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Kinetics of drug release from solid matrices: effect of compaction pressure

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Summary

Measurements have been made of the compactibility of drug/polymers and their mixtures with directly compressible excipients, and of the tensile strength of the solid matrices produced either by fusion or by physical mixing. It was found that at a relatively low compaction force a plateau is observed without appreciable change in tensile strength at greater pressure. The influence of compression force on dissolution rate in both the initial release phase and the matrix-controlled diffusion phase was determined. It was shown that dissolution of a drug from insoluble and partially soluble matrices follows the Higuchi square-root equation. Release profiles of solid matrices produced from isotropic dispersions obtained by fusion are susceptible to compression force in both the initial and terminal phases with significant differences in the slopes of square-root plots. Furthermore, drug release from physical mixtures of directly compressed formulations is not affected by an increase in compression force. There is no significant change in the slopes of release profiles which have consistently higher correlation coefficients.

Introduction

The compressional behaviour of drug substances or excipients is complex and may have a number of technological and biopharmaceutical implications. The effect of compression force on the dissolution rate of drugs from conventional tablets has been extensively evaluated and various dissolution characteristics have been reported (Polderman and Braakman, 1968; Van Oudtshorn et al., 1971; Smith et al., 1971; Finholt, 1974; Carstensen, 1980). When particle bonding is the predominant phenomenon, dissolution rates diminish with increasing pressure. The particles may undergo pure plastic deformation, with no additional surface area generated as the compression force is increased. Alternatively, fragmentation may occur, with an increase in surface area and hence in dissolution rate, if the fragmented surfaces are exposed to the dissolution medium. However, if the compression force is further increased, fragmented particles may undergo fusion with a resultant decrease in the dissolution rate. In general, the fundamental dissolution relationship from rapidly disintegrating dosage forms appears to follow an exponential decay law and frequently should adhere to a cube-root law.

The kinetics of release of a drug dispersed in a polymeric matrix are of general interest in the

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context of controlled drug delivery. It is usually desirable that the amount released be proportional to time.

In the matrix release system the drug substance is homogeneously embedded into the insoluble polymeric matrix. The drug is released by a leaching action of the penetrating solvent. The release is based on the diffusion principle and has been discussed by Higuchi (1963). A linear relationship exists when the amount of drug dissolved per unit area (Q) is plotted against the square root of time (t), as given by the equation $Q = K \cdot t^{1/2}$, where K is the matrix-controlled release constant (mg/cm^2 $\cdot$ t$^{1/2}$), and is given by the following:

$$K = \left[\frac{D\epsilon}{\tau}(2A - \epsilon C_S)C_S\right]^{1/2}$$

where C_S and D are the solubility and diffusion coefficients of the drug in the permeating fluid, ϵ and τ are the porosity and tortuosity of the matrix, and A is the initial concentration of solid drug in the matrix. The kinetics of diffusion from porous devices and of liquid penetrating these matrix systems depend on the matrix composition, porosity, tortuosity, pH, drug solubility and hydrodynamic conditions. These factors have been tested and verified by many authors (Lazarus et al., 1964; Desai et al., 1965; Desai et al., 1966; Roseman and Higuchi, 1970; Roseman, 1975; Chien et al., 1974; Fessi et al., 1978; Nicklasson et al., 1982; Fassihi et al., 1985). However, a number of other factors may come into play to modify the release pattern of sustained-action dosage forms. Many matrix-type delivery preparations can be formulated where the matrix is not completely insoluble, i.e. the tablet erodes to some extent during the dissolution process (Brossard et al., 1983).

The present work investigates the response of polymers to compression, and the influence of compression force on the tensile strength of the tablet and dissolution profiles of polymeric matrices. The following have been used: (i) a single unit non-disintegrating polymeric matrix prepared either by fusion or by physical mixture; and (ii) a matrix-type system containing soluble components used in conventional tablets. The drug theophylline was chosen for its compatibility with other formulation components, and the ease of in vitro dissolution assay. This allows the release behaviour to reflect the effect of the compression force used in tabletting.

