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CO-SOLVENT SYSTEMS IN DISSOLUTION TESTING: THEORETICAL CONSIDERATIONS.

O.I.Corrigan.
Department of Pharmaceutics, School of Pharmacy, Trinity College,
18 Shrewsbury Rd., Dublin 4. Ireland.

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ABSTRACT

The situation was considered where a co-solvent, added to enhance drug solubility and thus provide sink conditions for a drug, also resulted in a decrease in solubility and hence dissolution rate of a water soluble excipient present in the dosage form. Theory predicted that, in the absence of disintegration, at sufficiently high excipient content and or co-solvent concentration the drug dissolution rate may decrease, release becoming controlled by the now less soluble excipient. Solubility and dissolution studies using tolbutamide and lactose mixtures in water-ethanol mixtures provided results which were reasonably consistent with theory, indicating that the presence of the excipient may greatly reduce the drug dissolution rate below that expected for the drug alone.

INTRODUCTION

A major problem in the dissolution testing of relatively insoluble drugs is the provision of sink conditions. In the case of

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ionizable compounds one may employ a totally aqueous medium by resorting to altering the pH. However alternative strategies must be attempted for non-ionizable drug substances . The addition of a co-solvent which increases the drug solubility in the aqueous based dissolution medium has been employed to provide sink conditions in such cases [1,2]. The method has the attraction that for many drugs, the solubility will increase exponentially with increasing volume fraction (f) of co-solvent:

$$\log Cs = \log Co + (\sigma * f) \qquad 1.$$

where C_s and C_o are the solubilities in the presence and absence of co-solvent respectively and (σ) is the solubilizing power [3]. This type of relationship is likely to occur where the drug substance is more hydrophobic than the co-solvent, a likely possibility in practice. Consequently co-solvent have been employed widely even in Pharmacopeial tests to provide sink conditions[4]. However, anomalously low release characteristics have been reported in co-solvent systems providing sink conditions when compared to release in non-sink media. For example tablets of a low dose chlorthalidone formulation failed the USP XX specification for dissolution in aqueous methanol although the rate of dissolution in water or dilute acid indicated that their dissolution characteristics were satisfactory [1] Similarly Dodge & Gould found that on increasing the co-solvent methanol to 30% the dissolution rate of chlorpropamide tablets

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increased. However a further increase in co-solvent led to a reduction in release rate despite the continuing exponential increase in drug solubility [2]. These effects have been explained in terms of influences of the co-solvent on tablet disintegration [1,2,5]. Little attention has been given to possible effects on the intrinsic dissolution rate, particularly effects on the dissolution rate of the excipients present in the dosage form. In the absence of disintegration, dissolution of the drug may be retarded by reduced dissolution of a water soluble excipient present in the dosage form. The importance of providing sink conditions for an excipient was identified as long ago as 1967 by Levy [6], when he considered the dissolution of acetylsalicylic acid from tablets containing aluminium antacid. If 1% citric acid was added to the dissolution medium an increase in the dissolution of acetylsalicylic acid was obtained. The reason for the effect was the complexation of aluminium by the citric acid thereby providing sink conditions for the excipient. Citric acid had no effect on acetylsalicylic acid tablets which did not contain aluminium salts. Apart from the provision of sink conditions, addition of co-solvent alters the dissolution rate of drug relative to that of excipients.

Highly water soluble excipients are often chosen for dosage forms, particularly those containing a sparingly soluble drug. If such an excipient is more hydrophilic than the co-solvent, then the presence of co-solvent in sufficient concentration in the dissolution medium will result in a decrease in excipient solubility and hence in its dissolution rate. For example the common tabletting diluent,

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lactose, is considerably less soluble in alcohols than in water. In these situations the value of the solubilizing power (σ) for an excipient in a dissolution medium may be negative and hence the excipient solubility decreases exponentially with increasing volume fraction (f) as the drug solubility increases. Under these circumstances, depending on the proportion of excipient in the formulation, drug dissolution in the co-solvent system may become controlled by that of the now less soluble excipient.

