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The effect of film-inducing substances on the characteristics of binary powder mixtures

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Summary

Compaction of a brittle material, phenacetin, could be improved by proper choice of the diluent and film-inducing agent. Aspirin, potassium chloride and sodium chloride were used owing to their ability to relieve stresses by plastic flow. The effect of Aerosil, Eudragit-E and magnesium stearate on the characteristics of these binary mixtures as well as their mechanism were presented. In almost all systems the results of the repose angle and bulk density were consistent with those obtained from tensile strength measurement. Phenacetin tablets needed higher ratios of potassium chloride or sodium chloride to produce satisfactory compacts than in the case of aspirin. A linear relation was obtained by plotting log packing fraction of various potassium chloride to phenacetin binary mixtures versus log tensile strength. At a given pressure the tensile strength of phenacetin alone could be estimated.

Introduction

Over recent years the advantages and different mechanisms involved in direct compression techniques for tableting have been well established (Hiestand et al., 1977; Cole et al., 1975). However, very brittle materials such as phenacetin, do not adequately relieve local stresses by plastic deformation and fracture in shear occurs across the compact. Consequently, tensile strength could not be determined (El Gindy and Samaha, 1983). Phenacetin crystals were essentially needle-like and could

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be easily fractured. The pressure cycles for phenacetin were more like those of an elastic body, and the value for the Poisson ratio obtained from the slope was very low (Shotton and Obiorah, 1975). Nevertheless, fracture may not result if plastic flow occurs before stresses are high enough to cause fracture by crack propagation (Amidon et al., 1981). Hammouda et al. (1978) studied the use of sodium chloride as a directly compressible filler for preparing tablets of 5 drugs. For each combination, the optimum drug-to-filler ratio was determined.

This investigation has been carried out in order to directly compact phenacetin by the addition of different proportions of aspirin, potassium chloride and sodium chloride. These additives were studied before and shown to deform plastically and have viscoelastic properties (El Gindy and Samaha, 1983). The effect of film-inducing substances, which are usually included in tablet formulations to reduce friction with the die wall during compression and ejection, on the behaviour of the binary mixtures was also proposed.

Materials and Methods

Materials

The following materials were used: phenacetin (Monsanto); aspirin (B.P. 68); potassium chloride (Merck, Darmstadt); sodium chloride (Merck, Darmstadt); Aerosil 200 (Degussa, Frankfurt-am-Main); magnesium stearate (Merck, Darmstadt); and Eudragit-E (Rohm GmbH, Chemische Fabrik, Darmstadt).

A vibratory sieving machine was used to obtain 63–80 μm size fraction of all the powders. All materials were oven-dried at 60°C for 4 h and stored in a desiccator over silica gel until required.

Powder mixing

The powder mixtures were composed of phenacetin with either aspirin, potassium chloride or sodium chloride in different ratios (0 : 6, 1 : 5, 2 : 4, 3 : 3, 4 : 2, 5 : 1 and 6 : 0). The powder mixtures were rotated in a Turbula mixer [1] for 10 min, which was found to be sufficient for attaining homogenous mixtures. The film-inducing substances used were: Aerosil 200, magnesium stearate or Eudragit-E, at a constant concentration of 2% of the powder system, which was frequently used in tablet manufacturing.

Angle of repose for the powder systems was measured using the fixed funnel and free standing cone method (Train, 1958).

Apparent bulk density for the powder or powder mixtures were determined by carefully pouring the weighed dried sample at an angle of 45° into a 100 ml volumetric cylinder and tamping from a height of 2.5 cm onto a wooden surface for a total of 20 times. The bulk density in g/ml is given by $\varphi_b = W/V$, where W is the weight of materials in g, and V is the volume in ml. Bulk densities were determined twice. In all cases, the two values were identical.

[1] Turbula mixer, Willy Basel, Switzerland.

The packing fractions, φ_F, for the different binary mixes were then calculated using the following relation:

$$\varphi_F = \frac{\varphi_b}{\varphi_1 X_1 + \varphi_2 X_2} \quad (1)$$

where φ_b is the bulk density of the mixture, φ_1 and φ_2 are the particle densities of phenacetin and diluent, respectively, while X_1 and X_2 are their weight fractions in the mixture.

Tablet compaction

A Carver press [2] was used to produce compacts. Tablets were prepared by introducing 600 mg of each of the drug, diluent, and combinations of drug–diluent with and without 2% (w/w) of film-inducing substances, into a circular die 1.4 cm in diameter and compressed between flat-faced punches. All tableting was conducted at a compaction pressure of 112 $MN \cdot m^{-2}$. The tablets were immediately removed from the die, their diameter and thickness were measured using a micrometer and stored in a desiccator for at least 30 min before use.

The tensile strength was determined by the application of the diametral-compression test. Materials were compressed diametrically on a modified Erweka hardness tester [3]. A close procedure was followed as described in a previous publication (El Gindy and Samaha, 1983). The force readings were converted to tensile strength in the manner of Fell and Newton (1970). The tensile strength (σ_t) is calculated from:

$$\sigma_t = \frac{2F}{\pi Dt} \quad (2)$$

where F is the force applied; D and t are the corresponding diameter and thickness of the tablet, respectively. All tensile strengths reported are the average of 10 determinations.

