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INFLUENCE OF TECHNOLOGICAL FACTORS ON FORMULATION OF SUSTAINED RELEASE TABLETS

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ABSTRACT

Theoretically expected rates of release of solid drugs incorporated into solid matrices have been derived for several model systems. Mathematical relations have been obtained for cases (a) where the drug particles are dispersed in a homogeneous, uniform matrix which acts as the diffusional medium and (b) where the particles are incorporated in an essentially granular matrix and released by the leaching action of the penetrating solvent. A number of technological factors are influencing the formulation of sustained release tablets. It was found that the choice of matrix material, amount of drug incorporated in matrix, matrix additives, the hardness of the tablet, density variation, and tablet shape could markedly affect the release rate and also the formulation.

INTRODUCTION

Although the concept of sustained or controlled delivery of orally administered drugs has been with us for some time, there has been a remarkable increase in interest in this type of dosage form during the last decade. This is a consequence of the simultaneous maturation of various factors, including the prohibitive costs of developing new drug entities, the expiration of existing patents, and the discovery of novel polymer systems and devices suitable for controlled delivery of oral dosage forms (1-3).

Two mechanisms of release from these systems have been treated. (a) Extraction of the medicament by a simple diffusional process through and from an enveloping homogeneous matrix. The drug is presumed to go successively from the crystal surfaces into the uniform matrix and out into the bathing solvent which in turn acts as a perfect sink. (b) Leaching of the medicament by the bathing fluid which is able to enter the drug-matrix phase through pores, cracks, and intergranular spaces. The drug is presumed to dissolve slowly into the permeating fluid phase and to diffuse from the system along the cracks and capillary channels filled with the extracting solvent. Intragranular diffusion is assumed, in this instance, to be insignificant. The two mechanisms are depicted schematically in Fig.1 (4).

The amount of total drug released from a planar system having a homogeneous matrix, originally suggested by Higuchi, where the amount of the drug released after time t per unit exposed area is proportional to the square root of time, t:

$$\frac{W_r}{t^{1/2}} = S\left[DC_s\left(\frac{2W_o}{V} - C_s\right)\right]^{1/2} \qquad \text{(Eq.1)}$$

Where D is the diffusion coefficient, C_s is the solubility of drug in the matrix substance, W_r is the amount of drug released in time

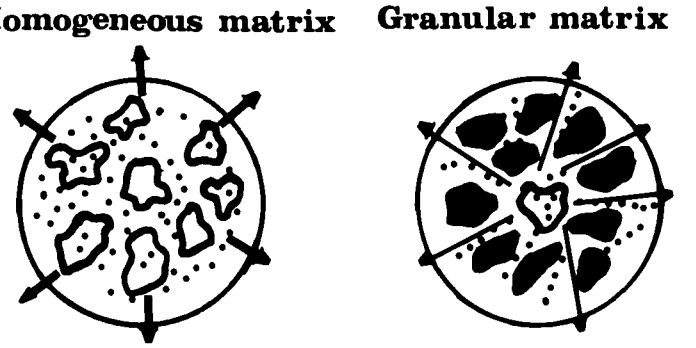

FIGURE 1

Two methods of drug release from the pellets (4).

t, W_o is the amount of the drug, S is the effective diffusional area, V is the effective volume of the matrix (4).

The analogous equation for the release of a single drug from one surface of an insoluble matrix or granular matrix is:

$$\frac{W_r}{t^{1/2}} = S\left[\frac{D\,\varepsilon\,C_s}{\tau}\left(\frac{2W_o}{V} - \varepsilon\,C_s\right)\right]^{1/2} \qquad \text{(Eq.2)}$$

Where ε is the porosity of the matrix, τ is tortuosity of the matrix. In this model, the drug is dissolved by a leaching action of the solvent which enters the matrix through connecting capillaries and the rate of drug release is dependent on the rate of drug diffusion but not on the rate of solid dissolution. The assumptions made in deriving Eq.2 are as follows.

1) A pseudo-steady state condition is maintained during the release process.

2) Drug particles are quite small relative to the average distance of diffusion and are uniformly distributed in the matrix.

3) The diffusion coefficient remains constant and no interaction between the drug and the matrix occurs.

4) A is greater than C_s or εC_s by a factor of three or four (4).

The release of a drug from an insoluble, inert matrix is described by the T.Higuchi equation if the rate-determining process is diffusion (Eq.2). The release of drugs from wax matrixes (5-7), methylacrylate-methyl methacrylate copolymer matrices (8,9), and compressed hydrophilic matrices (10,11) have also been shown to follow Eq.2. However, the aqueous solubility of a drug will affect the release mechanism from polymer matrices and therefore allows difficult mathematical interpretations of dissolution rate (4,11). Water penetration may be visualized as a front moving into the tablet, hydrating the polymer and dissolving the active material which then diffuses out through the swollen matrix. If the drug has limited water solubility so that it has not completely dissolved when the polymer is hydrated then diffusion will commence from a saturated solution. The expression describing drug release from the single face of a tablet is T.Higuchi equation (Eq.2).

If the drug has a high aqueous solubility and has completely dissolved when the matrix is hydrated then the following expression applies (11,12):

$$\frac{W_r}{t^{1/2}} = 2W_o\left(\frac{S}{V}\right)\left(\frac{D'}{\pi}\right)^{1/2} \qquad \text{(Eq.3)}$$

Where D' is the apparent diffusion coefficient of drug ($D' = D/\tau$) in the hydrated matrix. The other terms have the same meaning as in Eq.2.