THEORY

In order to illustrate the relative importance of excipient content and proportion of co-solvent, the theoretical effect of co-solvent on the dissolution of a simple two component drug-excipient compact may be derived as follows. The effect of co-solvent on the solubilities of drug (C_{sd}) and excipient (C_{se}) assuming the log-linear relationship are

$$C_{sd} = C_{od} * 10^{(\sigma_d * f)} \qquad 2.$$

$$C_{se} = C_{oe} * 10^{(\sigma_e * f)} \qquad 3.$$

where the subscripts d and e refer to the drug and excipient respectively. From the theory for diffusion controlled dissolution of two noninteracting, nondisintegrating components from a compact of constant surface area Higuchi, Mir & Desai (1965) derived the following relationships [7] when the drug forms the surface layer:

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$$G_d = D_d * C_{sd}/h \quad 4.$$

and

$$G_e = N_e * G_d/N_d \quad 5.$$

When the excipient forms the controlling layer:

$$G_e = D_e * C_{se}/h \quad 6.$$

$$G_d = G_e * N_d/N_e \quad 7.$$

where G, D and h are the dissolution rate per unit surface area, the diffusion coefficient and diffusion layer thickness respectively.

Substitution of equations 2 & 3 into Eq 4 & 6 give the following relationships between drug dissolution rate, and co-solvent composition:

$$G_d = (D_d/h) * C_{od} * 10^{(\sigma d * f)} \quad 8.$$

$$G_e = (D_e/h) * C_{oe} * 10^{(\sigma e * f)} \quad 9.$$

Equations 5,7,8 & 9 were used to plot the change in drug intrinsic dissolution rate with increasing co-solvent and increasing excipient content. If the co-solvent increases the solubility of the drug only and has no effect on the excipient(s) then σ_d is positive and σ_e is zero. The model predictions, for a drug of solubility 0.1 mg/ml with a

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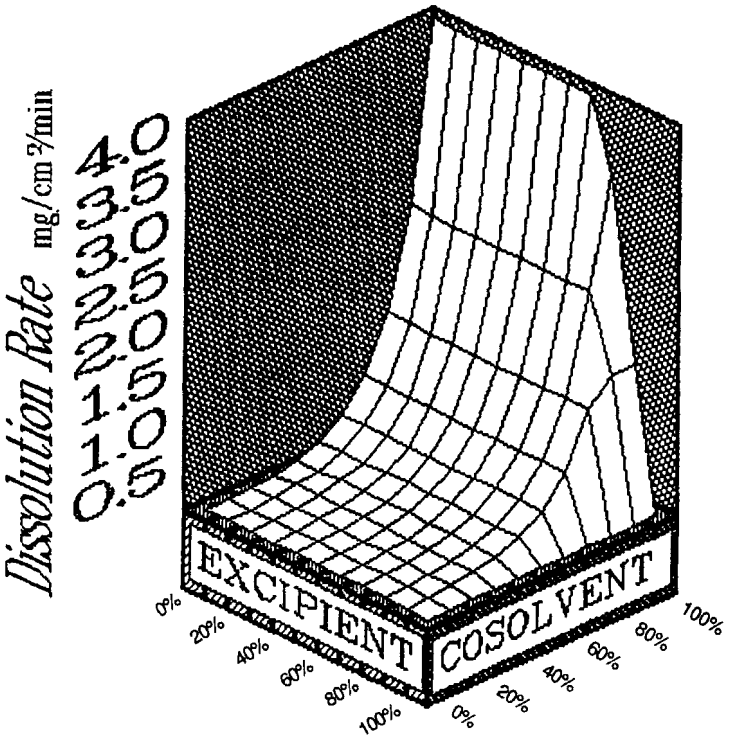

FIGURE 1.

