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INFLUENCE OF SODIUM CASEINATE ON THE DISSOLUTION RATE OF HYDROCHLOROTHIAZIDE AND CHLOROTHIAZIDE.

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ABSTRACT

The solubility and dissolution characteristics of drug-casein systems were investigated and their solid state properties examined. Systems of varying drug-sodium caseinate weight fraction were prepared by physical mixing and freeze drying. Enhancements in the intrinsic dissolution rates were obtained for freeze dried systems of both drugs. The relative enhancement for 50/50 systems in phosphate buffer pH 7.4 was 5 fold and 1.5 fold for chlorothiazide and hydrochlorothiazide respectively. A 35 fold increase was observed for the chlorothiazide system in water, The release of both drugs from mechanically mixed systems in phosphate buffer approximated to a non interacting model, while release from hydrochlorothiazide systems in 0.1N HCl showed a tendency towards matrix controlled release. Thus the magnitude of the effect is dependant on the nature of the drug, the content of carrier, the method of preparation and the dissolution medium.

INTRODUCTION

Water soluble synthetic polymers are frequently used to enhance the dissolution rates of poorly soluble drugs[1,2]. Imai et al have investigated the possibility of using egg albumin as a carrier in solid dispersions[3]. In this report the use of a polymeric group of natural materials, the caseins, as potential carrier materials for dissolution rate enhancement will be examined. The mechanisms whereby water soluble carriers improve drug dissolution include (a) enhancement of solubility through complex formation or micellar solubilization[4], (b) alteration of the mechanism of dissolution[5], (c) increasing solubility by solid state modification of the drug and/or carrier material[6].

The extent to which these effects contribute to enhanced drug release may be dependant on the processing method(s) employed in the preparation of the solid dispersion system.

The caseins are a group of phosphoproteins[7] comprised of four major caseins of average molecular weight 23,000 daltons[8]. Caseins and caseinates contribute both nutritional and functional value to food products[9]. Acid casein is insoluble in water but sodium caseinate is freely soluble except in the region around its isoelectric point (pH 3.5 to 5)[7] . The majority of casein protein in milk exists as a colloidal dispersion known as micelles[8] . In solution the caseins exhibit a high tendency for self association and also for complex formation with each other[10].

Macheras et al.[11] have observed increases in bioavailibility of drug-milk preparations relative to the pure drug. Subsequent binding studies in casein solutions showed increases in solubility which could not be explained by normal protein binding[11,12]. This report investigates the effect of sodium caseinate on the solubility, dissolution and solid state properties of the thiazide diuretics chlorothiazide and hydrochlorothiazide. These drugs were chosen since they have relatively high melting points and heats of fusion, low intrinsic solubilities, may exist in amorphous forms and their behaviour in the presence of other carrier materials such as PVP has previously been investigated[13,14].

MATERIALS AND METHODS

Sodium caseinate (NAC) was supplied by An Bord Báinne, Ireland. Chlorothiazide (CHL) and hydrochlorothiazide (HYD) were B.P. quality, and all other reagents were of analar grade.

Mechanically mixed systems were prepared by mixing the appropriate quantities of each component, sub 125 μm in an agate mortar.

The freeze dried systems were prepared by dissolving the drug in an NaOH solution, and combining this with a solution of NAC. The pH of this solution was adjusted towards neutrality by addition of HCl (pH range 7.5 - 8.5) and subsequently freeze dried.

Solubilities were determined at 37°C in both isotonic phosphate buffer pH 7.4 and distilled water incorporating various amounts of NAC using the dynamic solubility method[15]. Solutions of less than 50 mg/ml NAC were employed due to the high viscosity of more concentrated solutions.

Dissolution testing was performed also at 37°C by the static disc method[2].

The samples from the solubility determinations and dissolution tests were assayed by U.V. (Shimadzu 160) using calibration curves at 316 nm and 310 nm for HYD and CHL respectively, NAC did not interfere with the assay at these wavelengths. Pure NAC was assayed also by U.V. using an absorbance difference method ($A_{235} - A_{280}$), which gave linear calibration curves.

Solid state properties of the systems were investigated by, X-ray diffraction, (XRD), (Phillips), and differential scaning scaning calorimetry, (DSC), (Mettler).