Generally for Eqns. 2 and 3 to hold drug release should be examined under near perfect sink conditions and the amount dissolved should be less than 30% of the initial dose. S and V are larger than the corresponding values of the tablet prior to immersion in the solvent due to swelling of the matrix when hydrated. Eqns 2 and 3 predict a zero intercept but inevitably small negative intercepts will be obtained due to failure of the systems to attain immediately the state of diffusion described by Eqns. 2 and 3. Generally, however, a soluble drug is released by diffusion from the gel layer and by tablet erosion where as an insoluble drug is released by exposure through tablet erosion (13). These relationships indicate that the release of drug is a linear function of the square root of time. In practice it is often found that the linear relationship between the amount of drug released and the square root of time is only valid in part of the dissolved curve (75 to 80% of the time needed for complete liberation of the drug).

Farhadieh et al. (8,9) have suggested that this slope change is related to the geometric shape of the tablet, a flat tablet showing a linear release profile during a longer time than a spherical one. However, according to Fessi et al. (14), the change in slope is due to modification in the release process itself. This change appears when the tablet has been completely penetrated by the dissolution liquid. The Higuchi law is then no longer valid and drug dissolution occurs according to a simple diffusion model.Stamm et al. (15) also found similar results for tablets showing a high porosity (low hardness). But for tablets with low porosity (high hardness), the differences in density in the tablets are responsible for the change in slope.

Bamba et al. (16) have proposed a goodness of fit method to determine the mechanism of release from a system. They proposed the following process which could be rate determining in the release of drug from a system. They are a) the permeation of water, b) the gelation rate, c) the diffusion rate of the drug in the gel d) the

dissolution rate of the drug in the penetrating water, and e) the Higuchi porous penetration (4). If the release pattern of the drug from the formula is dictated by a, b or c processes then it is a first-order release and Eq.4 should be applicable. If the release is depicted by process d, then a cube root relationship should hold (Eq.5), and if it is governed by porous penetration then the Higuchi square root law should apply (Eq.6).

$$\ln W = - k_f.t + i \qquad \text{(Eq.4)}$$

$$\sqrt[3]{100} - \sqrt[3]{W} = k_c t \qquad \text{(Eq.5)}$$

$$100 - W = k_d.\sqrt{t} \qquad \text{(Eq.6)}$$

Where, W is the percentage of drug undissolved at time t (h), k_f (h^{-1}) and i are the first-order dissolution rate constant and the intercept of the log-linear plot of the type in Eq.4, k_c is the cube root dissolution rate constant ($mg.h^{-1/3}$) and k_d is the Higuchi constant. The application of such methodology allowed characterization of the mechanism and rate of drug release from sustained release matrix tablets (17-19). In the homogeneous case, drug release is directly proportional to the square root of time. Eq.2 then reduces to:

$$Q = k\, t^{1/2} \qquad \text{(Eq.7)}$$

Eq.7 also describes the case of granular matrix if drug release from the matrix is diffusion controlled and the value of release rate constant k remains constant throughout the leaching process. In this instance, one may control drug release from a sustained release matrix tablets by varying the following parameters:

1) Choice of matrix material,

2) Amount of drug incorporated in matrix,

3) Matrix additives,

4) Hardness of the tablet, density variation and tablet shape.

CHOICE OF MATRIX MATERIAL

For a study of this type, it was necessary to obtain a matrix which would satisfy certain minimum requirements. It should be inert, insoluble, should remain intact during experiment, provide a sustained release over a reasonable length of time, and most important, yield a reproducible straight line when the amount of drug released is plotted versus the square root of time. For the above reasons, it was felt that a plastic matrix would be preferable to one consisting of fats and waxes.

Desai et al (20,21) and Singh et al. (22) have made extensive experimental on inert matrices and further theoretical studies of Eq.2. In their approach several differents plastics and several drugs were involved. They independently determined the appropriate D, the solubility C_s, the appropriate ε (two ways), and τ by an independent experiment with the same matrix utilizing Eq.2. These investigators also showed (21) that in some instances (polyethylene matrices without surfactant in the solvent) wetting may be poor and therefore the effective τ values may be in the tens of thousands. More recent studies show that in these cases the diffusion controlled model probably fails, and the release rate is determined by the channel penetration rate of the solvent (22). In other instances (polyvinyl chloride matrices in water) wetting was efficient, but air removal from the matrix significantly altered the drug release pattern (23,24). Furthermore, the choice of the inert matrix strongly influences the observed amount released (W_r/S) versus $t^{1/2}$ plots. Polyvinyl chloride releases

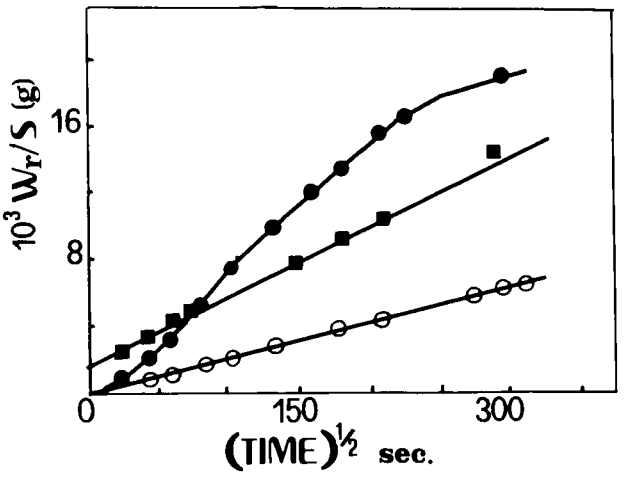

FIGURE 2

Comparison of release rates of various plastic matrices containing 5% sodium salicylate. Key: ●, polyvinyl chloride; ○, plaskon (=halogenated fluorocarbon homopolymer); ■, polyethylene (20).

sodium salicylate four to six times faster than plaskon and (W_r/S) versus $t^{1/2}$ plot is sigmoidal and this atypical behavior was attributed to the slow removal of air from the tablet (Fig.2).

