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Mechanism of drug dissolution rate enhancement from β-cyclodextrin-drug systems

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The influence of β-cyclodextrin on the physicochemical properties of bendrofluazide, chlorothiazide, hydrochlorothiazide and hydroflumethiazide was investigated using solubility, X-ray powder diffraction, differential scanning calorimetry (DSC) and intrinsic dissolution rate methods. The solubility of each drug was enhanced in the presence of β-cyclodextrin, the effect being greatest with bendrofluazide. X-ray diffraction data on equimolar freeze dried systems indicated the formation of a solid state inclusion complex only in the case of bendrofluazide. The relative increase in initial dissolution rate of drug from freeze dried systems varied from sixty fold for bendrofluazide to three fold for hydroflumethiazide. The observed dissolution rates were intermediate between those predicted by the classical two component soluble complex model and a carrier controlled model. It was concluded that the enhanced drug dissolution rates, which are above those predicted by the soluble complex model, are due to an extension of carrier phase dissolution control to higher drug weight fractions than predicted by the soluble complex model and that this was a consequence of the disparate solubilities of the carrier and drug.

β-Cyclodextrin (βCD) forms inclusion complexes with various drugs in solution (Lach & Cohen 1963) and in the solid state (Kurozumi et al 1975). These complexes, which can be formed easily by a freeze drying process (Kurozumi et al 1975), can increase drug solubility (Lach & Cohen 1963), dissolution rate (Hamada et al 1975), absorption rate (Frömming & Weyermann 1973; Nambu et al 1978) and may thus result in a potentiation of pharmacological activity (Uekama et al 1979).

Although the enhanced dissolution properties of drug-βCD complexes may be due to the formation of a complex in the solid state, or to the properties of the freeze dried system, studies using phenobarbitone βCD systems suggested that the enhanced dissolution rates observed were in agreement with those predicted assuming the formation of a soluble complex in solution (Corrigan & Stanley 1981).

In order to explore the more general applicability of this mechanism we have prepared, and examined the dissolution properties of, a number of benzothiadiazine 1–1, dioxide-βCD freeze dried systems. The drugs used were bendrofluazide, chlorothiazide, hydrochlorothiazide and hydroflumethiazide.

MATERIALS AND METHODS

Solubility determinations

The influence of βCD on drug apparent solubility was determined by a method similar to that of Shefter & Higuchi (1963).

X-ray diffraction and infrared analysis

Powder X-ray diffractometry was carried out using a Philips PW 1050/25 diffractometer employing nickel filtered copper radiation. A Perkin-Elmer 157 sodium chloride infrared spectrophotometer was used for infrared analysis of samples by the KBr disc method.

Differential scanning calorimetry (DSC)

Samples, approximately 4 mg, were examined using a Perkin-Elmer Model DSC 1B differential scanning calorimeter, at a scanning speed of 16 K min^{-1} in the range 300 to 600 K.

Preparation of βCD-drug systems

βCD (Teijin Ltd, Tokyo, Japan) was recrystallized from water and dried over phosphorus pentoxide under vacuum to constant weight. The water content was estimated at 7·7% by the Karl Fisher method. Chlorothiazide, hydrochlorothiazide (Merck Sharp & Dohme Ltd Herts), hydroflumethiazide and bendrofluazide (Leo Laboratories Ireland Ltd), all to B.P. specifications, were used as received. Equimolar freeze dried systems were prepared by freeze drying (Kurozumi et al 1975) using a Quick Fit (MF 45) Lyophiliser.

The βCD-drug physical mixtures were prepared from sub 180 μm sieved powders.

* Correspondence.

Assay procedures

Bendrofluazide (273 nm), chlorothiazide (279 nm), hydrochlorothiazide (273 nm) and hydroflumethiazide (273 nm) were assayed from linear Beers Law plots. βCD was assayed by anthrone colorimetry as previously described (Corrigan & Stanley 1981), no interference due to the presence of drug being evident.