Experimental

Materials

Stearyl alcohol and PEG 6000, (BDH Chemicals) ethyl cellulose (Hercules Co.), Eudragit retard (Rohn Pharma), dicalcium phosphate (Edward Mendell Co.), and anhydrous theophylline B.P. were used. The tablets were made by direct compression and solid dispersion (fusion).

Direct compression

The formulae used for direct compression are shown in Table 1. The PEG and stearyl alcohol were ground and sieved, and the fraction finer than 350 μm was used. Eudragit, ethyl cellulose and theophylline were also sieved and powders were mixed in a twin shell tumbling mixer for 15 min. Quantities of powder (0.2 g) were compressed, at the rate of 60 tablets per minute, at pressures of 49, 74, 98 and 122 MPa. Compression was performed on an instrumented single-punch

TABLE 1

Formulae used in this study

Formulation components [a]	Formulation (Solid dispersion) I	Formulations (Direct compression)	
		II	III
PEG 6000 [b]	30	30	–
Eudragit RS	20	20	30
Ethyl cellulose	20	20	–
Stearyl alcohol [b]	10	10	–
Theophylline	20	20	20
Talc	–	–	4
Magnesium stearate	–	–	1
Dicalcium phosphate	–	–	45

[a] Quantities listed are percent by weight.

[b] Ground, sieved through mesh no. 30 and mixed with other components of formulation II.

tablet machine (Manesty type F3), using flat punches. Cylindrical tablets of 7.5 mm in diameter and approximately 3.5 mm in thickness were produced. 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^{-1}. Experiments were carried out immediately after manufacture of the tablets and 48 h later. The tests were performed at 25 °C in a humidity controlled room at 52 ± 5% RH.

Solid dispersion (fused mixtures)

The fused drug/polymer mixtures were prepared by heating PEG and stearyl alcohol to approximately 80 °C. Ethyl cellulose and Eudragit were mixed and added in small proportions while the mass was mixed, and finally theophylline powder was gradually added. With constant stirring, the mixture was allowed to cool slowly to about 60 °C, and the entire mass then immediately cast on cold glass plates. The congealed mass was crushed into a finely divided state and screened through mesh 30. Tablets were produced by the same procedure as outlined above.

Determination of release rates

The dissolution rates were tested using a flow-through UV spectrophotometric monitoring technique at 273 nm under sink conditions. One tablet was placed in a basket which was positioned in a thermostatic bath at 37 ± 0.5 °C. The dissolution medium was distilled water (1000 ml), with a paddle speed of 50 (rpm) over a period of 12 h in a covered beaker. A flow rate of 2.5 ml · min^{-1} in the closed circuit, obtained by means of peristaltic pump, was found optimal for direct spectrophotometric measurement in a quartz flow cell. The experiments were carried out under identical conditions, maintaining similar hydrodynamic conditions. Release profiles were calculated as percentage drug released.

Results and Discussion

Table 2 shows the physical properties of the tablets produced at various applied forces. Formulations I and III produced compacts of similar strength, while the differences in tensile strength between formulations I and II are more than two-fold over the entire pressure range. All the tablets were of good quality and possessed good binding properties. They exhibited a weight loss of less than 0.8% on friability testing. The plots of compaction pressure against tensile strength are shown in Fig. 1. The tensile strength of the tablets increases with an increase in compaction force. The plots are non-linear with a gradual inhibition in the rate of densification and become flatter as illustrated by arrows in Fig. 1. Below the plateau region the material is undercompacted and with further increase in pressure along the plateau, overcompaction occurs, resulting in waste of energy in terms of resulting tensile strength. In the formulations containing a large quantity of poly-

TABLE 2

Tablet properties at various applied forces

	Compaction force at which tablets were made (MPa)											
	Formulation: I				II				III			
	49	74	98	108	49	74	98	122	49	74	98	122
Tensile strength [a] (MPa)	1.38	1.62	1.76	1.78	0.52	0.66	0.82	0.86	0.74	1.04	1.28	1.32
Tablet weight [b] (mg)	210	200	205	203	201	206	205	200	210	212	214	213
Compactibility factor [c] (K)			2.86				1.52				1.26	

[a] 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. All the specimens tested met the requirements for tensile failure. The results are the mean of 10 determinations and no significant differences were observed between S_T of tablets immediately after ejection and 48 h later.