Theoretically predicted dependance of drug dissolution rate on co-solvent concentration from compacts with increasing proportion of soluble excipient. (solubilizing powers: drug = 3, excipient = 0).

solubilizing power of 3.0 in a particular co-solvent, are illustrated in Fig (1). The solubility of the excipient was set at 150 mg/ml and the diffusion layer thickness at 50 x 10^{-4} cm. D_d and D_e were 5 x 10^{-4} and 4.5 x 10^{-4} cm^2/min.respectively. It is evident that under these circumstances, drug dissolution rate increases exponentially and the excipient has little effect on drug dissolution except at high co-solvent concentrations and excipient contents. In the latter circumstances the

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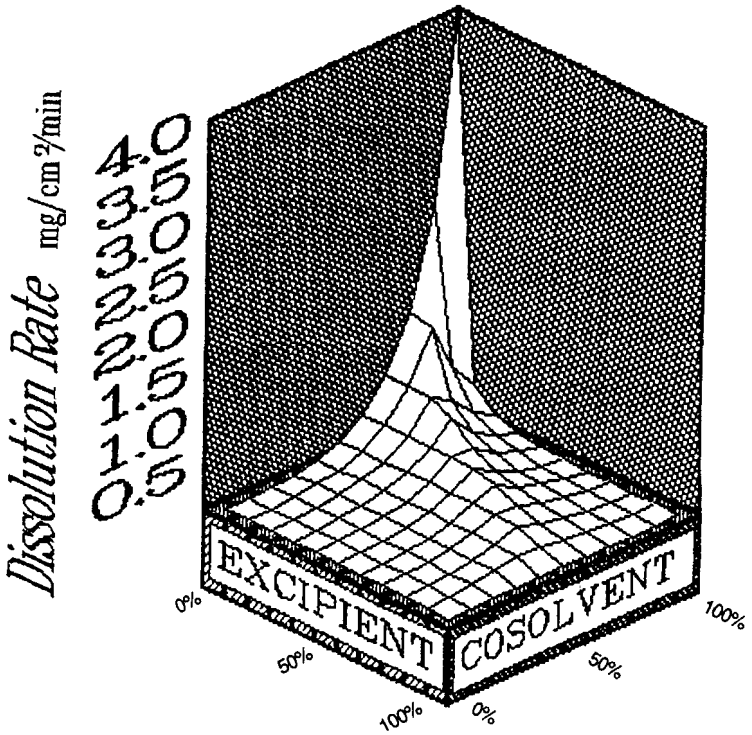

FIGURE 2

Theoretically predicted dependance of drug dissolution rate on co-solvent concentration from compacts with increasing proportion of soluble excipient. (solubilizing powers: drug = 3, excipient = -2.5).

drug solubility approaches that of the excipient and thus situations may arise where dissolution becomes excipient controlled.

The situation where the solubilizing power of the excipient (σ_e) is not zero but negative, eg. -2.5, is shown in Fig (2). At the lower co-solvent concentrations and excipient contents, the model still predicts an exponential increase in the intrinsic dissolution rate of the drug with increasing co-solvent concentration. However above a

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certain co-solvent concentration and excipient content, the critical mixture ratio, the drug dissolution rate declines. This decline in rate reflects the presence of a surface layer of excipient controlling drug dissolution. As the dissolution rate of the drug increases with increasing co-solvent in the dissolution medium, the critical mixture ratio moves to the left ie. towards higher drug content indicating greater dependence of drug release on the excipient dissolution rate. Since the excipient dissolution rate decreases with increasing co-solvent content, a situation is reached when the drug dissolution rate declines and may even reach values lower than the rate in the absence of co-solvent.

In order to explore these possible effects tolbutamide was chosen as a drug of low solubility whose solubility may be increased using ethanol as co-solvent. Lactose was chosen as a typical hydrophilic excipient, the solubility of which is expected to decrease in ethanol.

EXPERIMENTAL

Solubility determinations.

Solubilities of tolbutamide and lactose monohydrate were determined by the ampoule method [8] in a range of water-ethanol mixtures. Samples were filtered and diluted. The drug was assayed based on its UV absorbance and the lactose assayed by the lactose/D-galactose enzymatic method (Biochemica, Boehringer Mannheim

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GMBH). Calibration curves were constructed at each co-solvent mixture level to allow correction for the influence of ethanol on the assay method. The higher drug solubilities were determined gravimetrically.

Dissolution rate determinations.

