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Consolidation behaviour of polymeric substances in non-disintegrating solid matrices

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Summary

The compression behaviour of an isotropic mixture of polyethylene glycol (PEG)/acrylic resins/ethyl cellulose is described. The method involved mixing the polymers by melting under controlled temperature. The mixture was solidified, finely ground, sieved and the relevant physicochemical properties determined. Tablets were prepared at various compaction pressures using different-sized fractions, and the relative densities of compacts were calculated. It is shown that the polymeric mixture follows a simple Heckel relationship at low pressure and exhibits a sudden change at greater applied pressures. Isotropic mixtures of polymers exhibit a behaviour different from that of fatty acid powders, revealed by departure from the Heckel plot beyond a critical pressure. The compression characteristics of polymers show that both plastic deformation and particle fusion are operative during densification. Compression of a polymeric mixture immediately below the critical pressure zone implies achievement of a continuous matrix. This finding could be important for formulating tablets to meet specific pharmaceutical requirements in regard to dissolution and sustained drug release.

Introduction

The major factors influencing drug distribution in a matrix-type delivery system, and drug release from the matrix core, include particle size, drug solubility, core composition and core hardness. One of the purposes of the present report is to examine the effect of compression force on the tensile strength of polymeric matrices and to identify the types of mechanism(s) operative during consolidation.

Several stages during the compression of powders within the confines of a die have been distinguished. These include particle rearrangement, plastic deformation and fracture (Hiestand et al., 1977; Carstensen, 1973; Fell and Newton, 1971). With low melting point materials, localized melting at the asperities of contact points occurs (Rankell and Higuchi, 1968; York and Pilpel, 1973). Compression behaviour of powders is conveniently characterized by Heckel plots (Heckel, 1961), and various authors have successfully applied Heckel's equation to pharmaceutical powders

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to identify the types of mechanism occurring during compression (Hou and Carstensen, 1985; Roberts and Rowe, 1985). In the Heckel equation, the relative density, D, is directly related to the applied compression force, P.

$$\ln(1/(1-D)) = KP + c \tag{1}$$

where K and c are constants. The relative density is obtained as the ratio between the apparent density ρ_a ($g \cdot cm^{-3}$) of the compact at pressure P and the true density, ρ_t ($g \cdot cm^{-3}$), of the powder, i.e.

$$D = \rho_a/\rho_t \tag{2}$$

The plot of ln $(1/(1-D))$ versus increasing applied compressional force P should produce a straight line with a positive slope. Deviations from this line indicate the type of mechanism occurring during compression. Hersey and Rees (1971) and York and Pilpel (1973) distinguished 3 types of powder behaviour on the basis of the above equation. These are illustrated as Types A, B, and C in Fig. 1.

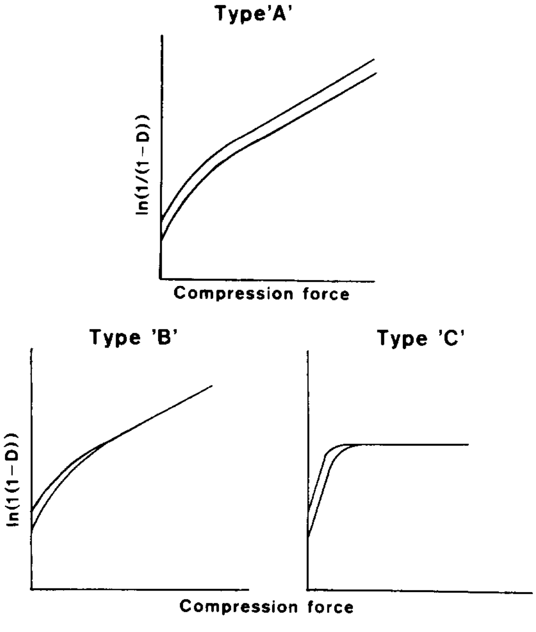

Fig. 1. The 3 different types of Heckel plots.