The importance of choice of matrix material on drug release in formulation of sustained release tablets is illustrated by many studies. McGinity et al. (25) examined the retardant properties of acrylic resin polymers in sustained release theophylline tablets. In addition, Khanna and Speiser studied the release properties of chloramphenicol from methacrylic acid and methylmethacrylate polymeric beads. Swelling and diffusion were the major factors influencing drug release (26). Carli et al. (27) reported that Eudragit RS and Eudragit RL copolymers had poor surface wettability. These polymers, however, were reported to have good liquid transport properties. Drug release was controlled by diffusion through the matrix pores, and copolymer containing a higher percentage of hydrophilic groups produced the fastest drug release

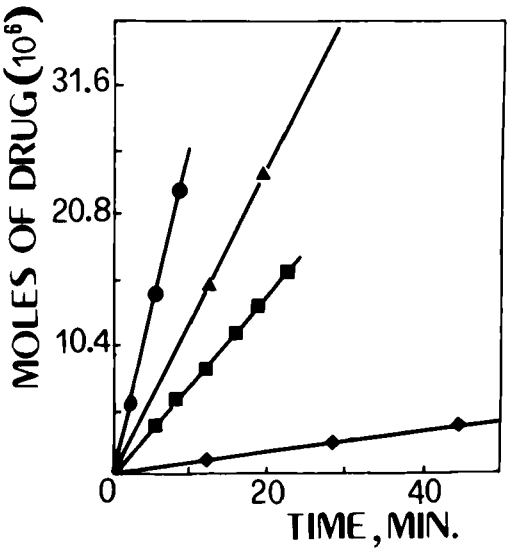

FIGURE 3

Drug release from various compressed polymer matrices. Key: ●, chlorpheniramine maleate from polyvinylpyrrolidone; ▲, sodium salicylate from sodium carboxymethylcellulose; ■, chlorpheniramine maleate from methylcellulose; ◆, chlorpheniramine maleate from sodium carboxymethylcellulose (11).

rates. Korsmeyer et al. (28) investigated that the release kinetics of potassium chloride from hydroxypropyl methylcellulose matrices prepared with several different compression forces deviates significantly from the classical $t^{1/2}$ dependence. They noted that this behavior was attributed to air entrapped in the matrix during preparation and removal of the air prior to release restored the traditional $t^{1/2}$ behavior.

In the case of compressed hydrophilic matrices, it appears that the polymer which forms the hydration layer least susceptible to erosion and dissolution will show the greatest retarding action on drug release. If the hydrated layer remains intact, the drug diffuses through that layer, and the release pattern is linear with

the square root of time. If the hydrated layer does not maintain its integrity, the release of drug will be linear in relation to time as is expected from a system of constant surface area subject to dissolution in a perfect sink (29,30). Figure 3 shows the release of chlorpheniramine maleate from a tablet where differents hydrophilic polymers had been used as the tablet matrix.

There are, therefore, other factors, not immediately apparent from Eqns.2 and 3. which control the release of a drug from compressed hydrophilic matrices. For instance the rate of hydration of the hydrophilic matrix compared to the rate of wetting and dissolution of the remainder of the tablet. Using constant tablet weights but different chlorpheniramine maleate : hydroxypropyl methylcellulose ratios, Lapidus and Lordi (11) noted that the Higuchian dissolution rates, plotted as a function of the dose within the tablet were linear for up to a 25% concentration of drug. The positive change in linearity above this level resulted from a change in the tortuosity of the hydrated polymer (Fig.4). Tortuosity, τ, can be related to D' and the actual diffusion coefficient D of the drug in the release media by

$$D' = \frac{D}{\tau}$$

and hence tortuosity may influence drug release. An increase in the polymer concentration showed a corresponding increase in tortuosity for the same concentration of drug. The term $(S/V)\ (D'/\pi)^{1/2}$ in Eqn.3 is therefore subject to variation as the drug: polymer ratio is varied. In addition, attrition of the tablet surface accounts for the positive deviation. If attrition is considered to be the wearing away of the external surface of the hydration layer, the eroded material will go into solution quickly and provide drug in addition to that already available from diffusion. On the other hand, electrolytes apparently increase the tortuosity of the