Results and Discussion

Three different diluents (aspirin, sodium chloride and potassium chloride) were chosen in order to improve the physical properties and compactibility of phenacetin. Although the measurement of the angle of repose is controversial in the study of flow properties of powder, its use has been recently supported (Dahlinder et al., 1982; Staniforth, 1982). Therefore, measurement of angle of repose and apparent bulk density of the mixtures, as a function of ratio of additive diluents, provided a simple mean to determine the proportion of additives that can be used to obtain satisfactory mixes for direct compression.

[2] Carver Laboratory Press, Fred S. Carver, U.S.A.
[3] Erweka-Apparatechau, Frankfurt, F.R.G.

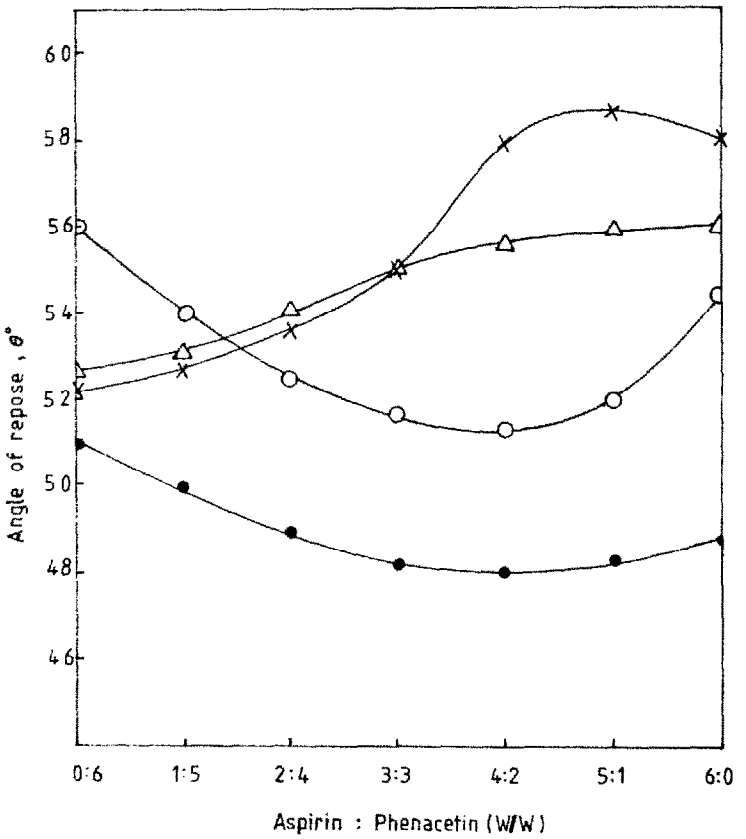

Fig. 1. Repose angle as a function of aspirin–phenacetin (w/w) ratios ○———○, with 2% of film-inducing agents: ●———●, Aerosil 200; △———△, Eudragit-E; ×———×, magnesium stearate.

The effect of aspirin on the flowability of phenacetin is shown in Fig. 1. An improved flowability with a decrease in angle of repose of phenacetin occurs until a ratio of 4 : 2 w/w aspirin–phenacetin. Upon increasing the aspirin ratio, the repose angle starts to increase but is still lower than for aspirin alone. This behavior can be explained by the filling of void spaces with aspirin, at this ratio (66.67%), where aspirin has substantially reduced the void space. Apparent bulk density determined for aspirin–phenacetin mixtures supported this explanation (Fig. 2). The bulk densities increase up to the same ratio above which aspirin may be present in the form of agglomerates with a corresponding decrease in density.

Where mixtures of aspirin and phenacetin are concerned, obviously the dose of each of these active ingredients will determine the actual ratio selected. At this ratio, mixers may be expected to possess good flow properties and to show no segregation.

Film-inducing substances are often used to improve the flowability of powders. Several postulates have been proposed to explain their mechanism of action, and many techniques have been used to study the effects of their addition to powders and granulations (Augsburger and Shangraw, 1966; Lerk et al., 1977). In this study, a 2% concentration of Aerosil 200, Eudragit-E or magnesium stearate was used. The effect of these glidants on the angle of repose of aspirin–phenacetin mixtures is

