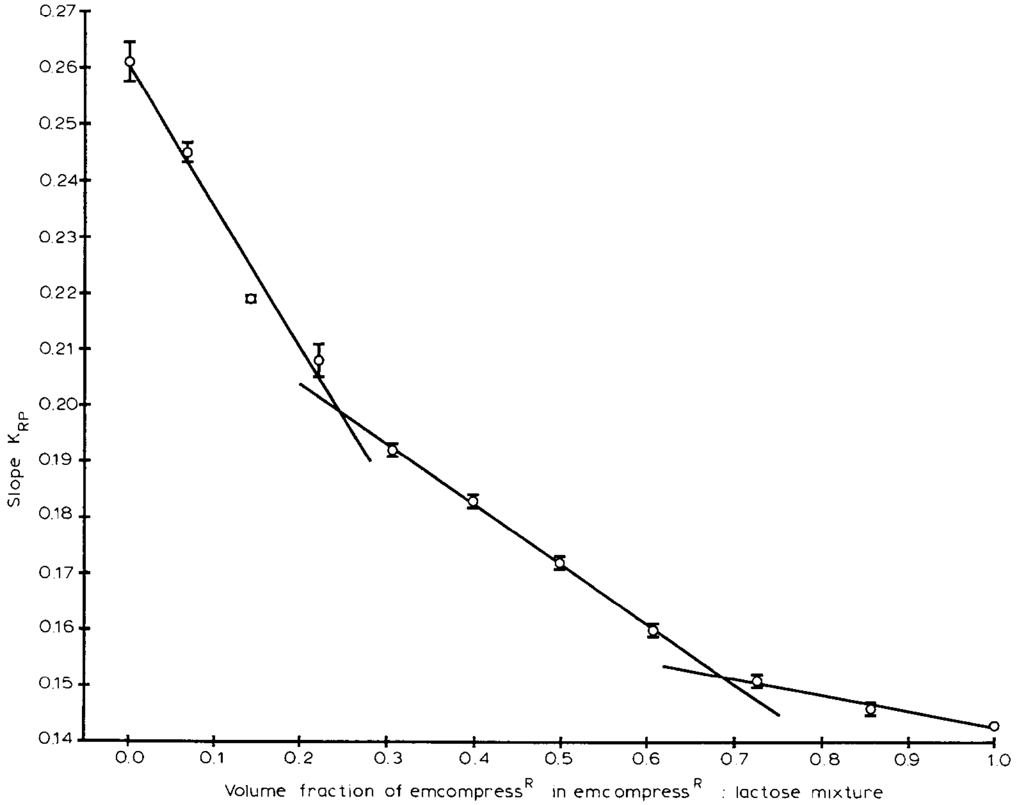

Fig. 7. The relationship between the slope, K_{RP} (mean ± S.D.) and the composition of Emcompress^R : lactose mixture ($n = 3$).

in determining the value of K_{RP}, in contrast to H_0 which is dominated by the harder component as long as it occurs as a percolating cluster.

Over the whole range of compositions, the Emcompress^R : Avicel^R mixture system exhibited higher K_{RP} values than the mixture system of Emcompress^R : lactose (compare Figs 7 and 8, and Tables 1 and 2). This is attributable to the fact that Avicel^R is more ductile and compressible than lactose. However, the difference in the mechanical properties of Avicel^R and lactose is not reflected in the K_{RP} values (0.265 ± 0.002 and 0.261 ± 0.003 for Avicel^R and lactose respectively — see Table 3) at the speed (15 rpm) at which they were compressed. This observation gives the impression that K_{RP} is not sensitive enough to distinguish between Avicel^R and lactose, two mechanically different materials. However, when the K_{RP} values of Avicel^R and lactose are compared at other speeds of compression, for example at 1.5 and 60 rpm, the differences in the K_{RP} values become apparent (see Table 3). This illustrates the unreliability of comparing compressibility at only one speed of compression.

For both Avicel^R and lactose the K_{RP} values increase with increasing speed of compression. A discussion of this behaviour is beyond the scope of this paper. It will be treated in a subsequent publication.