In Type A, the different-sized fractions have different initial packing densities and plots remain parallel as applied pressure is increased, owing to plastic deformation. In Type B, plots merge at higher pressure, an effect attributed to fragmentation of the particles during rearrangement. In Type C, the curves are initially steep and then merge in a common plateau at the high-pressure end of the plot. Sodium chloride and lactose are examples of Types A and B, respectively, while Type C applies, particularly, to fatty acids.

The phenomenological and dynamic events that a drug and its dosage form undergo are complex. Drug release and subsequent bioabsorption are controlled by the physicochemical properties and dose of the drug, the delivery system, gastrointestinal transit time and the interaction of constraining physiological and pathological factors. Controlled release of orally administered drugs has attracted much interest, and numerous delivery systems are commercially available (e.g. matrix tablets, coated pellets, pellets embedded in matrix, osmotic pumps, etc.). The purpose of these delivery systems is to release the drug continuously during its passage through the gastrointestinal tract, thereby giving a constant plasma concentration over a long period of time and also reducing side-effects. Controlled release is desirable for drugs with high plasma clearance and for drugs causing adverse effects locally or systemically. For these preparations the absorption phase must be completed within 8–12 h for most drugs to achieve good biological availability.

Controlled release matrix tablets, which normally contain larger amounts of drug than conventional tablets, should remain indivisible in the gastrointestinal tract and drug should be liberated by diffusion or erosion. It is apparent that these matrices must be mechanically strong. The major component of the matrix delivery system is a mixture of various polymers. It is therefore important to characterize the response of polymers to compression. The intention of the present work is to report on compression of commonly used polymers in relation to tableting, and on certain anomalies observed with respect to documented compression behaviours, applying Heckel's equation.

Materials and Methods

The materials examined in this study were chosen as being among the more commonly used polymers in matrix release formulation, and were used as received from the respective manufacturers: PEG 6000 (BDH Chemicals, Poole, U.K.), Eudragit SR (Rohm Pharma, Darmstadt), ethylcellulose (Hercules Powder Co.).

Differential scanning calorimetry (DSC)

Thermal analyses were performed on PEG 6000, ethylcellulose and Eudragit RS and their mixtures, using a Perkin-Elmer DSG2 model 3500 data station. All samples were run at a scanning rate of 10°K/min using nitrogen as the effluent gas. Aluminium pans and lids were used for all samples, with indium as calibration standard.

Tablet preparation

The proportion of each material used is shown in Table 1. A solid dispersion technique described previously (Fassihi et al., 1985) was used and selected fractions of powders were directly compressed into tablets of 400 mg using 10 mm flat punches. Compression was carried out using an instrumented Manesty F3 single punch machine at a constant punch velocity in the pressure range 30–120 $MN \cdot m^{-2}$. To attain a more homogeneous compact in regard to pressure-density distribution a Manesty B3 rotary machine fitted with 7.5 mm standard concave punches was used. One batch of formulation A was tabletted on a rotary machine at applied pressure immediately below the critical zone (see text). True densities of the polymeric mixtures were determined by pouring a molten mixture into an aluminium mold of known volume. After solidification the mass was removed and the true density, ρ_t, calculated.

TABLE 1

Composition of polymeric substances used for compression [a]

Polymer	Percent (m/m)	True density of the mixture (g/cm^3)
Polyethylene glycol 6000	40	
Eudragit SR	30	1.12
Ethylcellulose	30	

[a] The fused mixture was ground, sieved and two size fractions of: A = 0.59–0.80 mm and B = 0.95–1.25 mm were selected for further study.

Tensile strength was determined by the diametral compression test using an Erweka testing machine. Tablets were compressed diametrically at a rate of 0.3 cm/min. Experiments were carried out immediately after manufacture of the tablets, and again 2 weeks later.