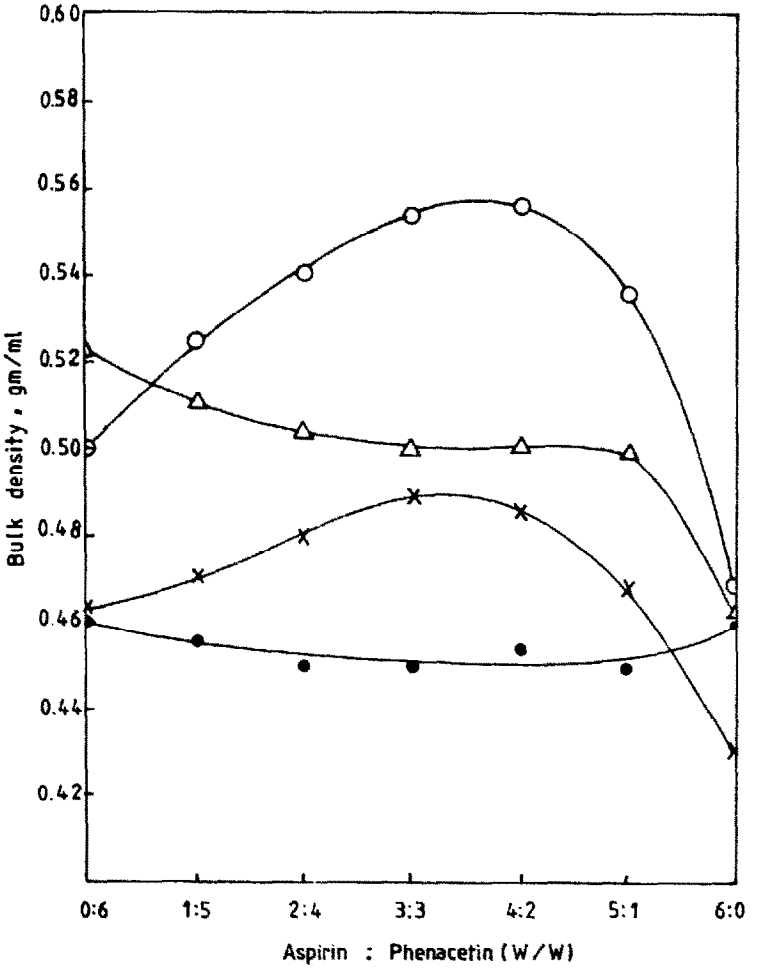

Fig. 2. Apparent bulk density as a function of aspirin–phenacetin (w/w) ratios O——O, with 2% of film-inducing agents: ●——●, Aerosil 200; △——△, Eudragit-E; ×——×, magnesium stearate.

illustrated in Fig. 1. Addition of 2% w/w Aerosil decreased the angle of repose from 56° to 51° for phenacetin alone, and from 54.5° to 48.8° for aspirin alone. For the other ratios of the mixes a fairly constant decrease of an average of 3.5° is achieved with 2% Aerosil 200. It has been proposed that the mechanism whereby fine silica operates to improve flowability is adherence to the surface of the host powder particles (York, 1975). If Aerosil 200 does adhere to particle surfaces rather than fill in void spaces, then the effect would be to increase particle diameter and to decrease the bulk density of the mixture, which was the case as illustrated in Fig. 2. The plot showed the decrease in bulk density (g/ml) with the addition of 2% Aerosil 200 to the different aspirin–phenacetin ratios.

The effect of magnesium stearate and Eudragit-E upon the angle of repose varied with the physical nature of the base material. Although they increased the flowability of phenacetin alone, yet the flowability of pure aspirin was decreased (Fig. 1). The results presented for the other ratios of aspirin–phenacetin indicate that, at 50% w/w concentration, an increase in angle of repose started to be more pronounced

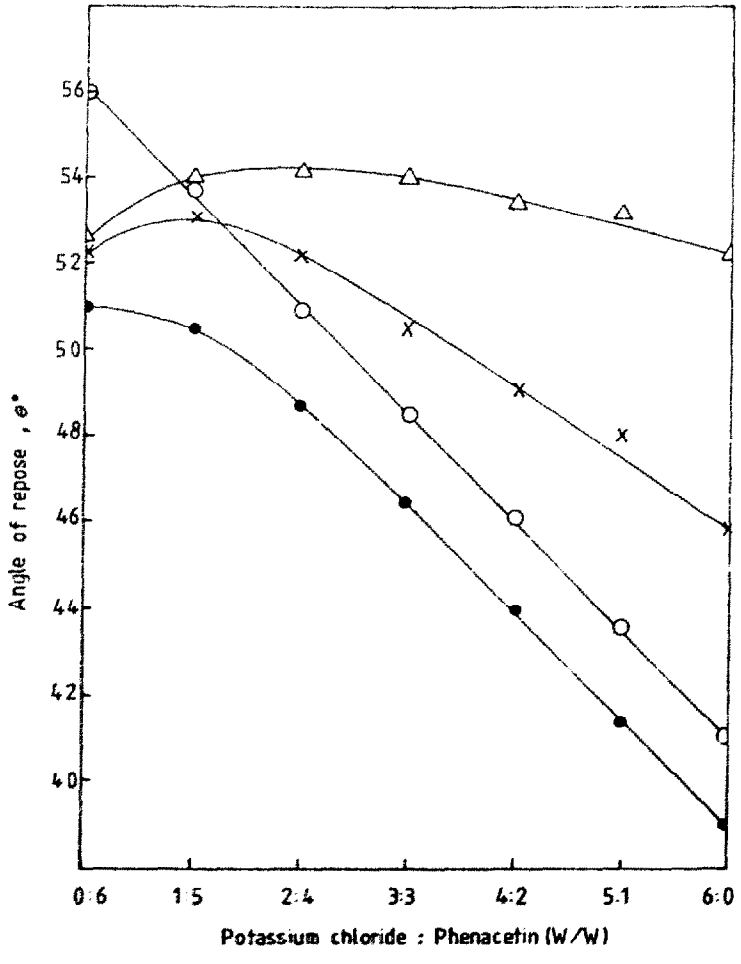

Fig. 3. Repose angle as a function of potassium chloride–phenacetin (w/w) ratios ○——○, with 2% of film-inducing agents: ●——●, Aerosil 200, △——△, Eudragit-E; ×——×, magnesium stearate.

