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THE RELATIONSHIPS OF RATE AND KINETICS OF RELEASE OF THEOPHYLLINE FROM A NEW MATRIX TABLET FORMULATION WITH CONTENT OF RELEASE CONTROL AGENT

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ABSTRACT

Theophylline tablet formulations containing 0.48-14.69% of glyceryl stearate as release control agent (RCA) were prepared and evaluated. The rate of release of theophylline from the tablets decreased as RCA level was increased and relative values have been expressed as a nonlinear dissolution coefficient, K, representing the fractional release after 1h. Over the range considered, K is proportional to concentration$^{-\frac{1}{2}}$ of RCA ($r=0.955$, $p<0.001$). Kinetics representing the mechanism of release also change with increasing RCA level: at low levels of RCA, dissolution follows cube-root kinetics, but at higher RCA levels, the process is

diffusion-controlled. These kinetics are related to values of the nonlinear dissolution exponent, n, which shows a proportionality with concentration^{-1} of RCA ($r=0.899$, $p<0.001$). These findings are discussed in relation to recently reported theoretical values of n.

INTRODUCTION

The formulation of controlled-release (C/R) solid dosage forms continues to be of interest, particularly where high levels of therapeutically active drug substances are to be incorporated. Many such systems have been described in the literature, often utilising lipid materials as release-control agent (RCA). Goodhart[1] described the release mechanism from a typical wax matrix formulation and stated that this took place by a diffusion process. Drug release is thought to occur from dosage forms of this type by uptake of the surrounding dissolution medium through channels, followed by solution of the drug substance and diffusion in the reverse direction of dissolved drug. Broadly similar processes would appear to take place both *in vitro* and *in vivo*. Schroeder *et al*[2] showed that interactions did not take place between either tripellenamine or tolazoline hydrochlorides with a wax matrix base which would be expected to result in dissolution rates substantially faster than those of the pure drug substances as had been reported earlier for binary mixes of these substances with urea [3,4] and, indeed, went on to show that when the combinations of tripellenamine or tolazoline with lipid matrices were compressed into tablets, retardation of the release was evident[5].

The presence of surfactants was shown to increase dissolution rates in a manner related to their aqueous solubility: the increased rates suggested that these agents make further channels available and increase the overall effective porosity of the matrix. Povidone has also been shown to increase release rates[6], presumably by a similar process when incorporated into a matrix system, but the opposite effect was apparent when the material was present in the dissolution medium, due to increases in viscosity resulting in reduced rates of liquid penetration.

Each of the formulations referred to above was prepared by the so-called 'hot-melt' process, where drug is dispersed in the molten base; the drug-wax base mixture is then chilled, broken up and compressed to form tablets. The use of both this and a solvent evaporation process were reported by Said[7] who showed that the insoluble, but strongly hydrophilic material, microcrystalline cellulose, could also be used to accelerate dissolution by increased channelling of the matrix, with drug release over a substantial range following the diffusion-controlled matrix model proposed by Higuchi[8].

$$Q=\left[\frac{D\,\epsilon}{\tau}\,(2A-Cs)-Cs.t\right]^{\frac{1}{2}} \qquad \text{.....(Eqn 1)}$$

where Q is the amount of drug released per unit area of tablet exposed to drug solvent

D is the dissolution coefficient of the drug in the permeating fluid

ε is the porosity of the matrix

γ is the tortuosity of the matrix

A is the concentration of drug in the matrix

Cs the solubility of drug in the dissolution medium

t is time.

Where A is large in relation to Cs, it is possible to simplify this equation to:

$$Q=Kt^{\frac{1}{2}} \qquad \text{.....(Eqn 2)}$$

Alternatively, the equation may be expressed as

$$M_t/M_f = Kt^{\frac{1}{2}} \qquad \text{..... (Eqn 3)}$$

where M_t/M_f represents fractional release, M_t=mass of drug released at time, t and M_f = final mass of drug released from the C/R dosage form and adequately represents the release data when a matrix diffusion controlled release process is occurring.

This situation, where the exponent term n = 0.5, however, represents only one of the possible release mechanisms. Where, for example, the fraction released in the dissolution test procedure is directly related to time, viz. $M_t/M_f=Dt+C$; where D is the dissolution rate (fraction released/min) and C is a constant[9], an equation of the general type indicated above, but with the exponent term n = 1, can also be applied to the data for such a zero-order releasing system. There seems no a priori reason why other values of the exponent term, n, should not be possible to give simple equations adequately representing alternative

mechanism of drug release, or to characterise the net situation where a number of processes are occurring simulataneously.