RESULTS AND DISCUSSION

Solubility Studies

The change in solubility (Cs) of both HYD and CHL with increasing NAC concentration in phosphate buffer pH 7.4 is shown in figure 1. The apparent partition coefficients (K) were

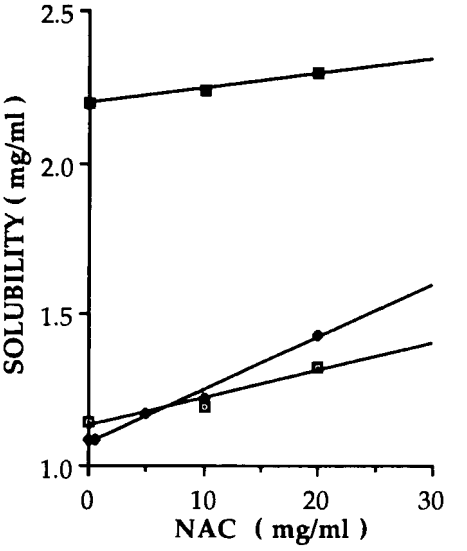

FIGURE 1
Effect of increasing [NAC] on solubility of CHL (■) and HYD (⊡) in buffer and HYD (♦) in distilled water.

calculated using the following equation[16]

$$Cs = mC_M + C^oS \qquad \text{Equation 1}$$

$$m/C^oS=K$$

where C^oS is the solubility of the drug in the absence of NAC, C_M is the micellar concentration and m is the slope. In the case of HYD a small but significant increase in solubility, K = 0.00775 was observed, the effect was much lower for CHL, K =0.00225. The solubility of HYD in distilled water was also determined and gave a K value of 0.01584. Data obtained for HYD and CHL with PVP gave values of 0.018 and 0.019 respectively[17]. A K value of 0.0166 was found in solubility studies of ibuprofen in NAC.

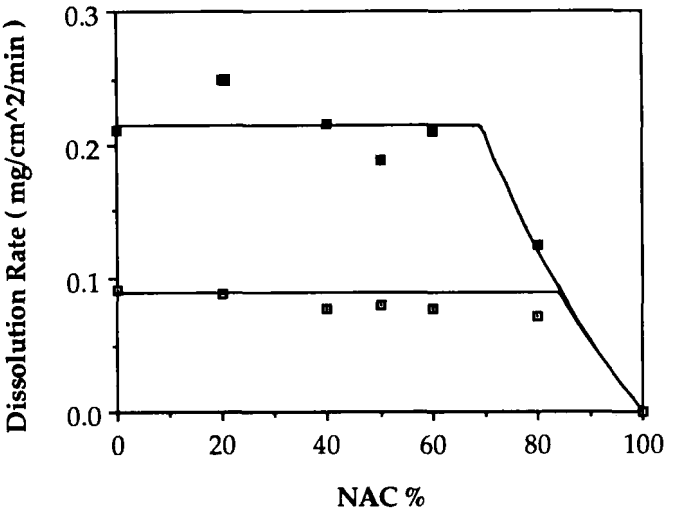

FIGURE 2
Effect of NAC content on dissolution rate of CHL (■) and HYD (⊡) from mixed discs.

Dissolution Studies

The effect of increasing NAC content on the dissolution rate of HYD and CHL from mixed discs in phosphate buffer pH 7.4 is shown in Figure 2. Rates were determined from the linear initial dissolution profiles, at later times the discs disintegrated. Little change in dissolution rate with increasing NAC content was observed. The results indicate that dissolution from these systems approximates to the classical two component non-interacting model[18].

The dissolution rate of pure NAC in pH 7.4 phosphate buffer was estimated to be 0.82 mg/cm^2/min. Thus the polymer dissolution rate is approximately 8 times that of HYD and 4 times that of CHL.

The curves in Figure 2 represent the predictions of the two component non-interacting model obtained using diffusion layer thickness of 6.5 E-3 and diffusion coefficients of 4.65E-4 and 5.8E-4. The critical mixture ratio (CMR) estimations for HYD and CHL were 85 and 69% NAC respectively. Were soluble complex formation to increase the dissolution rate the effect would be evident in the region of the CMR. The above parameters in conjunction with the K values calculated from the solubility data were used to simulate an interacting model. As expected the K values were too small result in a significant enhancement and this plot also approximated to the non interacting model.