TABLE 3

The values of the slope, K_{RP} (mean ± S.D.) measured at different compression speeds ($n = 3$)

Substances	Speed of compression		
	1.5 rpm	15 rpm	60 rpm
Avicel^R	0.260 ± 0.001	0.265 ± 0.002	0.274 ± 0.001
Lactose	0.241 ± 0.004	0.261 ± 0.003	0.320 ± 0.006

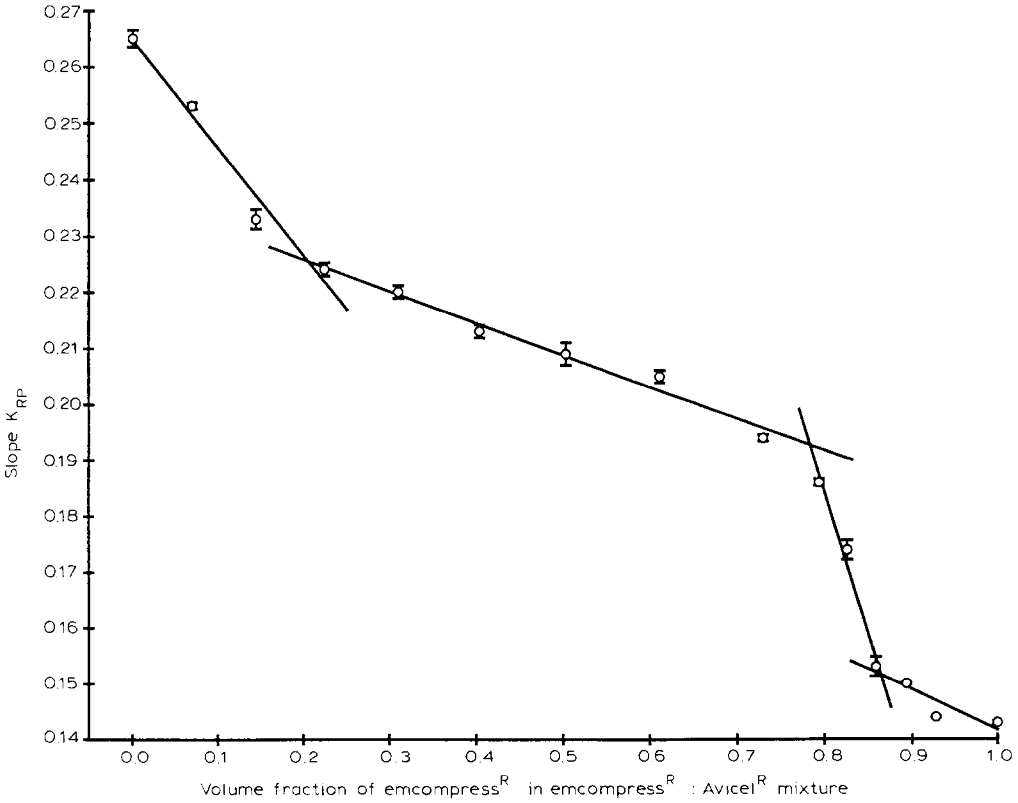

Fig. 8. The relationship between the slope, K_{RP} (mean ± S.D.) and the composition of Emcompress^R : Avicel^R mixture. (n = 3–6).

It is being proposed here, that in order to gain a meaningful measure of the mechanical-dependent compressibility of a material, K_{RP} must be determined at a minimum of three significantly different speeds of compression. This would serve as a discriminating compressibility characteristic of the material and can thus be used as a means of characterizing pharmaceutical substances.

The situation where Avicel^R and lactose exhibited the same K_{RP} value is attributable to the fact that K_{RP} is a complex mechanical parameter incorporating elastic, plastic (including strain-hardening and fragmentation), and viscoelastic characteristics of the substance under compression.

The slope, K_a

The slope, K_a, illustrated in Figs 1 and 2, is the slope of that part of the $P = f(\ln \sigma)$ relationship at high P values, where the pores occur as isolated, disconnected, discontinuous structures, dispersed randomly in the continuous solid matrix. It has been proposed that the compact can be considered as a continuum solid body in this region (Holman, 1991). This part of the $P = f(\ln \sigma)$ relationship is exhibited only by substances which flow extensively by plastic deformation (Holman, 1991). Consequently, K_a could be determined for only Emcompress^R : Avicel^R mixtures in the ratios of 8.25 : 1.75 v/v (8.75 : 1.25 w/w) to 0 : 10 v/v.