Evaluation of the surface density of the tablets

To assess the influence of compression force on the surface density of the tablets, polymeric powders were dyed using 1% m/m amaranth. The mixture was tabletted using standard concave-faced punches 7.5 mm in diameter on a rotary tabletting press. Differences in the color of the tablets' surfaces were then assessed under a light microscope and they were photographed.

Results and Discussion

Two size fractions of polymeric systems were prepared to investigate their compressional behaviour (Table 1). Powder mixtures obtained by solid dispersion will give rise to an isotropic homogeneous system, which in turn upon compression will result in a compact of low stress gradient with defined regions of differing relative density. The presence of polyethylene glycol will reduce both interparticle friction and friction between surfaces of punch and die. Heckel's equation (Heckel, 1961) was used to analyse the relationship between relative density (measured during compaction), and applied pressure (Table 2). By plotting graphs of $\ln(1/(1-D))$ versus compression force, it should be possible to test the applicability of the Heckel equation to isotropic polymeric systems (Fig. 2). The relations between applied pressure and density of the different-sized fractions of polymeric mixtures can be divided into several stages. The constant c in the Heckel equation applies to two stages of consolidation – one due to the initial packing fraction of the powder, and the other due to densification.

TABLE 2

Heckel plot parameters and tensile strength values for two size fractions of a polymeric mixture

Applied pressure P ($MN \cdot m^{-2}$)	Tensile strength ($MN \cdot m^{-2}$)		Apparent density of compacts ρ($g \cdot cm^{-3}$)		ln[1 − (ρ/1 · 12)]	
	Size fractions		Size fractions		Size fractions	
	A [a]	B [b]	A [a]	B [b]	A [a]	B [b]
30	0.156	0.261	0.777	0.803	−1.17	−1.26
40	0.286	0.411	0.836	0.865	−1.37	−1.47
50	0.390	0.562	0.907	0.931	−1.66	−1.77
60	0.525	0.857	0.910	0.932	−1.67	−1.78
70	0.851	1.640	0.922	0.934	−1.73	−1.79
80	1.311	1.771	0.927	0.936	−1.76	−1.80
90	2.100	2.021	0.928	0.936	−1.76	−1.80
100	2.221	2.140	0.926	0.937	−1.75	−1.81
110	2.251	2.200	0.930	0.939	−1.77	−1.82
120	2.370	2.331	0.951	0.954	−1.89	−1.90

[a] and [b] correspond to the particle size fractions of (0.59–0.80 mm) and (0.95–1.25 mm), respectively.

Note: Tablets were flat-faced, and the apparent density of the compact was obtained by geometric volume determination and weight. Tensile strength (S_T) was calculated using equation $S_T = 2P/\pi Dh$, where P is the applied load, D and h are diameter and thickness of the compact, respectively. The results are the mean of 8 determinations. No significant differences were observed between S_T of tablets immediately after ejection and two weeks later. All tablets exhibited weight loss of less than 0.8% on friability testing.

The second contant, K, has been shown to be equal to the reciprocal of the mean yield pressure (York and Pilpel, 1973). Large values of c indicate the onset of plastic deformation at relatively low pressures, and this stage corresponds to the linear section of the Heckel plots. Results illustrate that the relationship between the deformation resistance of a polymeric system and the product of compression force and relative density is not linear. The curves are initially steep and linear at the low-pressure end of the graph (up to 50 $MN \cdot m^{-2}$) and become gradually flatter with a distinct negative deviation as compression force and relative density increase. The pattern of consolidation of the polymeric substances under stress may thus be related to the component which is predominantly plastic in nature.