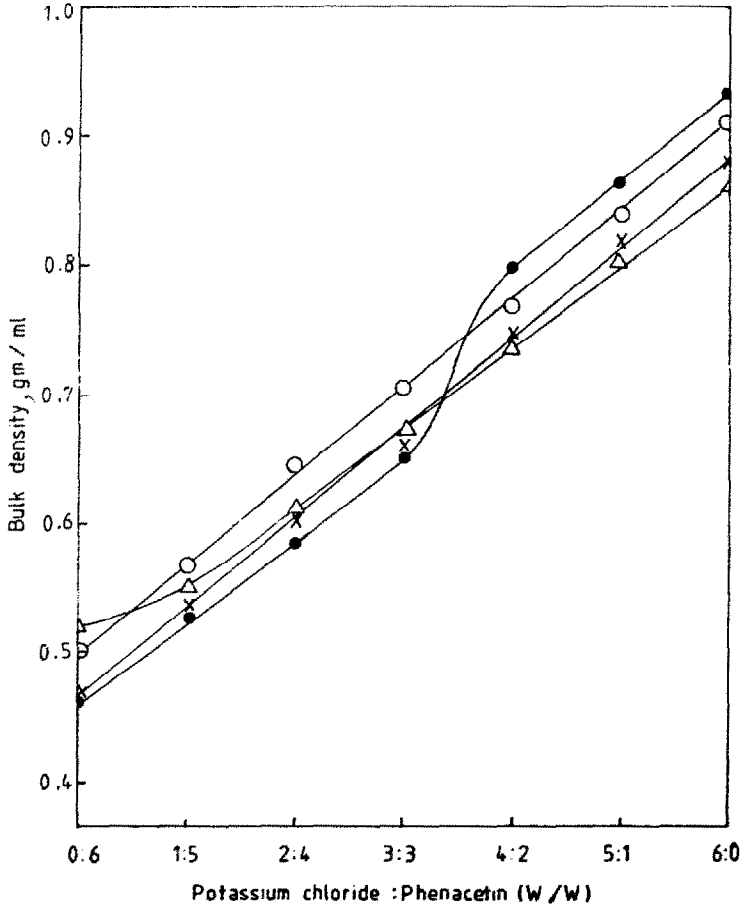

Fig. 4. Apparent bulk density as a function of potassium chloride–phenacetin (w/w) ratios ○——○, with 2% of film-inducing agents: ●——●, Aerosil 200; △——△, Eudragit-E; ×——×, magnesium stearate.

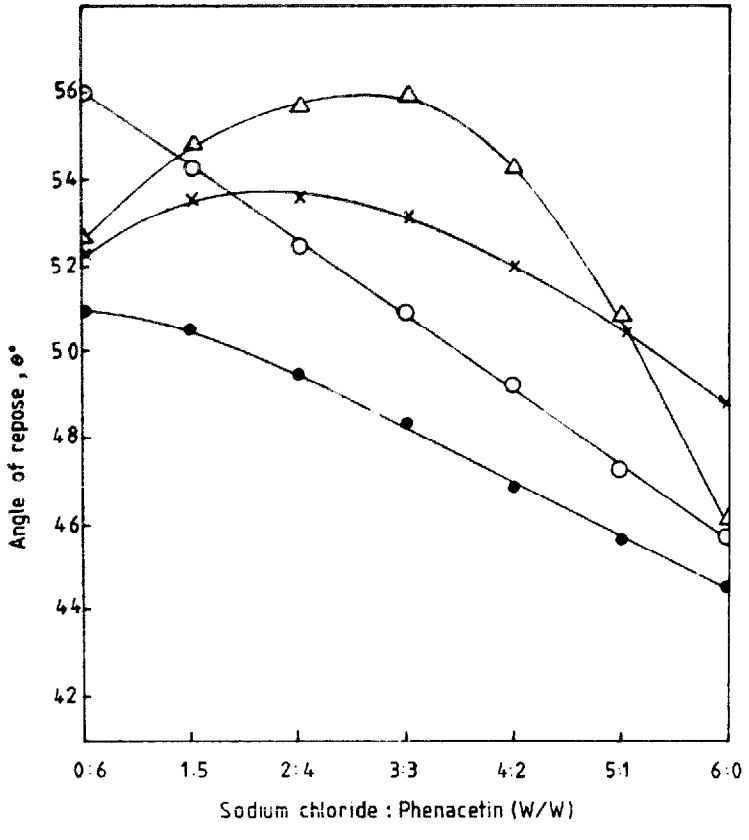

Fig. 5. Repose angle as a function of sodium chloride–phenacetin (w/w) ratios ○——○, with 2% of film-inducing agents: ●——●, Aerosil 200; △——△, Eudragit-E; ×——×, magnesium stearate.