A number of recent reports cite the use of simple equations, such as Eqn 3 but there has been confusion regarding the meanings of the various terms. de Haan and Lerk[10] report the use of the equation in relation to the dissolution of their megaloporous system, but refer to the exponent term as indicative of release rate, rather than its mechanism.

Peppas[11], however, reports the use of the equation to describe drug release from polymers and predicts that the fractional release of drug is exponentially related to time. He states that when n=0.5, Fickian diffusion is observed and the transport rate of drug from the system is proportional to $t^{\frac{1}{2}}$. This is representative of a system where release is entirely dependent on diffusion of drug solution out of the matrix as described earlier by Higuchi[8].

Subsequently, Ritger and Peppas[12] have reported mathematical modelling indicating that the equation can be used to adequately describe release of drugs regardless of release mechanism and where pure Fickian release is occurring from tablets, the exponent term, n, has theoretical limiting values of 0.43-0.50 depending on the ratio of tablet diameter to thickness. The same authors[13] have also stated that the equation may be used for those systems

where a moderate degree of swelling takes place, for instance, with a hydrophilic polymer base which is progressively passing from the glassy to a rubbery state.

The use of the equation is clearly attractive in that it simply and readily offers information on likely release mechanisms operative in drug release from a C/R system.

It does appear, however, that the equation has further utility, particularly in the industrial context, where comparative release data may be generated on a number of formulations in order to optimise the release characteristics of a proposed new product. The usefulness of the constant term, K, appears to have been overlooked previously in this context. At first sight, it does seem that comparison of the K terms from a number of formulations might be difficult, particularly where the n terms differ, because of the differing units then attributable to K. However, further consideration indicates that where t=1, for instance in dissolution studies on C/R formulations after 1 h, then the influence of the exponent term ceases to have any effect and K represents the fraction released at unit time. Thus, systems having relatively high release rates would be expected to have relatively high values of K; those with relatively lower release rates should have correspondingly low values of K and we have shown previously that this is so[14] and also that there is an inverse relationship between K and time to specified fractional release of drug.

In the drug-lipid base matrix systems referred to previously, relatively low drug concentrations (32.7-53.5%, by weight) have been achieved. Formulations recently reported by Lockwood, et al[15] also contain high lipid RCA levels, which preclude the production of satisfactorily small tablets containing active drug substances employed at high dosage levels. An alternative method of producing wax matrix tablets has been described[16] incorporating only about 7% of release control agent (RCA). The objectives of the studies reported here were, firstly, to determine the range of applicability of this system and secondly, to determine the usefulness of the K term, as defined above, to express comparative drug release rates together with a consideration of the release kinetics of the formulations.

MATERIALS AND METHODS

Tablets containing theophylline (Boehringer Ingelheim; 96.4% to 82.3% by weight expressed as % of final tablet composition (w/w)) were made by mixing the active ingredient with polyvinylpyrrolidone (Sigma; 2.6% (w/w)) and glycerol stearate (Precirol WL-2155; Gattefosse; 0-14.69% (w/w), respectively) by the matrix granulation process described previously[16]. The wet granule formed was tray-dried at 45°C overnight and the resulting dry granulate screened through an 850μm stainless steel sieve[17] and blended with 0.8% w/w of magnesium stearate (B.D.H.) as lubricant. Tablets were compressed from these granules using a Manesty F3 single punch machine fitted with circular normal concave punches.

Release patterns of replicate single tablets were determined by solution rate tests at 37°C ± 0.1°C using Apparatus 2 of the United States Pharmacopoeia[18] utilising acidic, followed by neutral pH dissolution media, as indicated below:

(a) pH 1.2: 85ml hydrochloric acid (36.5% w/w) diluted to 1000ml with distilled water.

(b) pH 6.8-7.0: 0.5g of disodium hydrogen orthophosphate (anhydrous) and 0.3g potassium dihydrogen orthophosphate were dissolved and diluted to 1000ml with distilled water.

10ml samples were taken at intervals during the solution rate tests, filtered through 0.45µm cellulose acetate membrane filters to remove particulate matter, suitably diluted with 0.1M hydrochloric acid and analysed for theophylline content by ultraviolet light absorption at the wavelength of maximum absorption at 270 nm, vs an appropriate blank. Samples taken from dissolution vessels were immediately replaced with equivalent volumes of the relevant buffer maintained at 37°. Drug release results have been expressed as the fraction (M_t/M_f) of the total content of theophylline expected from the formulation, related to the weight of the individual tablet tested.