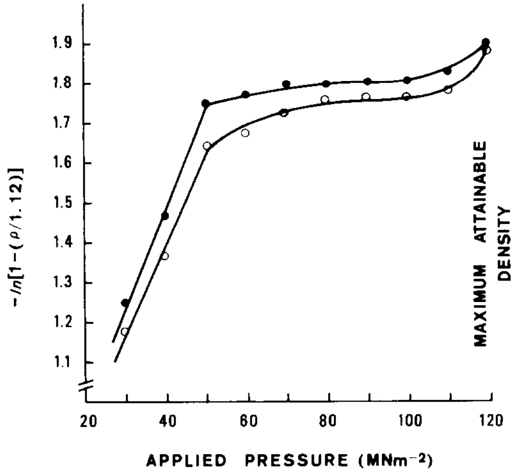

Fig. 2. Heckel plots of polymeric mixture (○ and ●) corresponding to size fractions 'A' and 'B', respectively.

The sharp break in the curve probably corresponds to the pressure at which all the voids between the particles are filled and the polymer particles begin to fuse. Consequently the negative effect of stress relaxation, which is usually associated with materials undergoing plastic deformation, on tablet properties such as friability and hardness, appears to be insignificant (see Table 2). This may be ascribed to a greater interparticle bonding resulting from asperity and surface melting of polymeric components of lower melting point (York and Pilpel, 1973). The DSC thermograms of the polymeric mixture used in this study are shown in Fig. 3, which identifies the melting range of individual components used in this study. The melting transition of PEG 6000 is about 333° K, while there is no definite melting endotherm for ethyl cellulose or Eudragit RS: both compounds eventually undergo decomposition at temperatures in excess of 600° K. The relation between tensile strength and melting point of the constituents of a polymeric mixture revealed that during compression process melting of PEG 6000 can easily occur, resulting in greater particle bonding and tensile strength. Fig. 4 shows the surface melting of a polymeric mixture compressed at 120 $\mathrm{MN \cdot m^{-2}}$, thus contributing to a sudden rise in tensile strength from 2.251 to 2.370 $\mathrm{MN \cdot m^{-2}}$, for size fraction A (Table 2). As density of the material under pressure approaches ρ_t then $\ln(1/(1-D))$ approaches infinity and rapid curvature of the plot ensues. An interesting feature is sample rupture or complete melting of the compact at a critical applied pressure, (above ~ 120 $\mathrm{MN \cdot m^{-2}}$), suggesting considerable squashing of contact points and probably a drop in the melting temperature: a phenomenon which has previously been documented (Rankell and Higuchi, 1968; York and Pilpel, 1972, 1973).

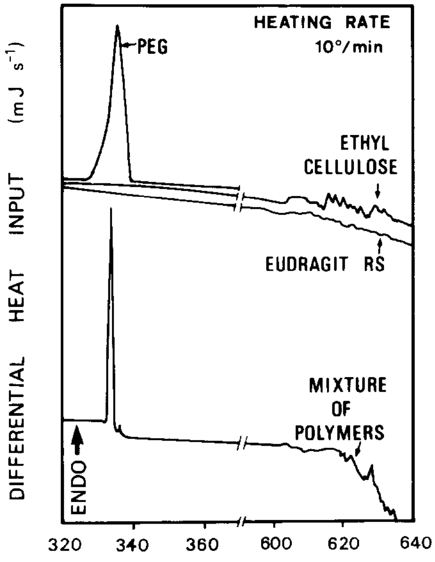

Fig. 3. DSC thermograms of pure polymeric substances and their mixtures used in the production of matrix tablets.

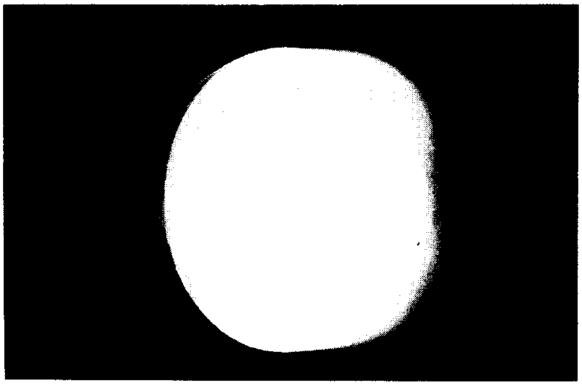

Fig. 4. Surface melting of polymeric mixture fraction (A) compressed at 120 $\mathrm{MN \cdot m^{-2}}$, resulting in rapid increase in tensile strength of matrix tablets from 2.251 to 2.370 $\mathrm{MN \cdot m^{-2}}$.