[b] Average weight of 20 tablets.

[c] The reciprocal of the slopes of log–log plot in Fig. 1 correspond to the compactibility factor (K).

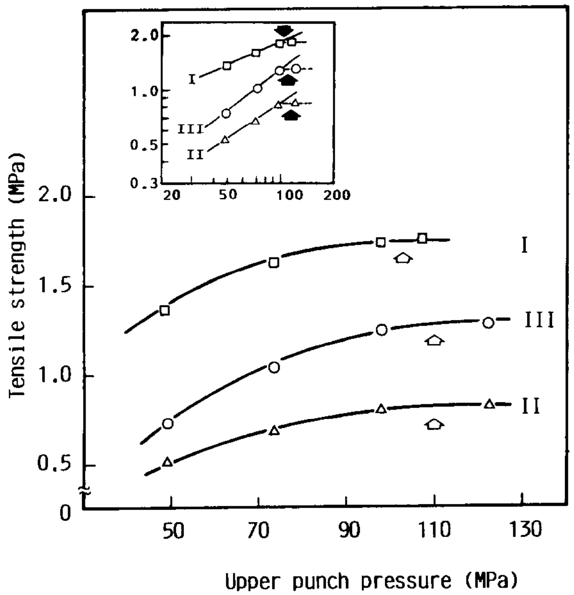

Fig. 1. The relationship between tensile strength and compaction pressure for 3 formulations (solid dispersion I, physical mixture direct compression II, and direct compression III). Insert: log tensile strength as a function of log MPa. The arrows indicate the plateau regions of the curves.

meric components the plastic deformation behaviour at low pressures accompanied by fusion at higher applied forces has been reported (Fassihi, 1986). The observed plateau regions of the curves probably correspond to the maximum consolidation of the materials under pressure. This can be attributed to different amounts of interparticle bonding resulting from melting of asperities on the particles at temperatures below their conventional melting points, when they are subject to very high pressures (York and Pilpel, 1973). The majority of excipients used in the production of the conventional tablets, i.e. lactose, sodium chloride, saccharose and dicalcium phosphate, do not show a plateau region similar to the one observed with polymeric substances. On the contrary, usually a linear relationship exists between tensile strength and compaction pressure (Shotton and Ganderton, 1960; Sheikh-Salem and Fell, 1982).

If the data used in Fig. 1 are replotted as shown (insert Fig. 1) linear plots with different slopes are produced. The reciprocal of such slopes corresponds to the compactibility factor *K*. The low *K* values in a particular multicomponent system represent greater compactibility. The *K* values for formulations studied here are given in Table 2. The lowest compactibility factor was observed for the formulation containing 45% dicalcium phosphate. Consequently, the tensile strength of direct compression formulation III is greater than that of formulation II prepared by the same procedure, indicating the greater ability of the formulation components to form a compact of superior mechanical properties. Release studies were performed on matrices produced at various applied forces. The percentage of drug released was plotted against the square-root of time (Figs. 2–4). It is noted that the square-root law is adhered to, confirming that these systems follow a diffusion process similar to that postulated by Higuchi (1963) for matrices. All the tablets prepared exhibited good physical properties and when used in dissolution tests remained intact at the end of the experiment. The skeletons of tablets were dried and amounts of polymers or other ingredients lost was calculated. The observed order of loss was formulation III > II > I.