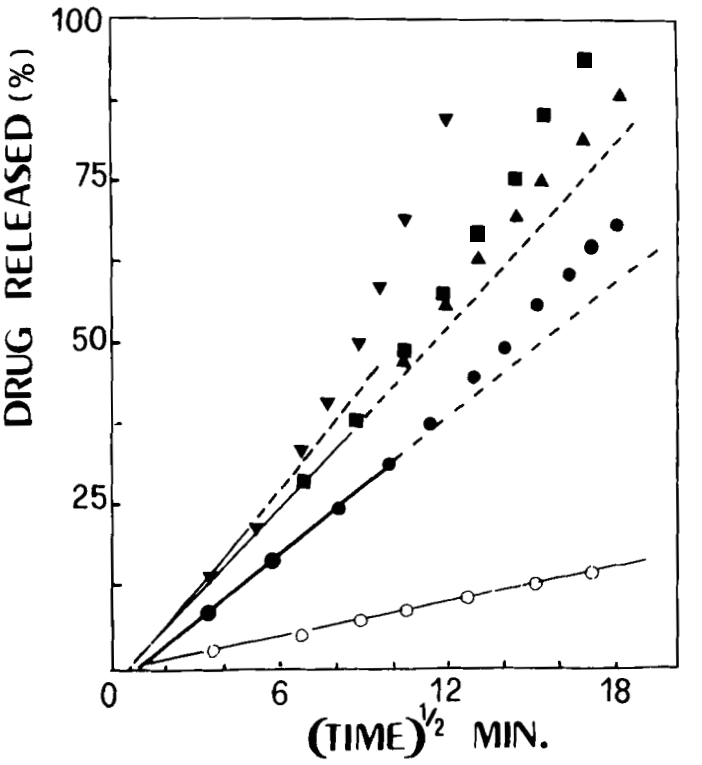

FIGURE 4

Chlorpheniramine maleate release from a whole tablet. Key: ▼, hydroxypropyl methylcellulose; ■, standard tablet in pH 1.5 solution; ▲, 33.3% w/w of polymer replaced with lactose in the standard tablet; ●, standard tablet in water; ○, planar surface of a standard tablet (11).

hydrated film. Since ions reduce the activity of water, hydration of the matrix should be reduced, resulting in a decreased drug release rate (10).

The influence of viscosity of polymeric solutions and viscosity grade of the polymer on the dissolution rate of drugs from matrix tablets were studied. Nakano et al. (31) indicated that the drug release rate was fast from the tablets made of the low-

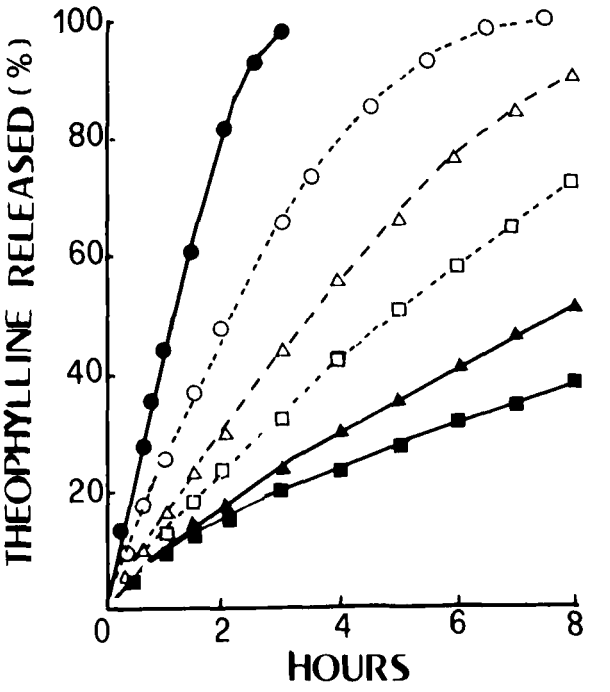

FIGURE 5

Release profiles of theophylline from tablets prepared from 1:1 mixture of theophylline (250 mg) and hydroxypropylcellulose of various compositions. Key: Viscosity grades of the polymer (●) low; (▲) medium; (■) high-viscosity grade polymer, and (○) (3:1) (△), 1:1, and (□) 1:2 mixtures of low-and medium-viscosity grade polymers (31).

viscosity grade polymer, while the release rate was slow from tablets made of the polymers of medium-and high-viscosity grades. Therefore, tablets made from mixtures of low-viscosity grade polymer and medium-viscosity grade polymer in the mixing ratios, as shown in Fig.5, were examined to obtain an appropriate release rate. With an increase in the contents of the medium-viscosity grade polymer, the release rates was decreased. Therefore, the drug release rate can be modified by changing the mixing ratio of two polymers with different viscosity grades depending on the required sustain period. Sarisuta et al. (32,33) investigated the influence of

viscosity on the dissolution rate of benzoic acid in aqueous solutions of methylcellulose, hydroxypropylcellulose, and guar gum. when the dissolution of one-component, nondisintegrating sphere occuring in a non reactive medium at sink conditions is diffusion controlled, the dissolution rate (R) may be expressed as:

$$R = \frac{DC_s}{h} \qquad \text{(Eq.8)}$$

where h is the effective film thickness. However, earlier work by Salomen et al. (34) indicated that the viscosity grade of hydroxypropylmethylcellulose only affected the lag time for potassium chloride diffusion to become quasi-stationary but did not affect the rate of release.

AMOUNT OF DRUG INCORPORATED IN MATRIX

The influence of the amount of drug incorporated in matrix is interesting and of practical importance in the field of sustained release tablets. This can be a very important factor, as frequently it is desirable to produce several tablet concentrations of the same drug and matrix to provide a variety of dosage schedules. To do this the tablet concentration dependency must first be determined.