Compressed pellets (13mm) were prepared from mixtures of tolbutamide and lactose (sub 180um sieve size) to contain 50% of each component. Dissolution profiles were obtained using the USP method (Sotax apparatus 11, paddle method at 75 r.p.m.) in 900 ml of phosphate buffer pH 7.4 , 30%, 50%, 60%, 70% & 90% ethanolic solutions .Samples were taken at 10min intervals for one hour and profiles were linear beyond the first time point.

RESULTS AND DISCUSSION.

The effect of ethanol on the solubility of tolbutamide and lactose are shown in semilog format in Fig 3. Tolbutamide solubility follows a log linear relationship, solubility increasing exponentially with volume fraction of ethanol.The best estimates of C_{so} and σ_d were 0.103 mg/ml and 2.916 respectively. A similar type of relationship was reported for the related compound, chlorpropamide in a binary water-methanol co-solvent system[2].Lactose solubility increased as the ethanol content increased to 20%v/v and then declined , falling below that of tolbutamide at ~ 50% ethanol. A maximum in the lactose

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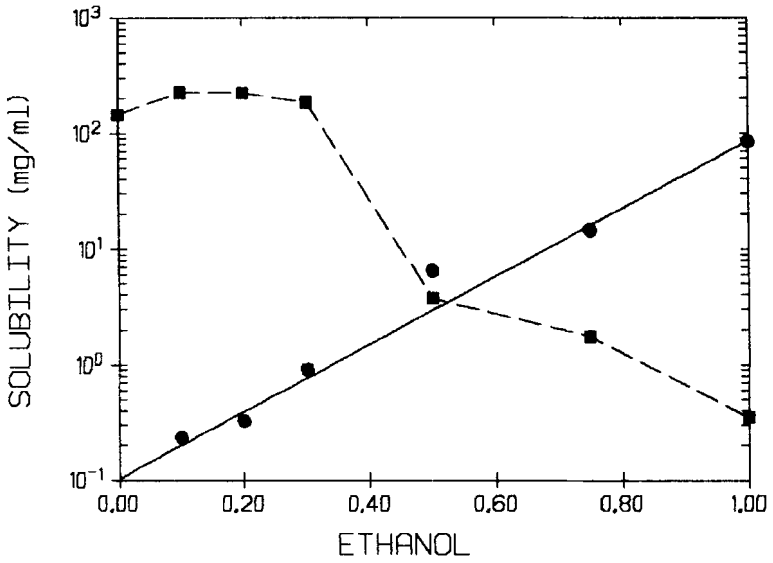

FIGURE 3.

Effect of ethanol volume fraction (v/v) on the solubility of tolbutamide (●) and lactose monohydrate (■).

solubility versus ethanol concentration profile is to be expected if the solubility parameter of the solute is intermediate between those of the two solvents[3]. Solubility parameter estimates for lactose of 19.5 and 17.1 have been reported[9] while values for water and ethanol are 23.4 and 12.55 respectively[10]. It is evident from Fig 3 that in the co-solvent concentration range where the excipient lactose is likely to retard drug dissolution the solubilizing power (σ_e) is negative, having a value of the order of -2.77.

During dissolution the drug excipient compacts maintained their original shape, underwent little detectable disintegration and

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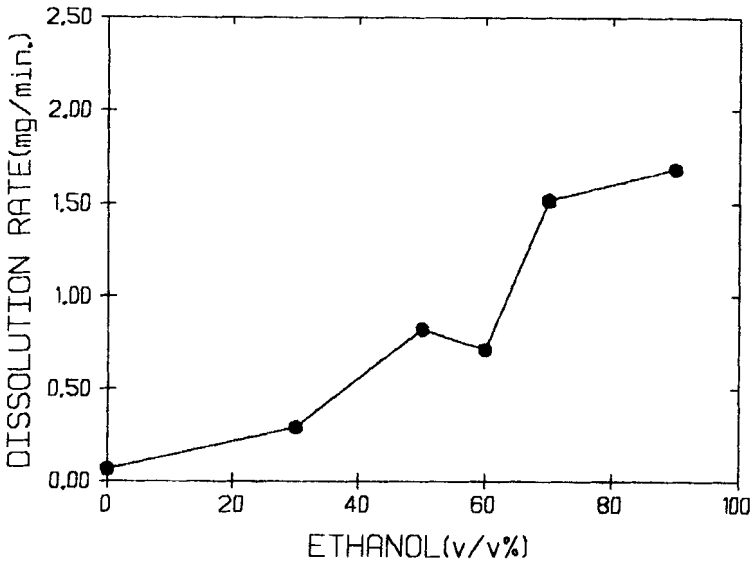

FIGURE 4.