Drug release profiles of tablets prepared from the solid dispersion formulation I are shown in Fig. 2. It is apparent that both the initial and

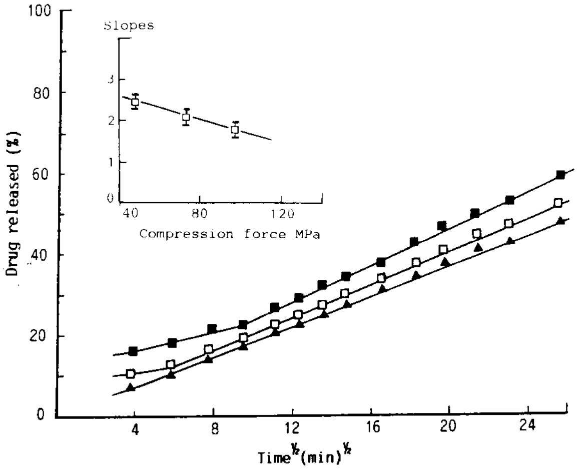

Fig. 2. Percentages of drug released as a function of square-root of time for tablets produced at various compaction forces (■, 49 MPa; □, 74 MPa; and ▲, 98 MPa) using solid dispersion formulation (I). Insert: the corresponding slopes as a function of compaction pressure.

matrix-controlled phases of drug release are susceptible to increases in compression force. Initial dissolution from the surface of an insoluble matrix is controlled by an aqueous diffusion layer and by the availability of the soluble drug particles. The influence of the diffusion layer is not significant for the given experimental conditions, and is assumed to be constant in all the measurements. Thus, the different dissolution rates obtained can be interpreted as reflecting a change in the degree of surface consolidation. During compression the pressure applied by the punch is exerted only on particles directly in contact with the punch surface, and stresses on the rest of the particles are due to particle-to-particle contact. This results in very high pressure at small individual areas of contact, and the formation of a continuous matrix with little or no porosity available for liquid penetration, thus retarding the dissolution rate. As can be seen in Fig. 2, the decrease in initial drug release is more marked at higher applied forces (7% and 17% at compaction pressures of 98 and 49 MPa, respectively).

In the matrix-controlled diffusion phase it is assumed that the solid drug dissolves and diffuses from the surface layer of the matrix. When this layer becomes exhausted of drug, depletion of the next layer begins. Thus release rates are controlled by effective porosity and tortuosity parameters. Therefore prolongation of "pseudo-steady-state drug release" can be achieved at higher compressional forces. It may be difficult to interpret the manner in which compression force influences the release pattern. However, it is assumed that the internal matrix structure and degree of porosity are directly influenced by applied pressures and hence play a major role in the present context.

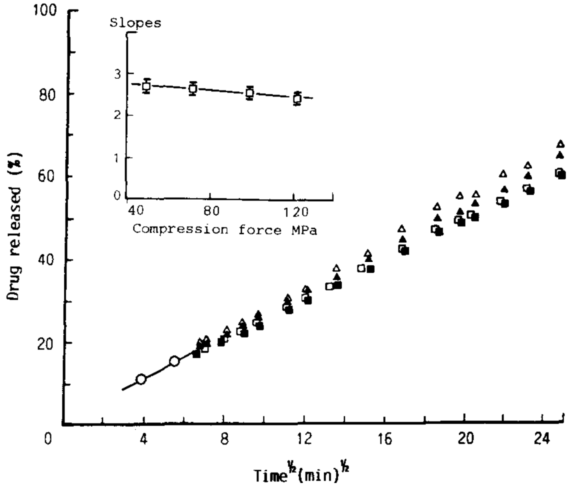

Fig. 3. Percentages of drug released as a function of square-root of time for tablets produced at various compaction forces (△, 49 MPa; ▲, 74 MPa; □, 98 MPa; ■, 122 MPa) using direct compression physical mixtures formulation (II); (○) points that are graphically indistinguishable between the 4 release rates. Insert: the corresponding slopes as a function of compaction pressure.

Figs. 3 and 4 show linear plots of square-root of time vs percent drug release for various pressures. The fits here are somewhat better, since the correlation coefficients are consistently higher (Table 3). However, in the case of formulation II, slopes of the plots are slightly affected by the compression force, indicating that the direct compression formulation II is less sensitive to applied pressure than the solid dispersion preparation (Fig. 3, insert). In contrast, drug release from formulation III is least susceptible to changes in compression force with no significant changes in the slopes of the plots (Fig. 4, insert).