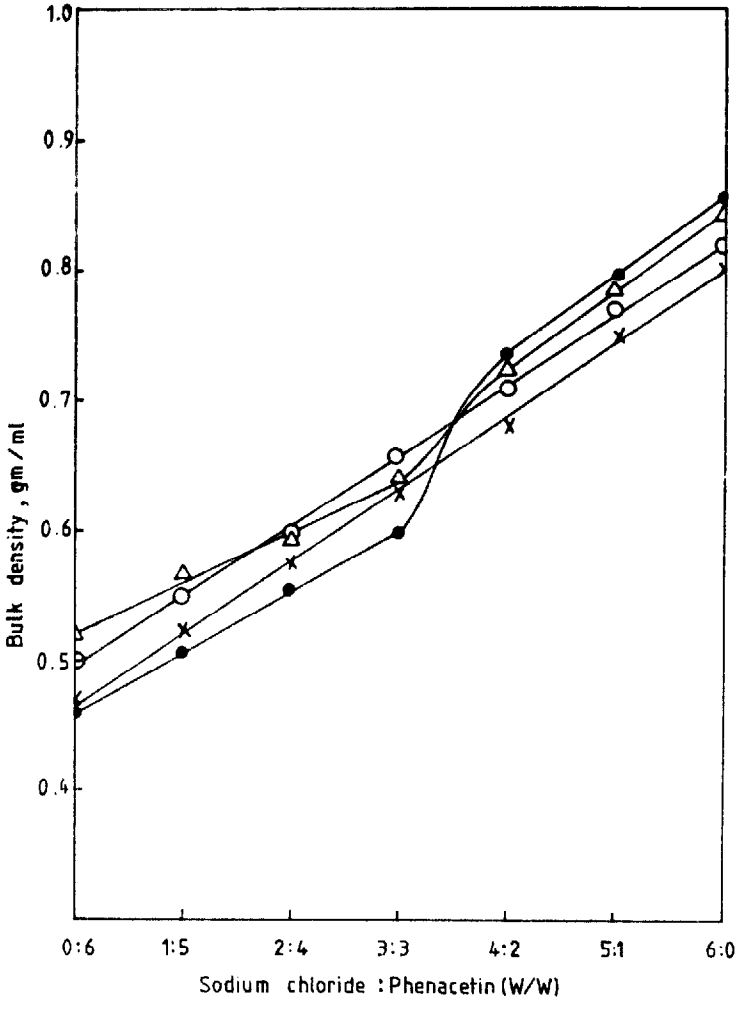

Fig. 6. Apparent bulk density as a function of sodium chloride–phenacetin (w/w) ratios ○——○, with 2% of film-inducing agents: ●——●, Aerosil 200; △——△, Eudragit-E; ×——×, magnesium stearate.

upon the inclusion of 2% magnesium stearate. Presumably, at this ratio magnesium stearate reduced the void space of drug–additive particles. It has been reported that magnesium stearate, unlike Aerosil 200, is hydrophobic and seems to function as a glidant by accumulation in voids between particles (York, 1975). The previous mechanism is supported by the results obtained for bulk density as a function of aspirin–phenacetin ratios (Fig. 2). Above the ratio of 3 : 3 w/w, a decrease in bulk densities has occurred in the presence of magnesium stearate.

It is known that Eudragit-E produces an adequate film rather than a monoparticular stratifying one. The mechanism of action of this film-inducing substance is by coating of particles, resulting in an increased fluidity. The process of coating the particles would increase the bulk volume and hence decrease the bulk density of the powder mixtures. The reduction in bulk density for the different ratios of aspirin–phenacetin obtained by the addition of 2% "Eudragit-E" (Fig. 2) supports the adopted coating mechanism.

The addition of different ratios of either potassium chloride or sodium chloride to phenacetin increased its flowability as can be seen in Figs. 3 and 4. The angle of repose of potassium chloride or sodium chloride–phenacetin mixtures decreased steadily as the percentage of diluent increased. The measured bulk densities were plotted as a function of potassium chloride–phenacetin (Fig. 5), and sodium chloride–phenacetin ratios (Fig. 6). The bulkdensity of phenacetin was 0.511 g/ml while that of the mixtures was increased until a value of 0.914 g/ml for potassium chloride and 0.818 g/ml for sodium chloride. The presented results imply that the flow characteristics of phenacetin powder was improved by mixing with both diluents. The influence of adding 2% of each of Aerosil 200, magnesium stearate and Eudragit-E, to the previous combinations of phenacetin, on the angle of repose, is also given in Figs. 3 and 4. All the glidants used caused an improvement in the flowability of phenacetin alone. Concerning the other ratios of drug-to-diluent, a similar pattern was obtained, for either potassium chloride or sodium chloride, with both Aerosil 200, and magnesium stearate while the effect was different with Eudragit-E. Since the mechanism of action of "Eudragit-E" is by coating, this dissimilarity could be attributed to the difference in surface free energy of potassium chloride and sodium chloride (El Gindy and Samaha, 1983). Recently, a study has been made (Malamataris and Pilpel, 1982) on the tensile strength of some coated pharmaceutical powders. The results have been expressed in terms of the range and magnitude of the interparticle forces which depend on the surface free energy of the coated particles. The inclusion of film-inducing materials to the previous systems showed little effect on the bulk density (Figs. 5 and 6).

