Increasing Dissolution Rates and Gastrointestinal Absorption of Drugs *Via* Solid Solutions and Eutectic Mixtures IV

Chloramphenicol–Urea System

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The dissolution rates of a number of chloramphenicol–urea samples were studied. Solubility studies indicated that urea increased significantly the solubility of chloramphenicol; this resulted in a large increase in the initial dissolution rate of chloramphenicol from physically mixed samples of the drug with urea. The α solid solution of chloramphenicol in urea was found to dissolve twice as rapidly as a physical mixture of the same composition, and almost 4 times as rapidly as the pure drug.

THE IMPORTANCE of particle size reduction as a means of increasing dissolution rates is well established. The methods by which a drug may be presented to the gastrointestinal fluids in finely divided form has been reviewed by Levy (1). Among the various ways to obtain microcrystalline dispersions *in vivo* is to administer a eutectic mixture composed of the drug and a substance which readily dissolves in water (2). This approach has been employed to enhance the dissolution rate of chloramphenicol (3). The results of this study were explained on the basis of particle size reduction of chloramphenicol in the drug–urea fused mixture (3).

Goldberg *et al.* (4) have raised a number of theoretical questions concerning the proposed mechanism of this phenomenon. Alternatively, these authors suggested that the enhanced dissolution rate was attributable to the presence of solid solutions in the system rather than simple eutectic formation. Indeed, the sample prepared by Sekiguchi *et al.* (3) at the eutectic composition manifested no enhancement in the dissolution rate of chloramphenicol as compared to the pure drug. An increase in dissolution rate became apparent only when a sample containing urea in excess of the eutectic composition was investigated.

The failure of the chloramphenicol–urea eutectic mixture to display increased dissolution of the antibiotic drug raises doubts concerning the general utility of the simple eutectic mixture in modifying dissolution. These doubts are heightened by a recent study by Goldberg and co-workers (5) on acetyl *p*-aminophenol–urea mixtures. This binary system showed practically no solid solubility. Examination of the results of this investigation indicated that particle size reduction in the eutectic mixture played a negligible role in enhancing dissolution. Conversely, a subsequent study (6) convincingly demonstrated the importance of solid solutions in modifying dissolution characteristics. The griseofulvin–succinic acid solid solution was found to dissolve 6–7 times faster than the pure drug.

The purpose of this present investigation was to examine the dissolution properties of various mixtures of chloramphenicol and urea in order to elucidate the mechanism involved in the reported enhancement of the rate of solution of chloramphenicol from these mixtures.

EXPERIMENTAL

Sample Preparation.—The fused mixtures of chloramphenicol[1] and urea were prepared by adding the powdered blend to a stainless steel crucible immersed in a temperature-controlled silicone fluid bath preheated to the melting point of the mixture. The mixture was constantly stirred until a homogeneous liquid resulted. The molten material was then cast immediately on chrome-plated stainless steel plates and allowed to congeal. The solidified mass was crushed with a mortar and pestle and then sieved through standard screens using a Syntron shaker.[2] Those particles passing through a No. 50 standard screen but retained on a No. 60 screen were used in the dissolution studies. The particle size of pure chloramphenicol was increased in the same manner. The samples investigated are listed in Table I. The chloramphenicol content of each sample was verified by spectrophotometric analysis.

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[1] Chloramphenicol used was generously supplied by Parke, Davis & Co., Detroit, Mich.
[2] Syntron TSS-25 Test Shaker, Syntron Co., Homer City, Pa.

Table I.—Chloramphenicol and Chloramphenicol–Urea Samples Prepared for Dissolution Studies

Sample	% Compn.	Description	% α Solid Soln.
A, Chloramphenicol	100	...	...
B, Chloramphenicol	92	Fused, β solid soln.	0
Urea	8		
C, Chloramphenicol	76	Fused, eutectic mixture	23
Urea	24		
D, Chloramphenicol	55	Fused	58
Urea	45		
E, Chloramphenicol	43	Fused	78
Urea	57		
F, Chloramphenicol	26	Fused, α solid soln.	100
Urea	74		
G, Chloramphenicol	26	Physical mixture	...
Urea	74		

Solubility Studies.—The solubility of chloramphenicol as a function of urea concentration was studied in aqueous solution. An excess of chloramphenicol was added to 30 ml. of distilled water containing various concentrations of urea, in 60-ml. screw-top vials. The vials were then placed in an incubator shaker[3] and maintained at 37° until equilibrium was established.