Desai et al. (20) showed that the slope of the release curve should be proportional to the square root of the amount of drug in tablet as it appears raised to the first power under the square root sign. Closer examination (4) would reveal a direct relationship. Fig.6 shows the effect of amount of drug incorporated in matrix on tablets containing 5, 10 and 20% sodium salicylate in polyethylene. Comparing the experimental results, the slope of the 10% tablet was only 1.3 times greater than the 5% tablet, and the 20% tablet was 2.9 times greater than the 5% tablet. This may indicate that the

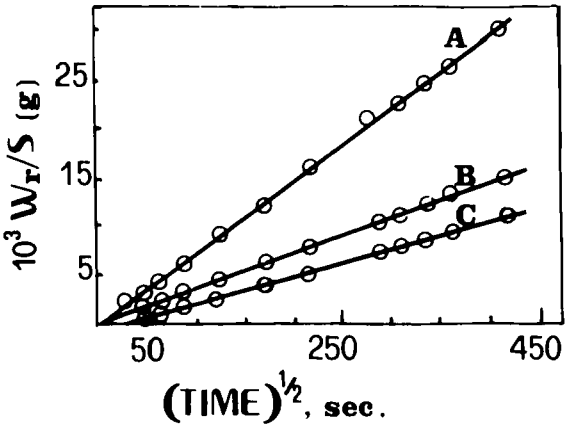

FIGURE 6

Sodium salicylate release as a function of its concentration in polyethylene tablet. Key: A, 20% w/w; B, 10% w/w; C, 5% w/w (20).

other factors in the Eq.2 are changing with the amount of sodium salicylate or that porosity was not proportional to the total amount of drug present in the matrix per unit volume.

Several other investigators also theoretically treated the matrix model and showed that the amount of drug influence the dissolution rate (35-38). In a planar system, the release of drug per unit time, dW_t/dt, is described by

$$\frac{dW_t}{dt} = S\left[\frac{DC_s\left(\frac{2W_o}{V} - C_s\right)}{t}\right]^{1/2} \qquad \text{(Eq.9)}$$

where W_o is the amount of the drug in the matrix, W_o/V is the drug loading, and C_s is the solubility of the drug in the matrix at time t.

When the drug loading becomes much greater than the solubility and a granular matrix (with the possibility of interparticle contact) is formed, Eq.9 usually is modified to give:

$$\frac{dW_t}{dt} = S\left[\frac{\frac{\varepsilon}{\tau} D \left(\frac{2W_o}{V} - \varepsilon C_s\right) C_s}{t}\right]^{1/2} \quad \text{(Eq.10)}$$

which becomes:

$$\frac{dW_t}{dt} = S\left[\frac{2\,\varepsilon\, D\, W_o\, C_s}{\tau . V}\right]^{1/2} t^{-1/2} \quad \text{(Eq.11)}$$

in the case where $(W_o/V) >> \varepsilon C_s$.

Thus, Eq.9 is modified by an effective porosity, ε, which can be related to the volume fraction of drug in the matrix, and an effective tortuosity, τ, which describes the tortuous diffusion path a drug molecule must follow. In addition, the D value is taken as the diffusivity of the solute in the receptor solution. In other words, it is assumed that the drug is released by leaching through channels that are formed in the continuous matrix.

When Eq.11 is rewritten as :

$$Q = K\, t^{-1/2} \quad \text{(Eq.12)}$$

with

$$Q = \left(\frac{1}{S}\right) \frac{dW_t}{dt} \quad \text{(Eq.13)}$$

and

$$K = \left[\frac{2\,\varepsilon\, D\, W_o\, C_s}{\tau . V}\right]^{1/2} \quad \text{(Eq.14)}$$

Table I - Release rate Constant for Salicylic Acid at Various Drug Concentrations in a Polyethylene Glycol-Ethylcellulose Film

Drug, mg/ml	Release Rate Constant, $mg/36cm^2/min^{1/2}$	
	Calculated	Measured
55	0.3	0.25
100	0.6	0.65
200	1.45	1.4
300	2.63	2.7
350	3.36	3.65

It can be seen that this model predicts that the release rate constant changes in proportion the square root of the initial drug loading, (W_o/V) or the amount of drug incorporated in matrix, the ratio ε/τ then expresses the fractional area available for release.

Recently, Chandrasekaran et al. (39) proposed an equation calculating the release rate of drug from the density of the dispersed phase, the drug loading, and the permeability of the drug in the pure polymer. Table I presents the release rate constant computed by Chandrasekaran et al. and measured by Samuelov (37). The relation between the release rate constants determined experimentally and those calculated from the model is in good agreement. The deviation at very high drug loading (> 30%) can be attributed to interparticle contact. The interparticle contact leads to the formation of channels in the membrane through which the drug can be leached.

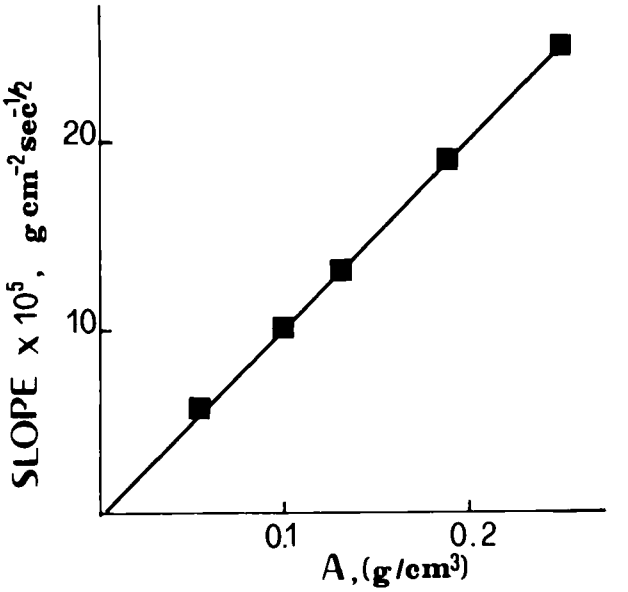

FIGURE 7

Slopes of release data (divided by surface area) as a function of A, the initial drug loading (40).