Dissolution rate determinations

The methods employed for the preparation of constant surface area discs and dissolution rate determinations were outlined previously (Corrigan et al 1979). The dissolution medium, 400 ml distilled water at 37 °C, was sampled at 2·5 min intervals for up to 20 min.

RESULTS AND DISCUSSION

The solubilities of bendrofluazide, chlorothiazide, hydrochlorothiazide and hydroflumethiazide increased with the addition of βCD in the range 0–11 × 10^{-3} M (Fig. 1). Apparent stability constants K, assuming the formation of a 1:1 complex in solution, were calculated according to equation 1.

$$K = \frac{S}{C_s(1 - S)} \quad (1)$$

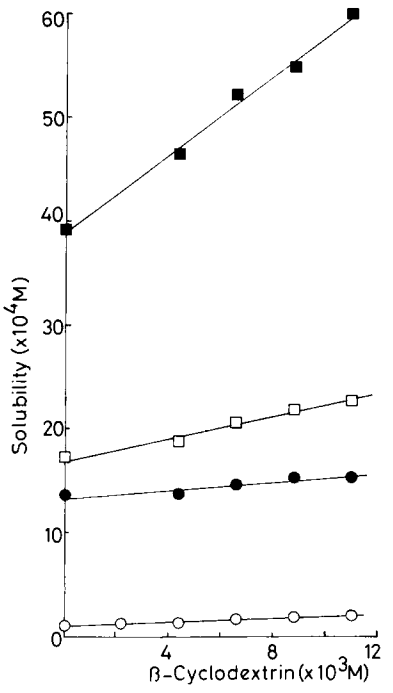

FIG. 1. Apparent solubilities (37 °C) of ○, bendrofluazide; ● chlorothiazide; □ hydroflumethiazide and ■, hydrochlorothiazide in βCD solutions.

where S is the slope of a plot of drug solubility versus βCD concentration and C_s is the drug solubility (Higuchi & Connors 1965). The estimates of K obtained using equation 1 ranged from 80·5 M^{-1} for bendrofluazide to 13·8 M^{-1} for chlorothiazide (Table 1). These values are lower than that obtained previously with phenobarbitone and are in the lower range of those reported by Hamada et al (1975) for some βCD-anti-inflammatory drug systems. The increase in solute solubility with the addition of βCD is generally considered to be mainly due to the formation of inclusion compounds (Schlenk & Sand 1961; Hamada et al 1975). However other interactions may be involved (Cohen & Lach 1963).

Table 1. Drug solubilities and drug-βCD apparent 1:1 stability constants.

Drug	Solubility (C_s) (M × 10^{-3})	Stability constant (K) (M^{-1})
Bendrofluazide	0·107	80·5
Chlorothiazide	1·49	13·8
Hydrochlorothiazide	3·90	58·5
Hydroflumethiazide	1·69	32·4

X-ray diffraction patterns of βCD-bendrofluazide systems are shown in Fig. 2. Two broad peaks at 4·7 and 7·1Å are evident in the freeze dried system. Kurozumi et al (1975) reported the presence of similar diffraction peaks at interplanar distances 7·2–7·7 and 4·8–5·0Å in freeze-dried inclusion complexes of 13 different drugs. Earlier Takeo & Kuge (1969) observed two such peaks in βCD-propyl alcohol and βCD-anthracene complexes. Both groups of workers attributed these broad peaks to the cylindrical structure of βCD, the 'guest' molecule being included in the 'host'. These results suggest that the freeze dried βCD-bendrofluazide system may be an inclusion complex. Alternatively, the data might be explained solely in terms of the formation of amorphous drug on freeze drying with βCD.

The chlorothiazide-βCD freeze dried system exhibited lower crystallinity than the corresponding mechanically mixed system; however, characteristic chlorothiazide peaks were still evident. The X-ray scans of both hydroflumethiazide and hydrochlorothiazide freeze dried systems were similar to corresponding mechanical mixtures.