RESULTS AND DISCUSSION

Dissolution tests on replicate tablets of each of the formulations considered gave curvilinear relationships

TABLE 1

The Relationship of the Nonlinear Dissolution Coefficient, K, and Nonlinear Dissolution Exponent, n, with Content of Release Control Agent

RCA Content (% w/w)	Nonlinear dissolution coefficient, K			Nonlinear dissolution exponent, n		
	mean	lower 95% confidence limit	upper 95% confidence limit	mean	lower 95% confidence limit	upper 95% confidence limit
0.48	0.224	0.212	0.236	0.691	0.628	0.753
1.01	0.209	0.176	0.243	0.640	0.514	0.767
1.36	0.202	0.187	0.216	0.504	0.486	0.523
3.33	0.204	0.194	0.213	0.493	0.457	0.530
6.44	0.148	0.132	0.163	0.505	0.464	0.547
9.36	0.135	0.120	0.150	0.525	0.474	0.577
12.11	0.131	0.121	0.142	0.508	0.493	0.524
14.69	0.137	0.126	0.148	0.461	0.449	0.474

representing the fraction of drug released vs time. The release data from each individual tablet was fitted to the exponential release model, Eqn 3.

Mean values of K, referred to as the nonlinear dissolution coefficient and n, referred to as the nonlinear dissolution exponent, ±95% confidence limits, together with mean values of the relevant determination indices, r^2, are given in Table 1.

The relationship of K, the nonlinear dissolution coefficient, with content of RCA was investigated by regression analysis

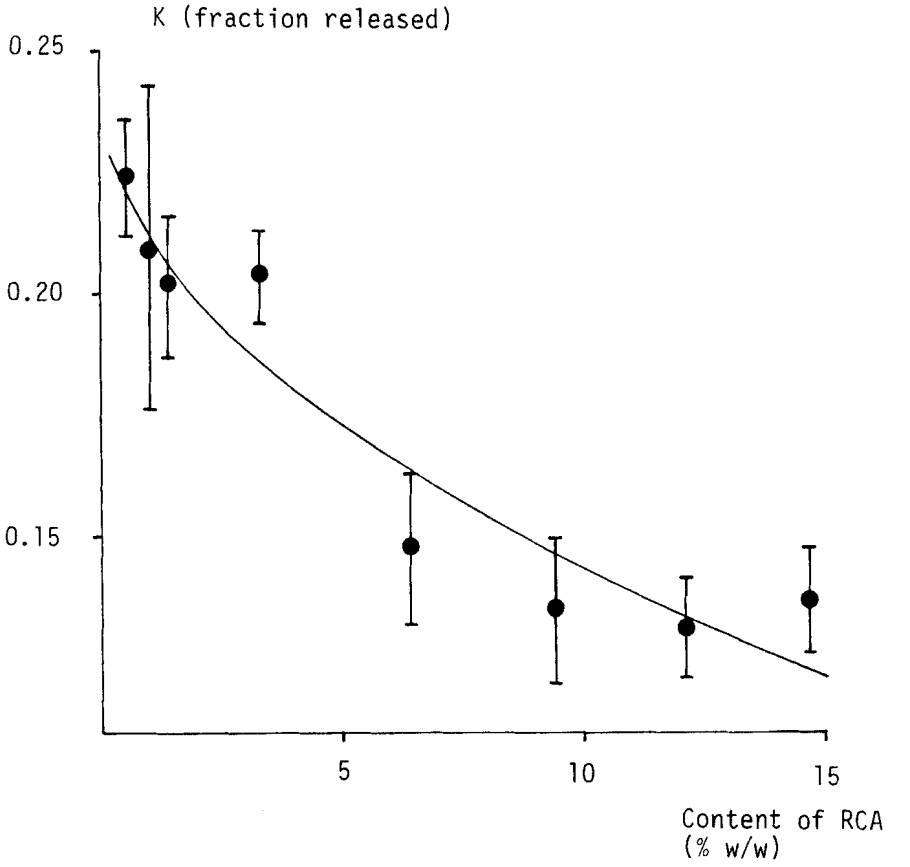

FIGURE 1

The Relationship of Nonlinear Dissolution Coefficient, K (mean ± 95% confidence limits), with content of Release Control Agent (% w/w)

employing the method of least squares: the best fit was apparent with the relationship K is proportional to concentration$^{-\frac{1}{2}}$ of RCA ($r=0.955$, $p<0.001$) and is shown in Figure 1. This high level of correlation representing the relationship between K and the level of RCA is indicative of the predictive value of K in relation to

the level of RCA required to achieve predetermined release characteristics. The line indicating the relationship represents the least squares best-fit taking account of all individual replicate data points making up the mean values indicated.