Solubility studies were also conducted with sample *F* (α solid solution) and sample *G* (a physical mixture corresponding in composition to the α-solid solution). An excess of each sample was placed in 30 ml. of water and incubated until the system reached equilibrium. This experiment was conducted to insure that fusion did not result in decomposition of the active ingredient.

Dissolution Rate Studies.—The dissolution rate of chloramphenicol from each of the samples listed in Table I was determined by means of the tape method (7). The quantity of material dusted on the adhesive surface varied with the individual sample but in each case corresponded to 10 mg. of chloramphenicol. The choice of a constant amount of drug is based on the assumption that if no interaction occurs, then the drug crystallizes from the melt to form particulates, within the mass, of approximately the same size regardless of urea concentration. If this hypothetical situation did exist, then all fused samples should show the same dissolution rate since the urea rapidly dissolves and leaves behind about 10 mg. of drug in the form of equal-sized particulates, having the same surface area. Under such conditions it would not be reasonable to maintain sample size constant since the apparent dissolution rate would decrease as the concentration of diluent increases and the corresponding effective surface area decreases.

The dissolution fluid consisted of 400 ml. of distilled water maintained at 37° in a 600-ml. beaker which was immersed in a constant-temperature water bath. The stir paddle was rotated in the fluid at a constant rate of 53.5 r.p.m. After immersion of the tape frame, 1-ml. samples were withdrawn at 3 and 5 min.

Assay Procedure.—Chloramphenicol concentration was determined spectrophotometrically. Each sample was diluted suitably with distilled water and the absorbance determined at 274 mμ using a Beckman DB recording spectrophotometer. Concentrations were calculated from a previously prepared Beer's law plot.

[3] Gyrotory Incubator Shaker, model G 25, New Brunswick Scientific Co., New Brunswick, N. J.

RESULTS AND DISCUSSION

Phase Diagram.—As noted by Goldberg *et al.* (4) the chloramphenicol–urea system exhibits a great deal of solid solubility. This is manifested by the existence of regions α and β in the phase diagram depicted in Fig. 1. At the eutectic point the mixture contains 76% chloramphenicol which is present as part of 2 distinct saturated solid solutions. The saturated α solid solution contains 30% chloramphenicol, while the saturated β solution contains

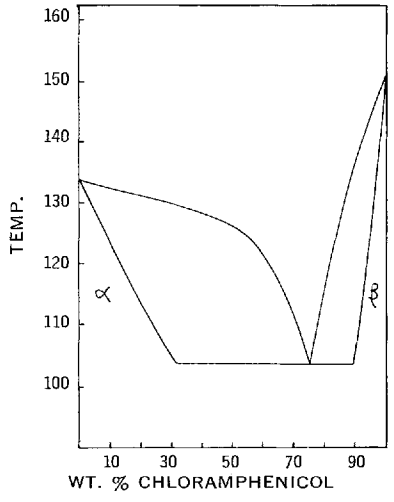

Fig. 1.—Phase diagram for chloramphenicol–urea system (3).

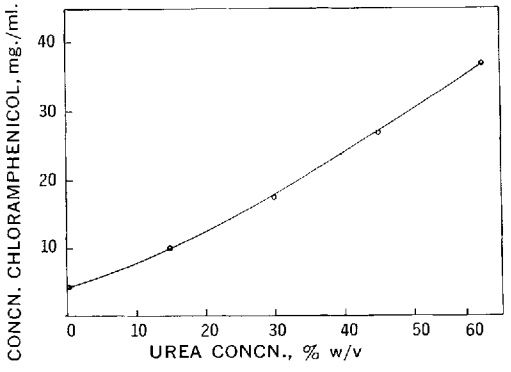

Fig. 2.—Solubility of chloramphenicol in aqueous solutions of urea at 37°.

TABLE II.—DISSOLUTION STUDIES OF CHLORAMPHENICOL FROM FUSED AND PHYSICAL MIXTURES WITH UREA

Sample[a]	Amt. Dissolved, mg./400 ml. 3 min.	5 min.	Relative Dissolution Rate at 3 min.
A, Pure drug	1.3	1.8	1.0
B, β solid soln.	1.3	1.7	1.0
C, Eutectic	1.7	2.3	1.3
D, 58% α solid soln.	2.4	3.0	1.8
E, 78% α solid soln.	2.8	3.8	2.2
F, α solid soln.	4.9	6.2	3.9
G, Physical mixture	2.4	2.9	1.8

[a] Refer to Table I for description of samples.