The DSC curve of βCD showed two endotherms at 375 and 580K, the former corresponding to loss of H_2O the latter to decomposition. Bendrofluazide melted giving an endotherm at 500K which was also present in the mechanical mixture but not in the

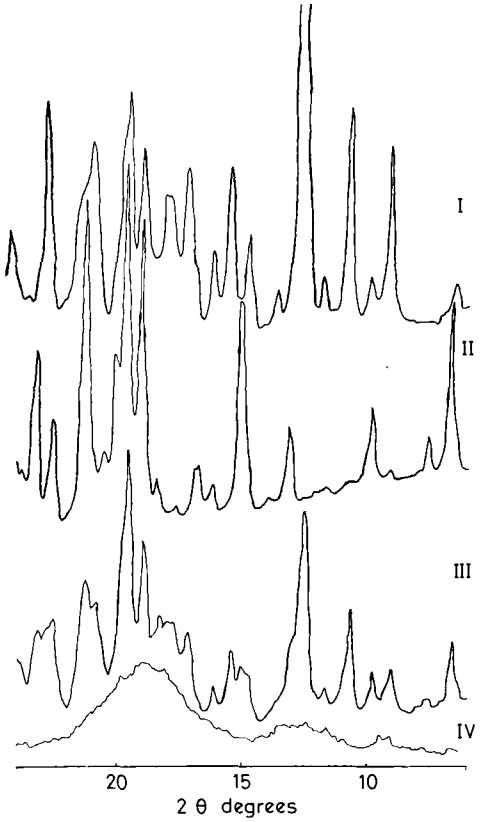

FIG. 2. X-ray diffraction patterns of βCD 1, bendrofluazide II, equimolar βCD-bendrofluazide physical mixture III and equimolar βCD-bendrofluazide freeze dried system IV.

freeze dried system. An endotherm at 525K was, however, evident in the latter system, Fig. 3, strongly suggesting the presence of a solid state complex on freeze drying. The hydrochlorothiazide-βCD and hydroflumethiazide-βCD freeze dried systems had thermograms similar to corresponding mechanical mixtures, a pure drug peak being present. Chlorothiazide-βCD freeze dried and mechanical mix systems also gave similar thermograms; however these systems decomposed below the melting/decomposition points of either component. The DSC results suggest therefore that an inclusion complex, in the solid state, is formed with βCD on freeze drying by bendrofluazide but not by hydroflumethiazide, hydrochlorothiazide or chlorothiazide. The greater propensity of bendrofluazide, the 3-benzyl derivative, to interact with βCD both in the solid state and in solution is likely a consequence of the good fit of a phenyl ring within the βCD cavity (Thakkar & Demarco 1971). Apart from the changes in peak resolution consistent with a decrease in crystallinity, no significant differences were observed on comparing infrared spectra of freeze dried and corresponding mechanically mixed drug-βCD systems (Fig. 4). Although changes in spectra of some βCD inclusion complexes, e.g., those formed with compounds containing C = O groups (Kurozumi 1976) have been reported, the use of infrared spectroscopy for examining βCD complexes is usually of limited value (Szejtli 1978).

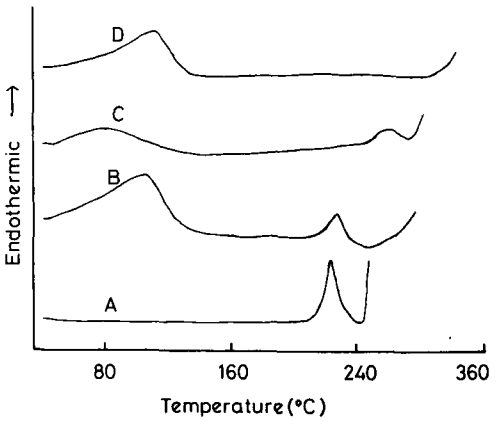

FIG. 3. DSC thermograms of bendrofluazide—βCD systems. A, bendrofluazide; B, equimolar physical mix; C, equimolar freeze dried and D, cyclodextrin samples.