Release profiles of hydrochlorothiazide from HYD/NAC mixed discs were also determined in 0.1N HCl. The profiles obtained are shown in Figure 3. The release profiles of drug from mixtures were lower than that of pure drug, and the profiles curved downwards indicating the possibility of matrix release. The profiles were fitted to the equation

$$W = AT^n \qquad \text{Equation 2}$$

where W is the amount dissolved, T is time and A and n are constants[19]. The n values ranged from 0.749 to 0.760. True matrix release would have resulted in an n value of 0.5, the higher value of n obtained here may be explained by limited dissolution of the carrier and/or swelling. The dissolution rate of NAC at pH 1.5 is thirty times lower than in water.

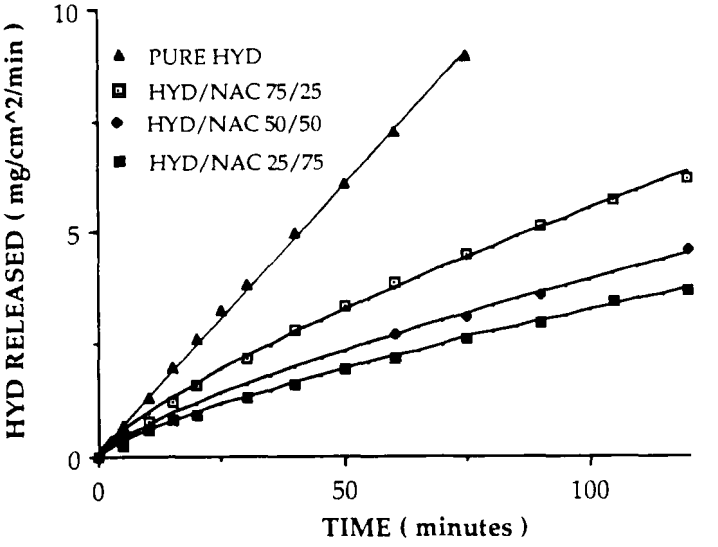

FIGURE 3
Dissolution profiles of HYD/NAC mixed discs in 0.1 N HCl with curves fitted using calculated values of A and n.

The dissolution profiles of CHL/NAC systems freeze dried with increasing NAC concentration are shown in figure 4. The profiles in water were linear the rate decreasing with increasing NAC content. When these experiments were repeated using pH 7.4 phosphate buffer as the dissolution medium, the absolute rates were approximately halved except in the case of pure drug where the rate in buffer was almost four times greater than in water, thus the relative enhancement in water was much greater. The results are summarized in table 1.

Thus processing, by freeze drying considerably enhanced the dissolution rate of CHL compared to the pure drug and the corresponding mechanical mixes.

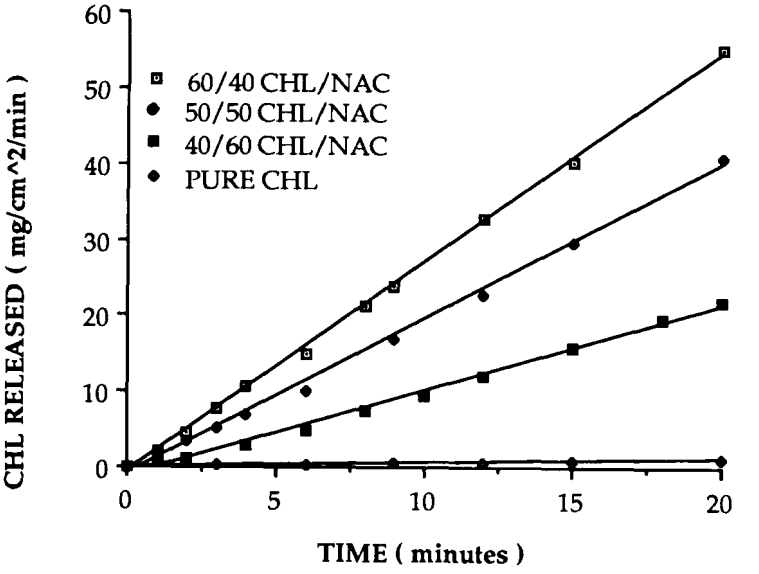

FIGURE 4
Dissolution profiles of freeze dried CHL/NAC systems in distilled water.