Effect of ethanol concentration on the dissolution rate of tolbutamide from 1:1 compacts containing lactose monohydrate.

gave linear dissolution profiles beyond the first sampling point. The drug dissolution rates estimated from these profiles are plotted versus co-solvent content in Fig (4). The dissolution rate increased as the ethanol content increased up to 50%. A lower rate was observed in 60% ethanol. At higher ethanol contents further increases in rate were observed. In order to compare the results with the predictions of the model the dissolution rate in co-solvent relative to the rate in the absence of co-solvent, ie the relative dissolution rate (G_{rel}), was plotted versus co-solvent concentration (Fig 5). Fig (5) includes the curve of the rate predicted from theory assuming no influence on drug dissolution from the excipient. In this case the relative rate should

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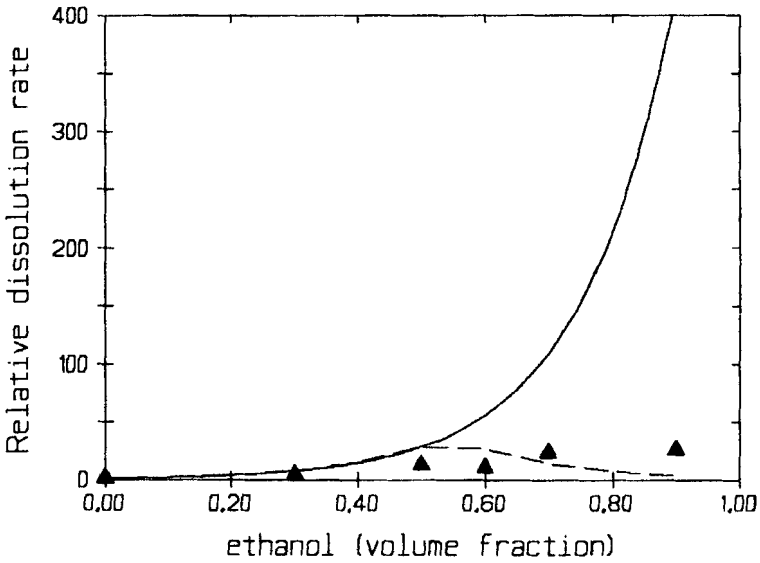

FIGURE 5.

Effect of co-solvent on the relative dissolution rate (G_{rel}) of tolbutamide.Key: experimental values: ▲, predicted curve assuming cosolvent only increases drug solubility: continuous line, predicted curve assuming solubilizing powers of 2.92 and -2.77 for drug and lactose respectively: broken line.

increase exponentially. Also included in Fig (5) are the predicted rates derived from the nondisintegrating two component noninteracting model, which takes into account the contribution from the decrease in solubility of the excipient. In this case the drug rate should mirror the increase expected for the pure drug up to an ethanol content of 50% and then decline. The experimental values are much closer to the latter predictions.The increase in dissolution rates beyond 60% ethanol concentration may reflect some disintegration of the compacts at the higher co-solvent concentrations. The results are consistent with a

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large inhibiting effect on drug dissolution arising from the reduction in excipient solubility and hence dissolution rate due to the presence of co-solvent.

The results show that, for soluble dosage forms, consideration must be given to the effects of the co-solvent on the solubilities and dissolution rates of the excipients present, when designing media to provide sink conditions. These considerations do not apply however to the use of co-solvents to provide sink conditions for matrix systems where drug release is controlled by solubility and diffusion of drug in the matrix, unless the matrix material becomes soluble in the co-solvent.

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