Fessi et al. (40) have shown for several systems of low loading type, that the square root equation (Eq.2) is obeyed, and that the slope is approximately proportional to the initial drug loading (Fig.7).

MATRIX ADDITIVES

Matrix additives or formulation additives further modify release rates. Daly et al (41) considered that the addition of surfactants may modify release from hydroxypropyl methylcellulose matrices by binding to the polymer and increasing the viscosity. More simple molecules, for example insoluble diluents such as tribasic calcium phosphate or water soluble diluents such as lactose may modify release rates. Lapidus et al. (11) showed that the ad-

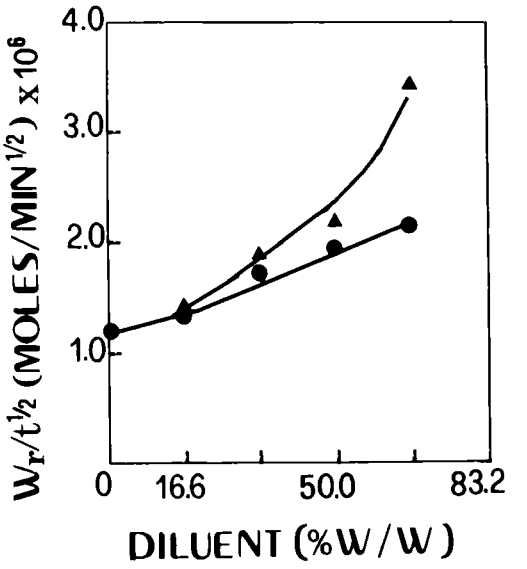

FIGURE 8

Effects of addition of tablet diluents on the rate of chlorpheniramine maleate release from a hydroxypropyl methylcellulose tablet matrix. Key: ▲, lactose; ●, tricalcium phosphate (11).

dition of lactose increased the release rate of chlorpheniramine more than the equivalent amount of calcium phosphate. The observed divergence can be explained by the difference in solubility of the diluents and their subsequent effects on the tortuosity factor. As the water-soluble diluent dissolved, it diffused outward and decreased the tortuosity of the diffusion path of the drug. On the other hand, the tricalcium phosphate did not diffuse outward, but rather became entrapped within the matrix and effected an increase in release of drug only by the fact that its presence necessarily decreased the gum concentration. This effect can be seen in Fig.8. F.Öner et al. (42) showed that the same effect in the sustained release isoniazid matrix tablets. Since the drug was more water soluble, the desired release rate was obtained by utilizing tribasic calcium phosphate as matrix additive.

Several investigators have described the incorporation of additives, such as channeling agents, into the matrix and improve drug release. Emori et al. showed that the release of phenacetin from a wax matrix was improved by the addition of an acrylic acid polymer. Increasing the amount of polymer increased the release rate of phenacetin due to the formation of pores and channels in the matrix resulting from leaching of the polymer (43). Dakkuri et al. (44) indicated that the utilization of povidone as a channeling agent in the formulation of a sustained-release tripelennamine hydrochloride core significantly influenced drug release. It appears that channel formation is the mechanism underlying the increase in the drug dissolution rate from cores containing the polymer.

Parab et al. (17) have shown that the addition of varying amounts of mannitol or hydroxypropyl methylcellulose into the wax matrix improve theophylline release. In addition, Ritschel et al. (18) examined the influence of channeling agents from theophylline matrix tablets prepared with acrylic resin. No difference in the amount of drug released, was found when lactose or dextrose were added to the internal phase before granulation. However, addition of dextrose after granulation into the external phase resulted in a small increase in the amount of drug released.

Influence of lactose and tribasic calcium phosphate on the release of cibenzoline succinate from plastic matrix tablets was studied by Costa et al. (45). Cameron et al. (46) also examined the release of theophyllline from matrix tablets containing an acrylic resin polymer as the retardant substance. Releasa rates were most rapid when microcrystalline cellulose was the filler excipient and the slowest when calcium sulfate was used as the diluent. More recently, the influence of matrix additives on the drug release rate of theophylline was investigated by Aerde et al. (47).

TABLET HARDNESS, DENSITY VARIATION AND TABLET SHAPE

Sustained release matrix tablets, which normally contain larger amounts of drug than conventional tablets, should remain indivisible in the gastrointestinal tract and drug should be released 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.