Table 1. Dissolution Rates and Relative Rates for CHL/NAC Freeze Dried Mixtures in pH 7.4 Phosphate Buffer and Distilled Water.

Ratio CHL/NAC	Phosphate buffer		Water	
	Rate ($mg/cm^2/min$)	Relative Rate	Rate ($mg/cm^2/min$)	Relative Rate
Pure CHL	0.212	1	0.056	1
60/40	1.388	6.6	2.74	49
50/50	1.005	4.7	1.99	35.5
40/60	0.697	3.3	1.23	22

Dissolution studies on HYD/NAC freeze dried systems were performed in pH 7.4 phosphate buffer. The relative enhancement in dissolution rate from the 25/75 and 50/50 systems was about 1.5. The 75/25 system disintegrated very rapidly. Thus the process of freeze drying with NAC had much less effect on HYD systems.

DSC Scans.

DSC scans of pure CHL, 50/50 MM and 50/50 freeze dried mixtures are shown in figure 5. Chlorothiazide gives a single melting point at 375°C with decomposition. The mechanical mix gave a broad peak between 50 and 100°C and two peaks at ≈ 300°C possibly representing melting and degradation. The freeze dried system has two endotherms below 100°C and a possible exotherm at ≈ 300°C. The possibility of salt formation during freeze drying was considered. A salt was prepared by freeze drying CHL from an alkaline solution in the absence of NAC, the scan from this salt is also included in figure 5. Peaks are evident in the 70 - 120°C range and suggests that some salt may be present in the freeze dried system.

The DSC scan for pure HYD exhibits one sharp endotherm at 271°C corresponding to the drug melting point. The drug peak in the mechanical mix was shifted to a slightly lower temperature of 258°C. The freeze dried systems have a broad endotherm at ≈ 100°C, no peaks were seen in the region 100-350°C.

X-Ray Diffraction

X-ray diffraction patterns for CHL /NAC systems are shown in figure 6. As expected the mechanically mixed systems gave peaks in

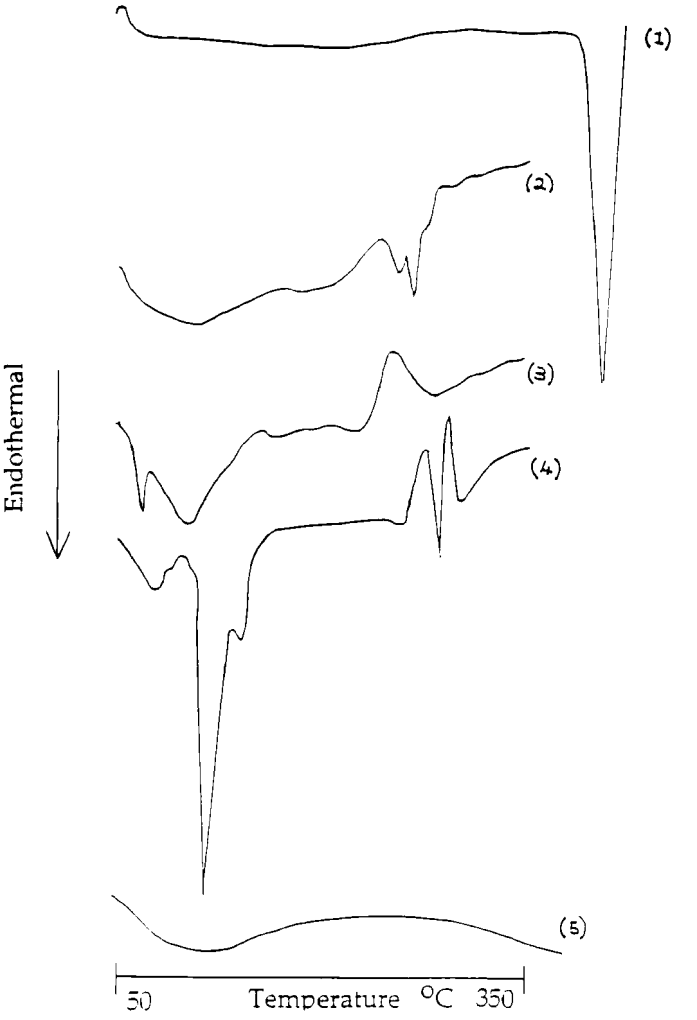

FIGURE 5
DSC scans of CHL/NAC systems: (1) Pure CHL, (2) CHL/NAC 50/50 mechanical mix, (3) CHL/NAC 50/50 freeze dried, (4) Freeze dried sodium salt and (5) Pure NAC.