Tensile strength of tablets

The tensile strength and flowability of powders are both determined by the range and magnitude of the physical and mechanical forces that act between the particles. Tensile strengths measured 30 min after compaction, to allow for plastic flow, are plotted as a function of the mixture composition (Figs. 7, 8 and 9). For the ratios 1 : 5 diluent-to-phenacetin more than 10 determinations were required in order to obtain reproducible data. The compaction of simple binary mixtures of phenacetin,

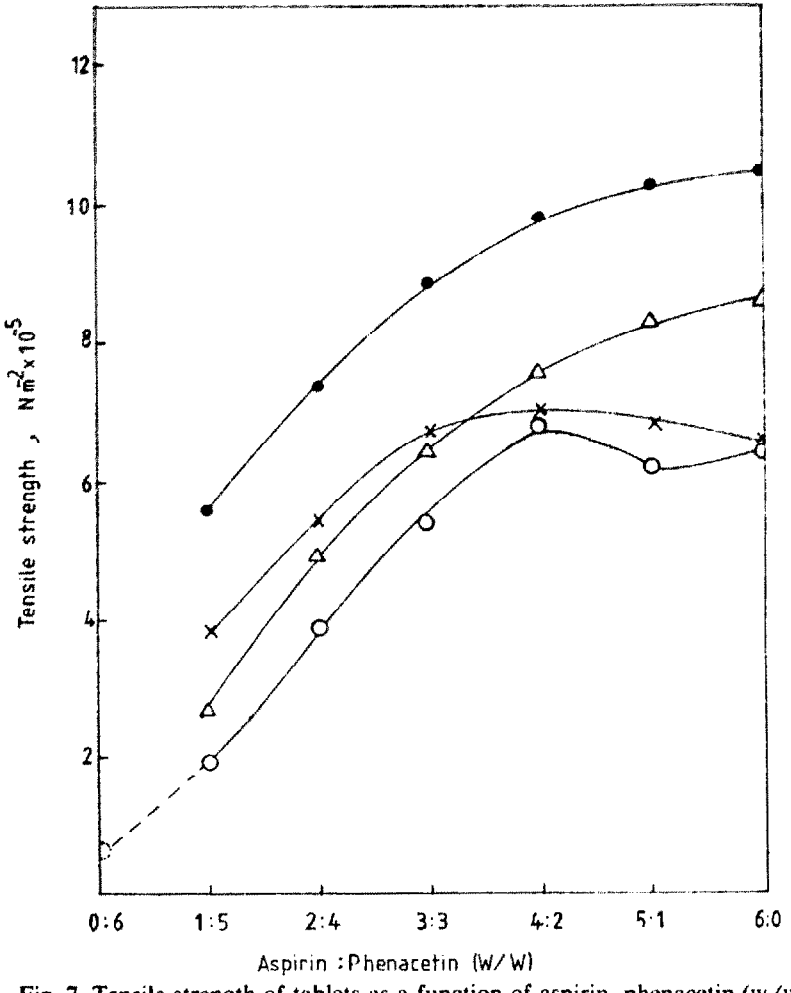

Fig. 7. Tensile strength of tablets as a function of aspirin–phenacetin (w/w) ratios ○——○, with 2% of film inducing agents: ●——●, Aerosil 200; △——△, Eudragit-E; ×——×, magnesium stearate.