Compression behaviour of powders is conveniently characterized by Heckel plots (48), and various authors have successsfully applied Heckel's equation to pharmaceutical powders to identify the types of mechanism occurring during compression (49,50). In the Heckel equation, the relative density, D, is directly releated to the applied compression force, P.

$$\ln (1/(1 - D)) = KP + C \qquad \text{(Eq.15)}$$

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

$$D = \rho_a/\rho_t \qquad \text{(Eq.16)}$$

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 et al. (51) and York et al. (52) distinguished 3 types of powder behaviour on the basis of the above equation. These are illustrated as Types A, B, and C in Fig.9. In Type A, the different-sized fractions have different initial packing densities and plots remain parallel as applied pressure is increased,

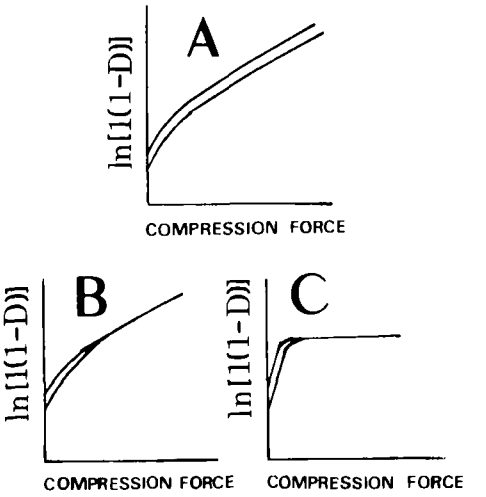

FIGURE 9

The 3 different types of Heckel plots (56).

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. Çapan (53) and Stamm et al (54,55) showed a linear relationship between compression force and the hardness of tablets prepared by different matrix materials. Fassihi (56) showed that the polymeric mixture follows a simple Heckel relationship at low pressure and exhibits a sudden change at greater pressures. Both plastic deformation and particle fusion are operative during densification.

Tablet Hardness and Density Variation

In an earlier report, Huber et al. (30) stated that tablet hardness did not show marked differences in release characteristics as evaluated by an in vitro method. They observed different release

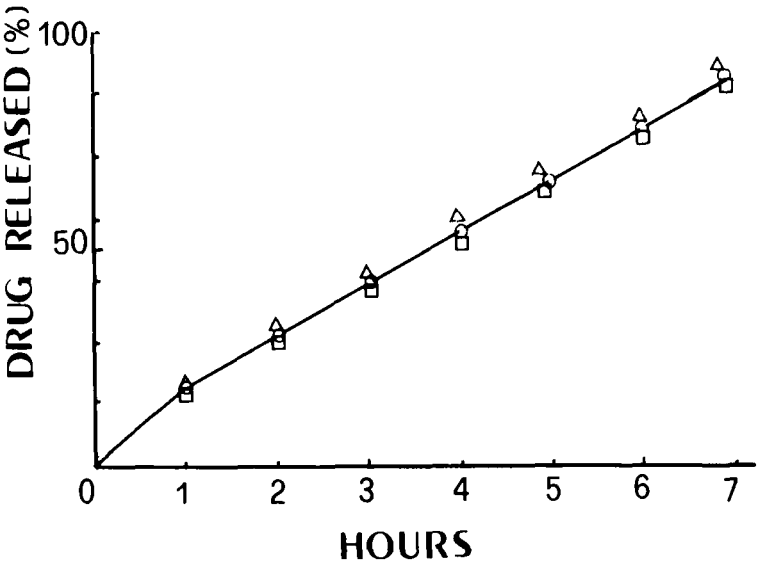

FIGURE 10

Influence of tablet hardness on in vitro dissolution of dye from hydroxpropyl methylcellulose tablets. Key: ○, 5.3 Kg. average hardness; △, 8.4 Kg. average hardness; □ 11.8 Kg. average hardness (30).

patterns with tablets prepared from different gums (Fig.10). Lapidus et al (11) utilized two different compression forces and observed no significant difference in drug-release patterns from tablets of differing density. In the examination of the effect of compression pressure on release rate, three pressure levels covering a ninefold change in perssure were applied to the mixture. Release patterns (not shown) of theophylline from hydroxypropylcellulose tablets thus prepared were practically superimposable. Thus, compression pressure and compression period are not important factors in modifying the release pattern of the drug (31).

The number of studies investigating the effect of compression pressure or hardness on release rates have yielded conflicting results. Hashim et al. (57) showed that compression pres-

sure (148-443 $MN.m^{-2}$) did not effect the release rate in accordance with data reported by Ford et al. (13) who used pressures ranging from 93 to 1395 $MN.m^{-2}$ for compressing promethazine hydrochloride hydroxypropyl methylcellulose (HPMC) mixtures. Similar data have been reported by Salomon et al. (34,58) working with potassium chloride/HPMC mixtures at pressures ranging from 57 to 283 $MN.m^{-2}$ and by Ventouras et al. (59) studying on sustained release lithium sulfate tablets, using hydrophilic matrices. Korsmeyer et al. (28) reported that compression pressure on the same system at pressures ranging from 28 $MN.m^{-2}$ to 280 $MN.m^{-2}$ showed some effect on the release rate. This effect was particularly marked during the first 4h of release and could be ascribed to entrapped air. Removal of the air prior to release restored the traditional $t^{1/2}$ behavior.

Farhadieh et al. (8) studied the drug release from methyl acrylate-methyl methacrylate copolymer matrix. They showed that the hardness of the tablet appears to have little effect on the release-rate constant. This can be attributed to compensating effects from tortuosity and porosity. Goodhart et al. (60) indicated that compression force was not a major factor effecting release of a water-soluble drug from a wax matrix tablet (Fig.11).

Several other reports have been presented on the effect of compression force on drug release from matrix tablets.Aerde et al. (47) indicated that the influence of compression force on drug release was important during the first four hours for theophylline sustained release tablets prepared by modified starches as matrices. Similar results were obtained by Brossard et al. (61).