90% of the drug. The eutectic mixture actually consists of 23% α and 77% β solid solution. The α and β solid solutions account for 7 and 69 parts, respectively, of the total 76 parts of chloramphenicol present in the eutectic mixture.

Solubility Studies.—The data presented in Fig. 2 clearly demonstrate the significant effect of urea on the solubility of chloramphenicol. A greater than sevenfold increase in the solubility of the drug was observed over the urea concentration range studied.

The solubility of the α solid solution was found to be identical with that of a physical mixture of the same composition. This finding is indicative of the absence of chemical reaction between the drug and carrier which could occur during the fusion process. Therefore, the samples differ only with respect to their physical state.

Dissolution Rate Studies.—The results of the dissolution studies are shown in Table II. Inspection of each of these rates reveals a number of interesting relationships as well as an insight to the complexities involved in the dissolution of chloramphenicol from the fused binary mixtures.

The chloramphenicol–urea eutectic was found to dissolve somewhat faster than the pure drug with a comparable particle size. Sekiguchi *et al.* (3) were unable to detect differences in the dissolution rate of the eutectic mixture and the pure drug. The experimental discrepancies between the former study and the present work may be ascribed to differences in the method of determining dissolution rate. The method employed by Sekiguchi and coworkers involved a higher degree of agitation than employed in this investigation. The use of high shear in *in vitro* dissolution investigations tends to obviate differences arising from microenvironmental factors which would be significant *in vivo*. Three individual (or possibly concerted) factors are involved in the dissolution of chloramphenicol from the eutectic. These include local solubilization, particle size reduction, and the presence of a significant amount of the rapidly soluble α solid solution.

The importance of the microenvironmental effect of urea on the dissolution of chloramphenicol may be appreciated by considering the dissolution rate of the physically mixed chloramphenicol–urea sample. As noted in Table II, the relative dissolution rate of the drug from sample *G* is almost twice as rapid as from the pure chloramphenicol. The solubility of chloramphenicol is significantly higher in the microenvironment (which approximates a saturated solution of urea) than in the bulk and the drug dissolves rapidly.

The significance of solid solution formation in the enhancement of dissolution can be realized by comparing the results obtained from samples *F* and *G*. Both samples are identical with respect to composition but differ in that sample *F* is a fused mixture and is actually composed of a homogeneous solid solution of chloramphenicol in urea. One would anticipate that the local effect of urea would be approximately the same in both samples or perhaps somewhat lower in the fused sample where urea exists in a more hydrophobic solid environment and conceivably dissolves at a slower rate. Despite this seeming equality, the initial dissolution rate of chloramphenicol from the α solid solution is more than twice that of the physical mixture and almost 4 times greater than the rate of solution of the pure drug. These differences may only be ascribed to the physical state of the chloramphenicol in the fused sample.

In a previous paper (4), Goldberg *et al.* theorized that the β solid solution of urea in chloramphenicol may demonstrate a strong crystal lattice. The results of dissolution studies conducted with the β solid solution indicate that despite the presence of a significant quantity of urea in the sample the solution rate is approximately equal to that of the pure drug. This is rather surprising in that the mere presence of a material as soluble as urea in the crystal would tend to increase the wetting of the particle and in this manner alone increase effective surface area and thereby increase dissolution rate. The inability to demonstrate this effect may perhaps be attributable to the formation of a crystal lattice in which the chloramphenicol is bound at least as tightly as in the pure crystal.

Comparison of the results obtained with samples *B*, *C*, *D*, *E*, and *F* reveals an interesting relationship. These samples range in α solid solution content from 0% (pure β solid solution) to 100% (pure α solid solution). The rate of dissolution of chloramphenicol from these mixtures was found to be a direct function of the α solid solution content of the sample. With an increase in the per cent α solid solution in the sample there was a corresponding increase in the rate of solution of the drug.

The findings of these investigations once again point out the potential importance and biopharmaceutical significance of solid state molecular dispersions in the enhancement of dissolution rate.

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