Dissolution profiles for bendrofluazide-βCD systems are shown in Fig. 5. Drug-βCD systems, particularly mechanical mixtures, tended to disintegrate during dissolution from compressed discs of constant surface area, the slope of amount released versus time profiles becoming positive. The freeze

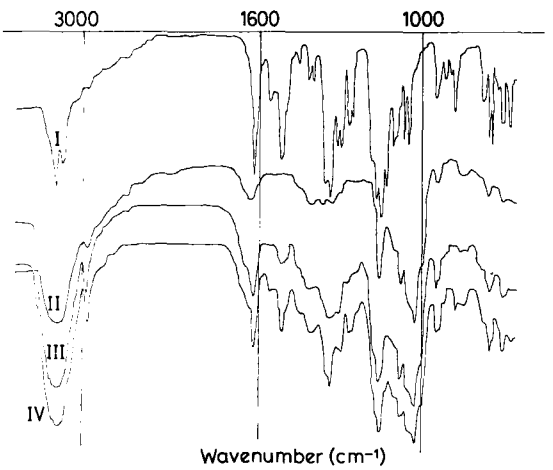

FIG. 4. Infrared absorption spectra of I, bendrofluazide, II, βCD; III, equimolar freeze dried and IV, equimolar physical mix samples.

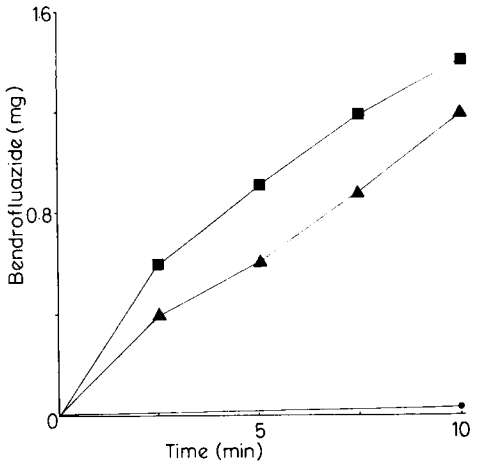

FIG. 5. Dissolution profiles from compressed discs of bendrofluazide ●, equimolar βCD-bendrofluazide physical mixture ▲ and equimolar βCD-bendrofluazide freeze dried system ■.

dried systems, with the exception of hydroflumethiazide which disintegrated readily, gave dissolution profiles whose slopes declined with time, suggesting the recession of a boundary layer of one phase of a two component system (Higuchi et al 1965; Corrigan & Stanley 1981). To compare drug release properties and minimize any possible contribution from surface flaking, apparent initial dissolution rates per unit disc surface area were estimated from the amount dissolved at the first sampling time. Data for the thiazide-βCD systems and for the pure drugs are summarized in Table 2. The relative increase in drug dissolution rate from the freeze dried systems varied from 60 fold to 3 fold for bendrofluazide and hydroflumethiazide respectively. It is apparent also that, whereas the pure drug absolute dissolution rates varied 36 fold, the freeze dried systems only differed by a factor of two to three. The dissolution rate of βCD from these systems varied over a narrow range (i.e. 1·4 fold) and were in rank order agreement with the drug release rates.

Table 2. Initial dissolution rates of drug and equimolar drug-βCD systems.

	Dissolution rate (mM cm^{-2} h^{-1}) × 10^3		
		Equimolar βCD-drug systems	
Drug	Pure Drug	Freeze dried	Mechanical mix
Bendrofluazide	0·43	25·75	17·2
Chlorothiazide	7·78	64·79	44·6
Hydrochlorothiazide	15·28	56·15	47·1
Hydroflumethiazide	8·51	27·83	25·8

The dissolution rates from equimolar mechanical mix systems were lower (65 to 93%) than those obtained on freeze drying.