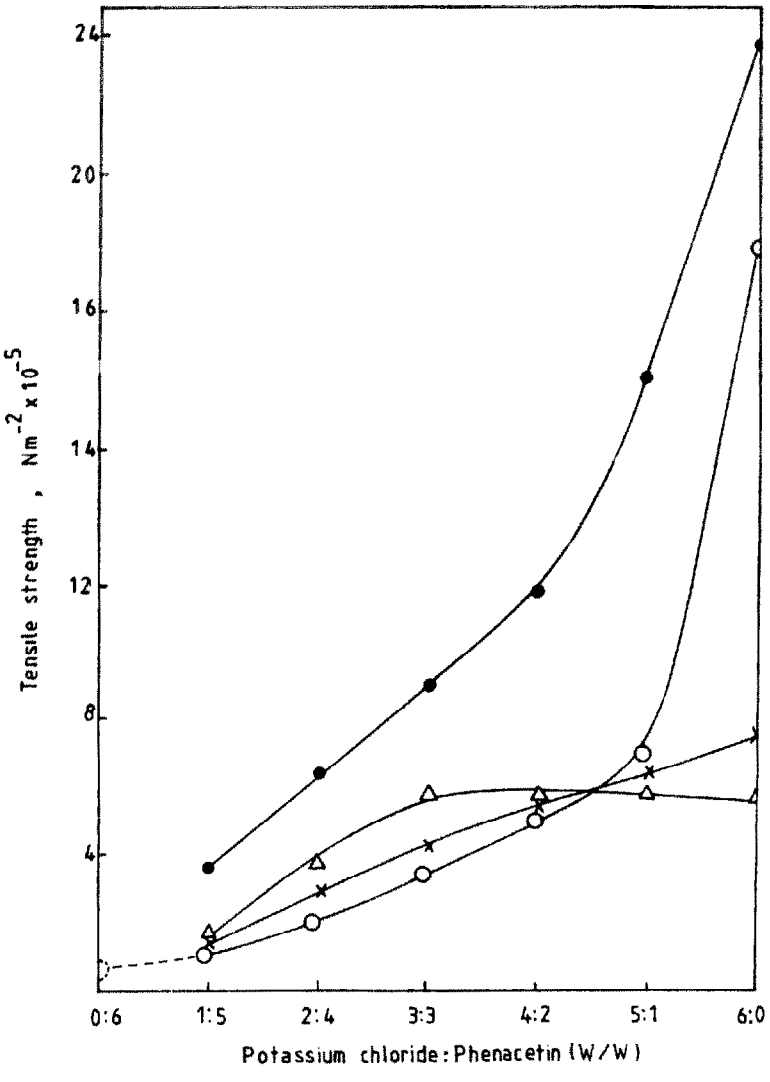

Fig. 8. Tensile strength of tablets as a function of potassium chloride–phenacetin (w/w) ratios ○——○, with 2% of film-inducing agents: ●——●, Aerosil 200; △——△, Eudragit-E; ×——×, magnesium stearate.

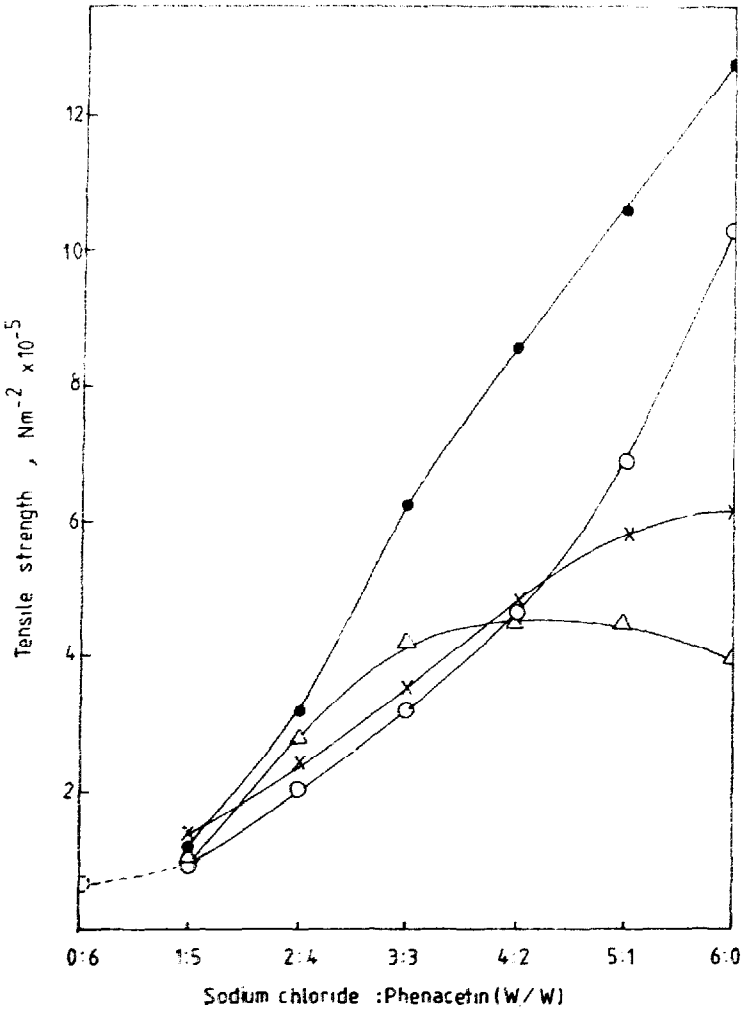

Fig. 9. Tensile strength of tablets as a function of sodium chloride–phenacetin (w/w) ratios ○——○, with 2% of film-inducing agents: ●——●, Aerosil 200; △——△, Eudragit-E; ×——×, magnesium stearate.