Train (1956) investigated the distribution of pressures and densities within a compact. His findings suggest that the regions of high density and pressure correlate well (viz. at the edge of the upper punch, where the pressure is applied). However, compression involving movement of both upper and lower punches should significantly reduce the density variation within a compact. Several other factors may influence the structure of a compact and the degree of pressure distribution at the maximum compression force. When isotropic homogeneous powders were compressed on a rotary machine, regions of greatest density were produced in a peripheral ring parallel with and near to the points of greatest pressure (Fassihi, 1986). Scanning electron micrographs of fractured tablets revealed the existence of high density areas at the proximity of the surfaces (Fig. 5). This figure shows the structure of the fractured compact clearly indicating the lower degree of consolidation in the central part of the tablet. It appears that the formation of high density zones is due to the conversion of mechanical energy to thermal energy (Bowden and Ridler, 1936; Fassihi et al., 1977), causing asperity melting as the pressure applied by the upper and lower punches is exerted only on particles directly in contact with the punch surfaces. This results in very high pressure at small individual points of contact and formation of localized hot spots. Such high temperature areas can attain the melting point of the substance being compressed (Rankell and Higuchi,

Fig. 5. SEM photomicrograph of fractured polymeric tablet compressed on a rotary machine, illustrating the existence of high density areas at the proximity of the surfaces.

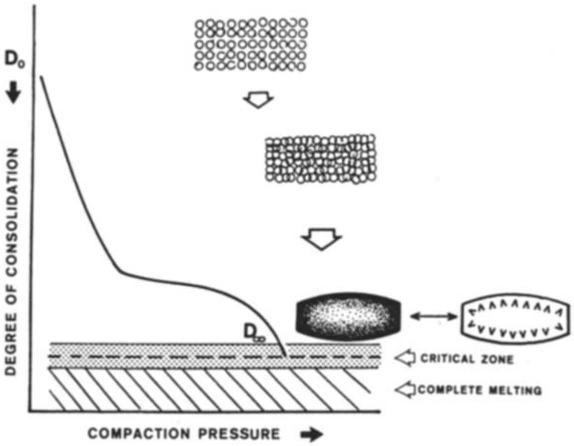

Fig. 6. Schematic representation of degree of consolidation as a function of compression force for polymeric matrices prepared on a rotary machine, illustrating differential density zones. D_0 = bulk density; D_∞ = maximum attainable density.