It is also apparent from Table 1 that the values of the exponent term, n, tended to be higher at low RCA levels, and conversely, appeared to be somewhat lower at high levels of incorporation of RCA, indicating that not only does the level of RCA have an effect on release rate (as expressed by comparative K values) but also has an effect on the kinetics of release. The exact relationship on n with RCA level was therefore also investigated by regression analysis and it was found that n shows proportionality with concentration^{-1} of RCA, as shown in Figure 2, confirming the original overview of the data, ($r=0.899$, $p<0.01$). The line indicating the relationship represents the least squares best-fit taking account of all individual replicate data points making up the mean values indicated.

Evidenced by the change in n values with concentration of RCA, it is apparent that release kinetics change as the RCA level is increased. In order to investigate this further, the release data from replicate tablets of each of the formulations was fitted to models representing zero-order, Higuchi square-root of time, or Hixson-Crowell[19] cube-root kinetics, indicative of release mechanisms related solely to time, drug diffusion or its solution

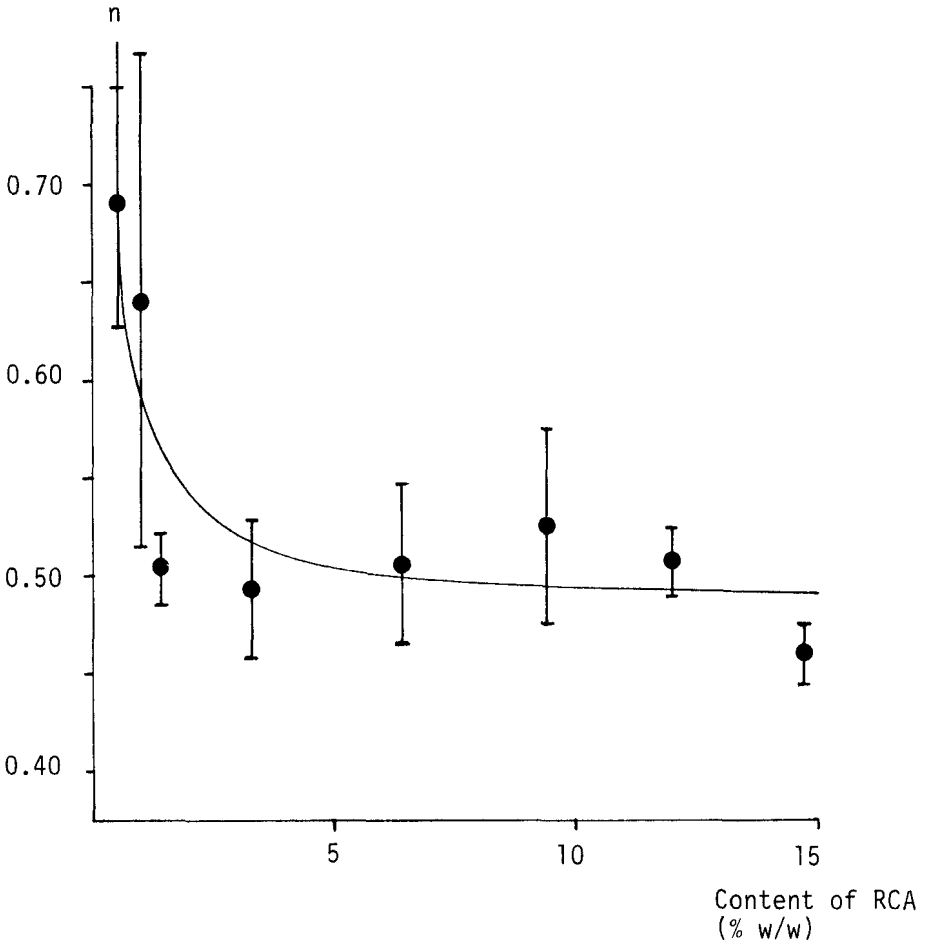

FIGURE 2

The Relationship of Nonlinear Dissolution Exponent, n (mean ± 95% confidence limits), with content of Release Control Agent (% w/w)

rate, respectively. These three possible processes are considered to be those which may exert rate-limiting steps in the overall process of drug release from the tablets.