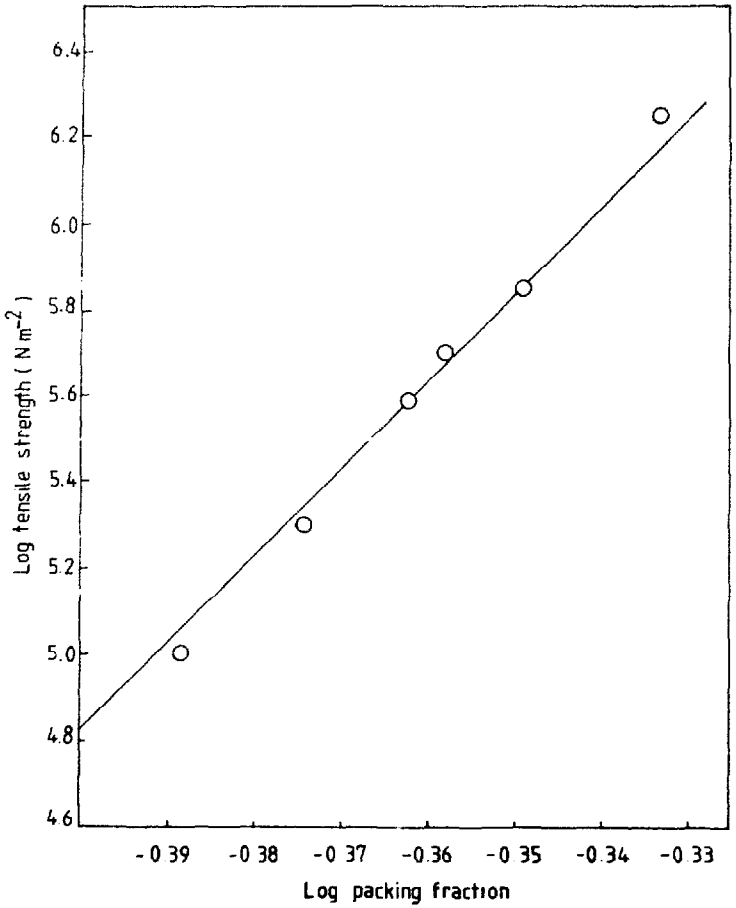

Fig. 10. Relation between the logarithm of tablet tensile strength and the logarithm of the packing fraction for mixtures of potassium chloride–phenacetin (w/w).

which fractures in the die if compacted alone, with diluents which flow plastically, produced satisfactory tablets. The inclusion of aspirin, potassium chloride or sodium chloride improved the compaction characteristics of phenacetin. For aspirin–phenacetin mixtures (Fig. 7), good compacts were obtained when the concentration of aspirin exceeded 16% w/w. However, there was a maximum tensile strength attained at the concentration of 66.67% aspirin. This observation was consistent with the results obtained from the flowability study. Concerning the other two additives, good compacts were obtained at a higher diluent ratio (50% w/w) than in the case of aspirin (Figs. 8 and 9). The plastic flow mechanism dominates at higher concentrations of either potassium chloride or sodium chloride than that of aspirin. The difference in behavior between these two diluents and aspirin may be attributed to the strength of interparticulate bonding. With potassium chloride and sodium chloride failure takes place across the grain indicating a strong interparticle bond, whereas in aspirin tablets break occurs around the grain indicating a weak interparticle bond (Shotton and Ganderton, 1961). Thus, the weakening of the interparticulate bond, resulted when aspirin was mixed with phenacetin, reduced the capping tendencies of phenacetin at a lower aspirin concentration than with the other two diluents.

The inclusion of 2% w/w of film-inducing materials to the previous systems was also illustrated in the same figures. Aerosil 200 increased the tensile strength of all prepared tablets. Meanwhile, Eudragit-E and magnesium stearate increased the tensile strength (although to a lesser extent than Aerosil 200) until the ratio of 4 : 2 w/w diluent-to-phenacetin. Above this ratio their effect on tensile strength was composition dependent.

In order to estimate the tensile strength of phenacetin alone, the packing fraction (Eqn. 1) of the different combinations with one of the diluents, viz. potassium chloride, was plotted versus their tensile strengths (Fig. 10). The linear relation obtained could be expressed by:

$$\sigma_t = a\varphi_F^b \tag{3}$$

or

$$\log \sigma_t = \log a + b \log \varphi_F \tag{4}$$

where σ_t is the tensile strength of tablets measured after 30 min of compaction, φ_F is the packing fraction of their mixtures and a and b are constants dependent upon the particular material. These constants were calculated by regression analysis, and the equation of the best-fitted line is:

$$\log \sigma_t = 12.824 + 20 \log \varphi_F \tag{5}$$

Accordingly, the tensile strength of the phenacetin compact, σ_t, was estimated from its packing density and was found to be 7.31×10^4 N · m^{-2}. By using Eqn. 4, prediction of tablet tensile strength (at a given pressure) for any drug combination could be obtained from their corresponding packing fractions.

This investigation demonstrates the feasibility of using materials having plastic flow for the successful tableting of a very brittle substance exhibiting capping problems when compacted. By changing one of the variables affecting the production of good tablets (the ratio of diluent-to-drug), tablets of different strengths could be manufactured.

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