Tablet Shape

Influence of shape factors on kinetics of drug release from matrix tablets were investigated by several workers (62-69). Higuchi was the first (4) to derive an expression describing the release of drug through a unit tablet surface. The basic Higuchi equation

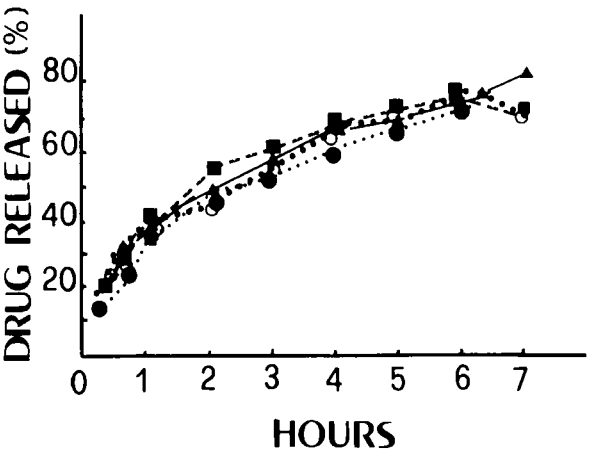

FIGURE 11

Effect of compression force on release profiles of phenylpropanolamine from wax matrix tablets. Key: ●, 226.8 kg; ○, 453.6 kg; ▲, 544.3 kg; ■, 907.2 kg (60).

(Eq.2) may be adapted, to describe drug release from cylindrical tablets (64), to

$$f_t = k_H (t^{1/2} - t_o^{1/2}) \qquad \text{(Eq.17)}$$

where f_t is the fraction of drug released at time t and k_H is the Higuchi release rate constant for drug release from a single planar surface tablet of constant area. It may be shown that the Higuchi rate constant is equal to

$$k_H = \frac{1}{(W_o/V)\, H_o} \left[\frac{D\, \varepsilon\, C_s}{\tau} \left(\frac{2W_o}{V} - \varepsilon C_s \right) \right]^{1/2} \qquad \text{(Eq.18)}$$

where H_o is the initial thickness of the tablet.

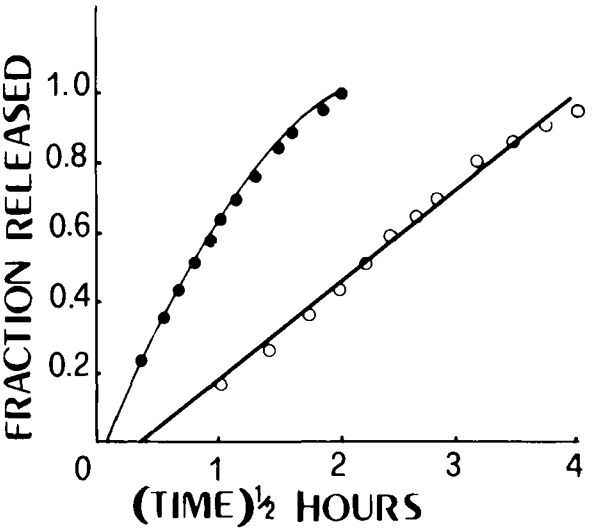

FIGURE 12

Fraction of sodium salicylate released (ft) for all-surface and one-planar-surface cylindrical tablets having a matrix: drug ratio of 3:2 at a dissolution fluid pH of 3.0. Key: (●) all-surface tablets; (○) one planar-surface tablets (64).

Jambhekar et al. (65) derived cubic equations describing the release of drug through all surfaces of a slow-release tablet. For a cylindrical tablet, the fraction of drug released at time t is given by:

$$f_t = (q + 2)\, k_r\, (t^{1/2} - t_o^{1/2}) - (2q + 1)\left[k_r\, (t^{1/2} - t_o^{1/2})\right]^2 + q\left[k_r\, (t^{1/2} - t_o^{1/2})\right]^3 \qquad \text{(Eq.19)}$$

where k_r and t_o are the computer-determined release rate constant and lag time, respectively. Higuchi rate constant (k_H) and the release rate constant (k_r) inherent in the cubic equation for cylindrical tablets:

$$k_H = \frac{qk_r}{2} \qquad \text{(Eq.20)}$$

where q is the ratio of initial tablet diameter to thickness. Examples of influence of shape factors on kinetics of drug release from matrix tablets are shown in Fig.12. Inspection of the profiles suggests that the data were fitted adequately by the cubic equation (Eq.19) when the entire tablet surface was exposed to the dissolution fluid and by the linear equation (Eq.17) when only one planar surface was exposed.

Accordingly, tablet formulation can proceed in a systematic manner by utilizing tablet shape to adjust drug release to the desired rate. Furthermore, the relationship between the two rate constants (k_H and k_r) indicates that both may be described in terms of basic physicochemical properties, such as tablet porosity and tortuosity and drug solubility and diffusion coefficient. It may be shown, by combining eq 18 and 20, that

$$k_r = \frac{1}{(W_o/V)\, r_o}\left[\frac{D\,\varepsilon\, C_s}{\tau}\left(\frac{2W_o}{V} - \varepsilon\, C_s\right)\right]^{1/2} \qquad \text{(Eq.21)}$$

where r_o is the initial radius of a cylindrical or biconvex tablet. Therefore, the release of drug from a cylindrical or biconvex tablet may be predicted from fundamental parameters.

CONCLUSIONS

Technological factors influencing release from sustained release matrix tablets could be stated as; choice of polymer as

matrix material, polymer concentration, viscosity of polymers and viscosity grade, drug loading, formulation additives, channeling agents, shape factors. Especially no significant difference was observed in drug release patterns from hydrophilic matrix tablets of differing density and different hardness.

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