The effect of varying the composition of the binary mixture and thereby varying the mechanical properties of the material on K_a is illustrated in Fig. 9. If the K_a value for Avicel^R is ignored, it appears that the K_a values increase with increasing concentration of Emcompress^R in the Emcompress^R : Avicel^R mixture. The reason for this behaviour is not clear at the moment and is

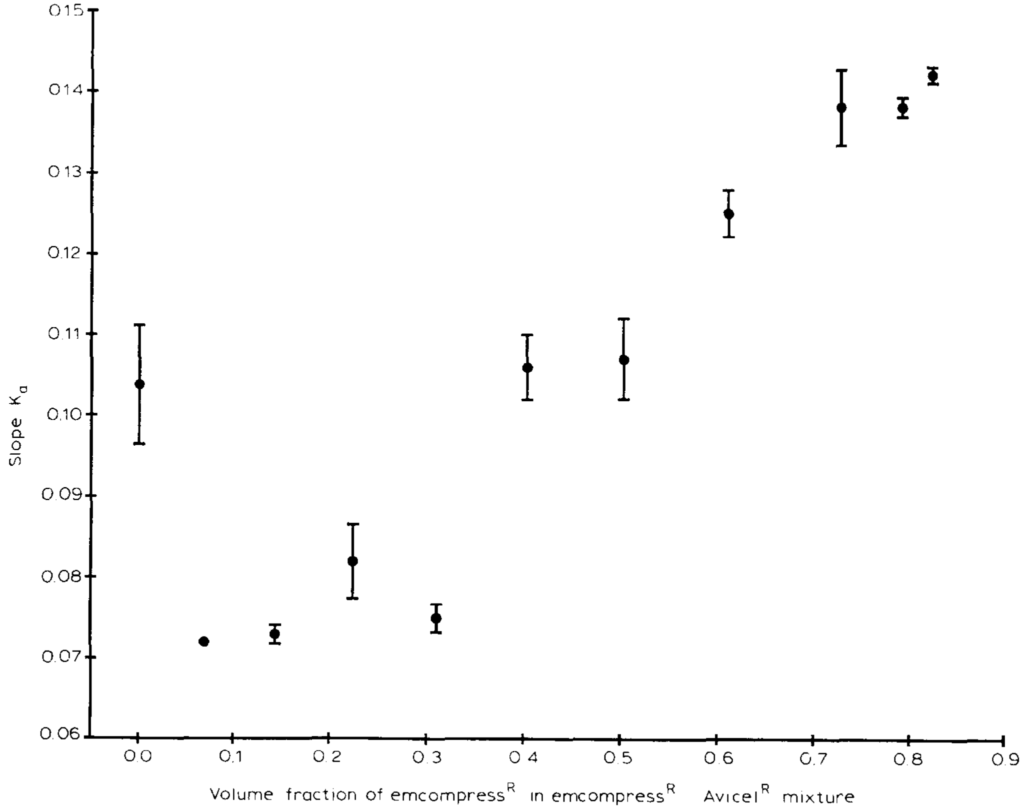

Fig. 9. The slope, K_a (mean ± S.D.) as a function of the composition of Emcompress^R : Avicel^R mixture (n = 3–6).

being investigated. It is, however, clear that K_a shows no dependency on the mechanical properties of the materials under compression. If K_a were dependent on the mechanical properties of the substances being compressed, K_a would continuosly decrease with increasing Emcompress^R concentration.

Conclusion

In the main, it can be said that of all the different slopes of the $P = f(\ln \sigma)$ relationship representing compressibility of the particulate system in the different states which it goes through during compression, only K_{RP} reflects a mechanical property (ductility) of the substance under compression.

K_{RP} is a composite of mechanical properties (elastic, plastic and viscoelastic) and has been shown to be dependent on the speed of compression. When K_{RP} is determined at three significantly different speeds, preferably at slow, moderate and fast speeds, it can be used as a discriminating characterization parameter.

By varying the composition of the binary mixture systems of Emcompress^R : Avicel^R and Emcompress^R : lactose, it has been shown that, although K_{RP} is influenced by the overall composition of the binary mixture, it is dominated by any material(s) existing as percolating cluster(s) in accordance with percolation theory.

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