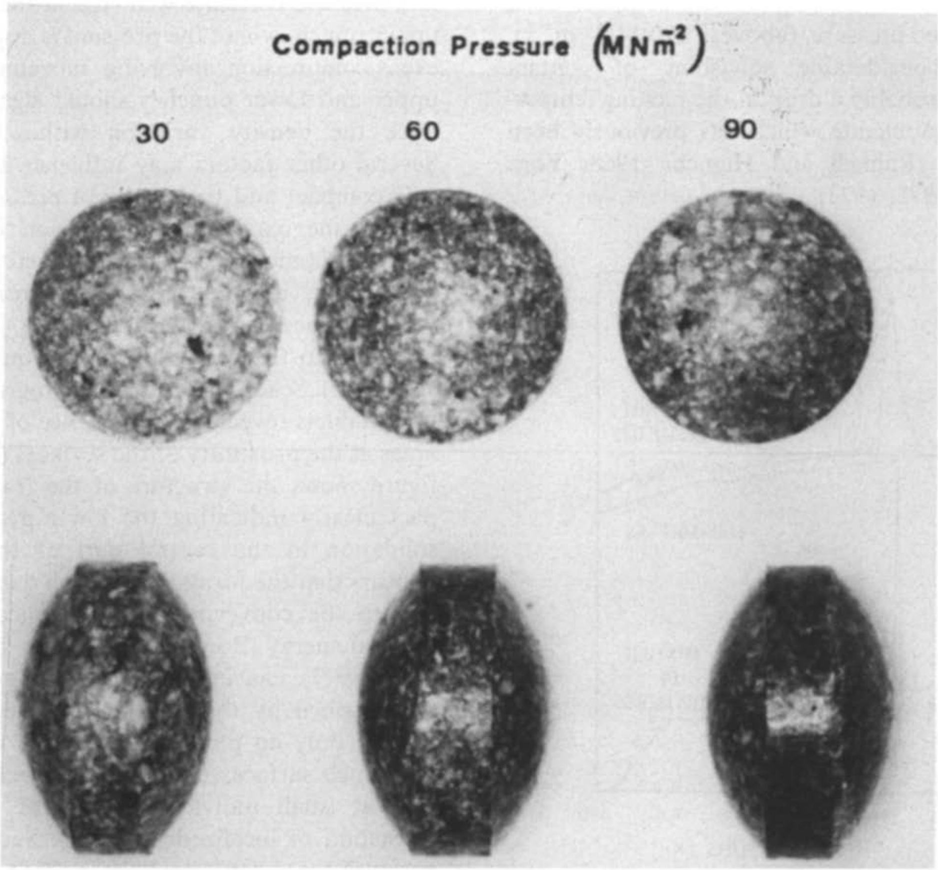

Fig. 7. Changes in surface density (colour intensity) of polymeric matrices with increasing compression pressure.

1968). The lowering of the melting point of a material with increasing pressure has been explained by applying the thermodynamic equation of Skotnicky (1953).

Using an isotropic polymeric mixture, for tablets prepared on a rotary machine, the degree of consolidation as a function of compaction pressure may be depicted as in Fig. 6. The graphic representation illustrates formation of a differential density zone. Incorporation of a red dye into the polymeric mixture compressed at various applied pressures also confirms the increase in surface density with increase in the applied pressure (Fig. 7). The influence of surface melting on the strength and pore structure of the matrix is apparent, and further work is underway to incorporate active drugs into these matrix type systems.

Conclusion

The ultimate objective of studies on the physicomechanical nature of pharmaceutical powders is to use the known properties of pure materials to predict the compaction behaviour of mixtures of the materials in multicomponent drug formulation. This requires a comprehensive understanding of the nature of interparticle interactions under pressure, which in turn presupposes the ability to predict quantitatively the effects of such tests as disintegration, dissolution, tensile strength and state of drug delivery system. From results obtained in the present investigation two trends are immediately evident from the Heckel plots. Firstly, the curves are initially steep, indicating the compressibility of the polymers. Secondly, as compression force increases, the slope decreases, indicating a fall in the rate of densification. It is shown that, in the case of the composition studied, polymeric mixtures obey the Heckel relationship only at low pressures (not exceeding 50 $\mathrm{MN \cdot m^{-2}}$). This behaviour may be referred to as that of Type A, where the lines remain parallel as the compressive stress is increased. At higher pressures structural rearrangement predominates and asperity melting occurs. When the pressure reaches the critical zone, particles in direct contact with punch surfaces melt and produce a continuous film. A further increase in pressure beyond the critical zone may result in sample rupture or complete melting.

This mechanism, viz. asperity melting, would be expected to contribute to the tensile strength of tablets as illustrated in Fig. 4. The amount of bonding that will take place as a result of asperity melting may be related to the conventional melting points of the constituents of a formulation. Such melting points should therefore be considered when selecting the components of matrix-type systems of a specific formulation.

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