A t-test was performed on various combinations of pairs of formulations at different compression forces to determine if there were signifi-

TABLE 3

Slope and correlation coefficient of the release profile of tablets prepared at various compression forces

Formulation	Compaction force (MPa)	Slope of percent drug release vs $t^{1/2}$ plot	Correlation coefficient
I	49	2.36 [a]	0.989
	74	2.18	0.988
	98	1.89	0.997
II	49	2.81	0.998
	74	2.75	0.997
	98	2.55	0.996
	122	2.48	0.996
III	49	2.18	0.998
	74	2.20	0.995
	98	2.16	0.995
	122	2.16	0.997

[a] The square-root component of the release profile.

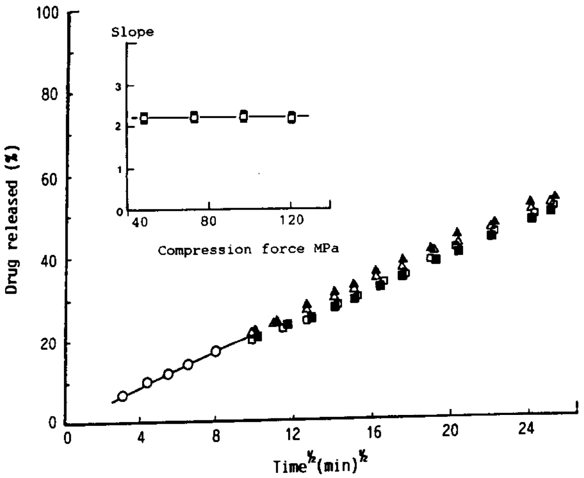

Fig. 4. Percentages of drug released as a function of square-root of time for tablets produced at various compaction forces (△, 49 MPa; ▲, 74 MPa; □, 98 MPa; ■, 122 MPa) using direct compression formulation (III); (○) points that are graphically indistinguishable between the four release rates. Insert: the corresponding slopes as a function of compaction force.

cant differences in the release profiles. The results (Table 4) reveal that the differences in the release profiles of formulation I are statistically significant. However, direct formulations II and III are not significantly affected by increase in compression forces. Fig. 3 (formulation II) also shows that the amount of drug released over the same period is greater than that released from formulation III. This was also apparent when the time for half the drug release (t_{50}) was determined graphically for each formulation. These values were as follows: formulation II, 18 min$^{0.5}$, formulation III, 24 min$^{0.5}$. This is probably due to the fact that the compactibility factor for formulation II is greater than that of formulation III (Table 2), resulting in a low tensile strength value which is normally associated with a greater degree of porosity. Thus the matrix structure provides extra channels for drug diffusion.

TABLE 4

Results of statistical analysis of percent drug released from various combinations of pairs of solid matrices produced at 49, 74, 98 and 122 MPa for sampling times of 10 and 24 min$^{0.5}$

Formulation	Combination of various compression forces (MPa)	t value [a]		
		Sampling time:	10 min$^{0.5}$	24 min$^{0.5}$
I	49– 74		17	33
	74– 98		7.0	8.877
II	49– 74		3.0	2.781
	74– 98		2.421	2.632
	98–122		2.112	2.131
III	49– 74		1.972	1.611
	74– 98		1.012	1.126
	98–122		0.976	0.811

[a] The critical value of t at 0.05 level of significance and 3 degrees of freedom is 3.1825.

Note: each dissolution profile represents an average of 4 determinations based on the percent of theophylline released at 10 and 24 min$^{0.5}$ sampling times.

Conclusion

Tablet formulations are designed as multicomponent systems in order to satisfy the stringent quality control specifications and to fullfil the necessary biopharmaceutical requirements. The various formulation constituents and methods of preparation have been shown to affect the tensile strength of tablets at a relatively low compaction force. A large change in tablet tensile strength is seen when additives such as dicalcium phosphate are included into the polymeric components of the matrix formulation. From dissolution profiles it is apparent that compression force can significantly modify patterns of drug-release from insoluble polymeric matrices prepared by fusion, in both the initial release phase and matrix-controlled diffusion processes. On the other hand direct compression formulations are less sensitive to changes in applied pressure and release rates are not affected significantly. A satisfactory release prolife may thus be achieved by control of this parameter. These findings could have application in formulating matrix tablets with desired properties.

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