The dissolution from two component mixtures forming a soluble complex in solution can be expressed by equation 2 (Higuchi et al 1965) under sink conditions

$$G_{ma} = \frac{D_a C_a^o}{h} + \frac{D_c C_a^o C_b^o . K}{h} \qquad (2a)$$

$$G_{mb} = \frac{D_b C_b^o}{h} + \frac{D_c C_a^o C_b^o . K}{h} \qquad (2b)$$

where G_m is the maximum dissolution rate observed, D_a,D_b and D_c are the diffusion coefficients of the dissolving components a,b, and the complex respectively, C_a^o and C_b^o are the component solubilities and h is the thickness of the aqueous diffusion layer. This equation describes the continuous dissolution from a constant surface for the critical mixture ratio and should according to theory also approximate to the initial dissolution rate at other mixture ratios. The relative enhancement in drug dissolution, i.e. G_m/G_o, can be obtained from equation 3, since the intrinsic dissolution rate of drug (G_o) equals $D_a C_a^o/h$.

$$\frac{G_m}{G_o} = 1 + \frac{D_c C_b^o . K}{D_a} \qquad (3)$$

This equation was applied to the current data, using the following parameter values: $D_c = 4{\cdot}2 \times 10^{-6}$, $D_a = 9{\cdot}5 \times 10^{-6}$ for bendrofluazide and $10{\cdot}3 \times 10^{-6}$ cm^2 s^{-1} for the remaining drugs based on previous reports (Corrigan et al 1979; Corrigan & Stanley 1981); $C_b^o = 31{\cdot}2 \times 10^{-3}$ M (Corrigan & Stanley 1981) and K in each case was determined from the solubility data (Table 1).

Table 3. Predicted and estimated relative initial drug dissolution rates for freeze dried equimolar βCD-drug systems.

	Relative rate		
System	Experimental	Soluble complex*	Molecular† dispersion
Bendrofluazide-βCD	59·9	2·11	204·0
Chlorothiazide-βCD	8·3	1·18	19·1
Hydrochlorothiazide-βCD	3·7	1·74	9·4
Hydroflumethiazide-βCD	3·3	1·41	12·1

* Equation 3.
† Equation 9.

The predicted and observed relative rates are summarized in Table 3, the latter being much higher than predicted. This lack of agreement with theory contrasts with the reasonably good agreement reported previously for phenobarbitone-βCD systems (Corrigan & Stanley 1981).

Higuchi et al (1965) have shown that in the steady state the dissolution rates of two components from a mixture are related by

$$G_a = G_b \frac{N_a}{N_b} \quad (4)$$

On combining equations 4 and 2, for both components, it can be shown that the component ratio present at the critical mixture ratio (i.e. neither component controlling release, dissolution of both components being linear and congruent) will be given by equation 5,

$$\frac{N_a}{N_b} = \frac{(D_a C_a^o + D_c K C_a^o C_b^o)}{(D_b C_b^o + D_c K C_a^o C_b^o)} \quad (5)$$

where the subscripts a and b refer to the individual component parameters. It is evident from equation 5 that the greater the difference in solubility between the drug and carrier and the smaller the value of K the smaller will be the proportion of the less soluble component (i.e. drug) present at the critical mixture ratio. The drug percentages predicted by equation 5 at the critical mixture ratio were approximately 10, 5, 3 and 0.6% w/w for hydrochlorothiazide, hydroflumethiazide, chlorothiazide and bendrofluazide respectively. Since the proportions of the drugs present in the equimolar systems are greater than these values, the formation of a surface drug layer during dissolution is to be expected, resulting in a decline in dissolution rate with time. It is however highly unlikely, that at drug weight fractions greater than the critical mixture ratio, where a surface drug layer is expected but only a low proportion of drug is present in the disc, that an intact surface drug layer of the required porosity could be maintained. As a consequence shedding of fine drug particles will result, giving drug relative dissolution rates higher than theoretically predicted by equation 3. Furthermore, dissolution of the intrinsically more soluble carrier phase will thus not be retarded and release will tend to remain carrier phase controlled at drug weight fractions greater than predicted by the theory.