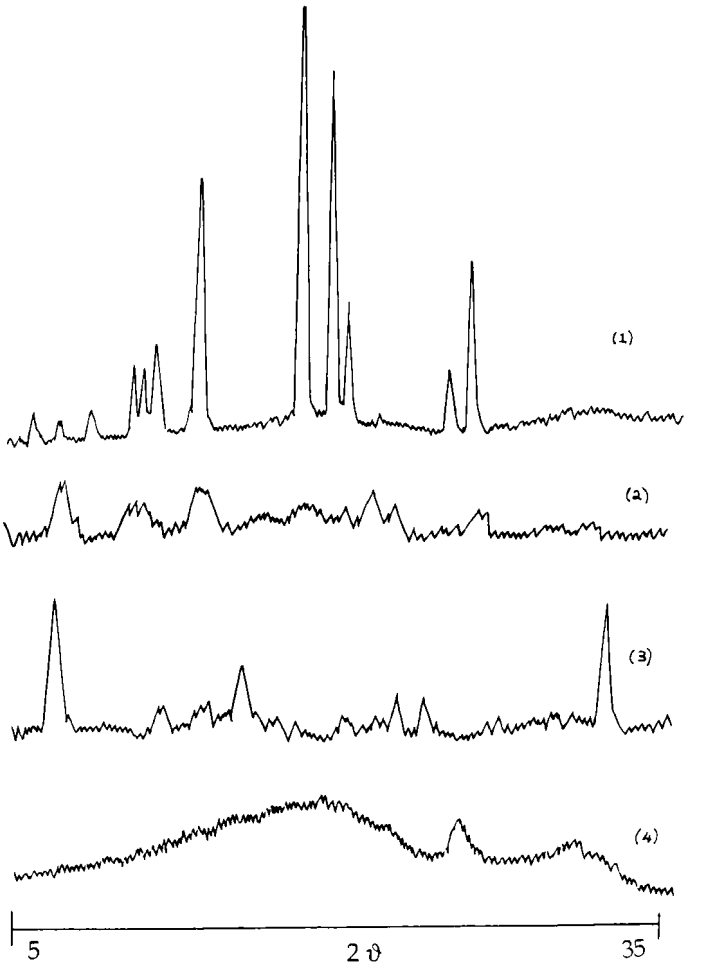

FIGURE 6
X-Ray diffraction patterns of CHL/NAC systems: (1) CHL/NAC 50/50 mechanical mix, (2) CHL/NAC 50/50 freeze dried, (3) Freeze dried sodium salt and (4) Pure NAC.

identical positions to the pure drug, but of lesser intensity. The absence of peaks in the NAC pattern indicated its amorphous nature. The freeze dried systems exhibited a few broad peaks indicating a marked decrease in crystallinity. There are differences between the patterns from the freeze dried salt and the freeze dried drug-NAC systems (Figure 6). All the systems were tested for the presence of disulphonamide a possible degradation product in alkaline solution and proved negative. Thus the unexplained peaks could not be attributed to disulphonamide. The nature of the drug in the freeze dried systems is undergoing further investigation.

The X-ray patterns from pure HYD and HYD/NAC mechanical mixes similarly gave patterns typical of highly crystalline materials. However the patterns obtained from the freeze dried systems exhibited no peaks and were typical of amorphous materials.

CONCLUSIONS

The enhancements in rate observed in freeze dried systems of both drugs with casein appears to be due to solid state changes during processing rather than to an effect on drug solubility. The freeze dried systems were partially if not totally amorphous. The greater dissolution rate enhancement with chlorothiazide may reflect the much higher melting point of the unprocessed drug.

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