The determination index, r^2, and respective Student t values were calculated for each of the relationships and arranged into

TABLE 2

The Relationship of the Nonlinear Dissolution Exponent, n, with Independently Assessed Dissolution Kinetics

RCA content (% w/w)	Nonlinear dissolution exponent, n	Independent best-fit to kinetics		
		model	r^2	t
0.48	0.691	Cube-root	0.9911	10.55
1.01	0.640	Cube-root	0.9838	7.79
1.36	0.504	Cube-root	0.9833	7.67
3.33	0.493	Higuchi sq-root	0.9661	5.34
6.44	0.505	Higuchi sq-root	0.9953	14.55
9.36	0.525	Higuchi sq-root	0.9982	23.55
12.11	0.508	Higuchi sq-root	0.9965	16.87
14.69	0.461	Higuchi sq-root	0.9972	18.87

order of best fit according to t values (which may be compared directly, since numbers of replicates were the same and conversion to p values results in lack of precision, since all r values were high). The goodness of fit for each possible kinetic model was verified by plotting residuals: none of the relationships showing the highest determination index value gave a plot of residuals with any obvious visible pattern indicating that no systematic error was present in these assessments. The values of n, together with the best-fit relationship from the possible kinetics models chosen together with respective determination indices and Student t values are given in Table 2.

From the results in Table 2, it can be seen that at low levels of incorporated RCA, values of the exponent are relatively high and correspond with independent assessments of kinetics indicating that theophylline release is occurring by a cube-root law controlled process. Visual examination by low-power microscopy of tablets with RCA levels of less than 3% shows that, in essence, an erosion process is taking place. The content of RCA is sufficient to hold the drug in a single non-disintegrating unit as dissolution proceeds, but the surface is seen to be eroded and theophylline crystals are thus "held" at the surface of the dissolving unit dose form while dissolution takes place at the crystal surfaces. As the process continues, fresh surfaces are exposed and dissolution continues until the unit becomes exhausted.

It is interesting to note, that while the "model" column of Table 2 indicates an abrupt change from cube-root to Higuichi diffusion-controlled kinetics with tablets containing more than 3% of RCA, reductions in the values for both the determination index and t are apparent with the independent kinetics assessments over the range 0.48 to 3.33% RCA, indicative of a gradual change in the overall mechanism of release reflected by dissolution kinetics. Clearly, with tablets containing small amounts of RCA, the overall dissolution process from the tablets relates principally to the process of solution at the theophylline crystal surfaces, but as the level of RCA is increased, other processes undoubtedly also

occur with increasing influence on the overall release characteristics from the dosage-form. With the sample containing 3.33% of RCA, the r^2 values relating to the diffusion-controlled, compared with a particle solution rate controlled release process, were 0.9961 and 0.9621, respectively, with corresponding t values of 5.32 and 5.04, indicating that a single choice of operative process is finely balanced.

In circumstances such as this, where it is apparent that no single dissolution process is operating in isolation to act as the rate controlling step, the value of the nonlinear dissolution exponent becomes evident. In the studies reported here, n shows a clear change from values of 0.6, and greater, where dissolution is controlled by the dissolution of the drug itself, to values of 0.5 or less where independent assessment indicates the overall dissolution process to be rate-controlled by diffusion. The n values we have obtained where Hixson-Crowell cube-root law dissolution kinetics obtained are somewhat lower than those reported recently by Franz, et al[20], who obtained values in the range 0.723-.0993 and cube-root model correlations of 0.9884, or better.

However, no formulation series appears to have been reported previously where a change in release kinetics has been related to a specific formulation parameter and where n values have been derived simultaneously. It is interesting to note that exponent

values we have obtained with tablets containing small amounts of RCA fall within the range proposed by Peppas[11] for anomalous (non-Fickian drug tranport mechanism), but that as the level of RCA is increased, diffusion controlled drug transport corresponds well with those proposed for systems where Fickian transport is taking place[11] and closely with the theoretical value (0.46) for tablets having an aspect ratio of 5[12]; the average aspect ratio for tablet formulations reported here was 4.65. Extrapolation using the relationship n α 1/content of RCA, gives exponen values of 0.487-0.484 on introducing hypothetical values of 25-90% of RCA into the formulation: these values also accord well with those proposed for tablets releasing drug by diffusion processes.

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