In the light of these observations an alternative approach is to consider the drug to be molecularly dispersed in the carrier phase, dissolution of drug being controlled solely by dissolution of the carrier. Under these conditions the rates of boundary movement of each component will be equal and as a first approximation the carrier dissolution will be given by

$$G_b = \frac{D_b C_{sb}}{h} = \frac{A_b dS_b}{dt} \quad (6)$$

where subscript b refers to the carrier phase, A to the component concentration in the system and dS_b/dt to the rate of recession of the surface boundary. The dissolution rate of the drug will be given by

$$G_a = \frac{dS_a}{dt} A_a \quad (7)$$

where the subscript a refers to the drug. Combining and rearranging equations 6 and 7, when $dS_b/dt = dS_a/dt$, gives for G_a

$$G_a = \frac{G_b A_a}{A_b} = \frac{D_b C_{sb} A_a}{h A_b} \quad (8)$$

which when expressed in terms of the relative rate becomes

$$\frac{G_a}{G_o} = \frac{G_b A_a}{G_o A_b} \quad (9)$$

It is evident therefore that, if this model is operative drug release will be given by the product of the carrier dissolution rate and the fraction of drug dispersed (eqn 8).

Qualitatively this molecular dispersion model predicts that the relative rate from a given carrier is inversely proportional to the drug solubility, a trend evident in the results obtained. The much higher relative rate observed for bendrofluazide is in agreement with this theory and is expected since this system forms an inclusion complex and hence is initially molecularly dispersed. In addition the βCD to drug solubility ratio is the largest for this system, resulting in a very small amount of drug to form the critical mixture ratio.

The relative rates calculated using this model (eqn 9), which assumes no contribution from complex formation in solution, are also included in Table 3. These rates are much higher than those predicted by the soluble complex model and, although considerably higher than the experimentally determined values, represent a better approximation. The observed rate for bendrofluazide is still less than one third that predicted. The theory also predicts that from an equimolar mixture the molar release rates of drug and βCD should be equal. Comparison of the observed rates revealed this not to be the case, the βCD molar rate being considerably higher, approximately six fold in the case of bendrofluazide. This suggests either the presence of unincluded drug or the formation of a surface solid drug phase on dissolution of the complex. The presence of such a phase would be consistent with the observed declining slope of the dissolution vs time profile, and indicate a tendency to revert to drug surface phase control and the classical model.

If crystalline drug is dispersed in the carrier, as is the case with the mechanical mix systems, particulate drug will be passively carried into the dissolution medium as the carrier dissolves, giving a dissolution rate intermediate between that predicted by the two theories.

The freeze dried systems containing chlorothiazide, hydroflumethiazide or hydrochlorothiazide with βCD also contained crystalline drug, as revealed by the DSC thermograms and X-ray diffraction scans. Rates intermediate between those predicted by the two theories are therefore to be expected for these systems. Furthermore, if freeze drying produced smaller drug crystallites, consistent with the X-ray and infrared results then, if flaking of the dissolution surface is occurring, the drug dissolution rates from these systems should, as was observed, be higher than those of the corresponding mechanical mixtures.

It should be emphasised that the enhancement in dissolution rate from drug plus carrier systems of low drug weight fraction over and above that predicted by the classical two component model (Higuchi et al 1965) is due to an extension of carrier phase dissolution control to higher drug weight fractions than predicted by the model and is a consequence of the disparate solubilities of the carrier and drug, resulting in insufficient drug to form an integral surface layer at drug weight fractions greater than the critical mixture ratio. In the absence of such an effect both models would predict similar drug release rates at low drug weight fractions since, in the classical model (Higuchi et al 1965), above the critical mixture case a carrier layer will also be controlling drug release. The reason why the two component soluble complex model more closely approximated the phenobarbitone-βCD data (Corrigan & Stanley 1981), where an inclusion complex was also present, is due to the higher solubility of phenobarbitone and a much larger K (eqn 5) resulting in a physically more stable critical mixture ratio.

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