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

Theoretical Considerations and Discussion of the Literature

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The theoretical aspects of solid solutions and eutectic mixtures as well as their application to pharmaceutical systems are discussed. A mechanism is considered by which such solid systems may enhance dissolution rates and, in turn, the gastrointestinal absorption rate and availability of poorly soluble drugs. A degree of ambiguity exists in the literature published to date in this area. This report proposes that results previously attributed to eutectic mixtures are properly explained by the existence of solid solutions. The sulfathiazole–urea and chloramphenicol–urea systems are examined in detail.

A NUMBER of modern therapeutic agents are poorly soluble in the aqueous fluids of the gastrointestinal tract. Consequently, the *in vivo* dissolution rate of these compounds is low, and their gastrointestinal absorption tends to be incomplete and erratic (1). Since dissolution rate is directly proportional to surface area (2), one may increase the rate by decreasing the particle size of the drug. The greater surface area of drug in contact with biological fluids then will bring about more rapid dissolution and thereby more rapid gastrointestinal absorption, provided that absorption is rate limited by the dissolution process. Levy (1) notes that, "In those instances where the intrinsic dissolution rate is so low that the drug is ordinarily not completely absorbed when administered in solid form, the more rapid absorption attained by increasing the specific surface area will cause also an increase in the total amount of drug absorbed from a given dose." Recent studies with sulfadiazine (3), sulfaethylthiadiazole (4), and griseofulvin (5) support these hypotheses. As a result of the last-mentioned investigation (5), manufacturers now market griseofulvin in a finely micronized form which permits 50% dosage reduction as compared to the original unmicronized form.

At present, the degree of particle size reduction required to increase significantly the specific surface area of these drugs is usually attained by micronizing the material in a suitable fluid energy mill (6). In 1961, Sekiguchi and Obi (7) developed a unique technique to achieve particle size reduction and thereby permit sparingly water-soluble drugs to become dispersed finely in the fluids of the gastrointestinal tract. Their method involves the formation of a eutectic mixture (which is solid at room temperature) of the drug and a pharmacologically inert, readily soluble carrier. The drug and carrier are melted and mixed, the resulting homogeneous liquid is cooled until it solidifies, and then the mass is finely powdered by some simple comminution technique and sieved. The crystals in a eutectic mixture are usually quite small and fine-grained (8, 9). Therefore, when the eutectic mixture is placed in water, the soluble carrier substance dissolves rapidly, and extremely fine particles of the drug are released.

The ultimate achievement of this approach to fine particle production lies in the formation of a solid solution. A solid solution of a water-insoluble drug in a rapidly soluble carrier should theoretically optimize the absorption of the drug. When the solid solution is exposed to the fluids of the gastrointestinal tract, the carrier dissolves and releases the drug in a molecular state. This possibility has recently been noted by Kanig (10).

It is the purpose of this communication to consider some theoretical aspects of eutectic mixtures and solid solutions and to examine critically recent findings (7, 11) relevant to the enhancement of drug absorption *via* eutectic mixtures.

THEORETICAL CONSIDERATIONS

If two solids are melted together, the resulting liquids are either completely miscible, partially miscible, or immiscible. If the two liquids are partially or totally immiscible, it may be assumed that their solid forms will exhibit little interaction. On the other hand, if the two liquids are totally miscible, the solids formed upon cooling may exhibit one of four possible interactions. They can form (*a*) a new compound with a congruent melting point,

Received March 19, 1965, from the College of Pharmacy, Columbia University, New York, N. Y.
Accepted for publication May 13, 1965.
* Research Fellow, under a research grant from the Bristol-Myers Co., New York, N. Y.

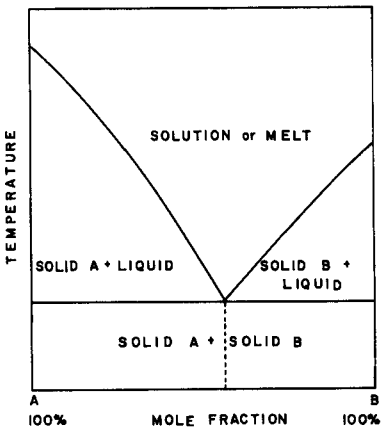

Fig. 1.—Phase diagram of a hypothetical eutectic mixture of compounds A and B.

(*b*) a new compound with an incongruent (peritectic) melting point, (*c*) a eutectic mixture, or (*d*) a solid solution (9). The scope of this report will be limited to the latter two possibilities, *viz.*, eutectic formation and solid solutions.

Eutectic Mixtures.—The melting points of various proportions of mixtures of two solids may follow one or another of several different patterns. One such pattern is eutectic formation and is exemplified by a phase diagram such as that illustrated in Fig. 1. The existence of eutectic mixtures is in agreement with the fundamental laws of thermodynamics (12), and a physical state of matter such as this conforms to the conditions of the Gibbs phase rule (13). The possible mechanism of eutectic formation has been reviewed recently (8).

If one draws an analogy between eutectic crystallization and the crystallization of a solute from a mother liquor, it would appear that the size of the formed crystals is a function of the rate of cooling and the presence of other solutes. Thus, the method of preparation of eutectic mixtures may have a significant effect on the efficiency of this technique of particle size reduction.

It has recently been reported that the fine-grained characteristics of a eutectic mixture may be lost with time (8). This phenomenon appears to be analogous to the well-known Ostwald ripening effect and involves solid state diffusion. The usefulness of the eutectic mixture approach to enhancement of dissolution rates may be minimized if such solid state transitions are common.

Solid Solutions.—The phase diagram of a eutectic mixture, illustrated in Fig. 1, is idealized since components A and B are depicted to be completely insoluble in one another in the solid state. In practice, some solid state solubility can be predicted for all two-component systems (13). However, the extent of solubility is usually small enough to be considered negligible.

In those systems where the solubility of one component in the other in the solid state is significant, a solid solution is said to exist. For practical purposes, solubility of greater than 5% of one component in the other can be considered to be a solid solution. Solid "solutions"[1] are homogeneous one-phase systems which exhibit a mixed crystal (9, 13, 14).

Two distinct types of solutions are recognized (15). An *interstitial solid solution* exists when the molecule of one component resides in the interstitial spaces of the crystal lattice of the second component. The situation is comparable to clathrate formation, and size and steric factors are of prime importance. A *substitutional solid solution* is formed when a molecule of one component can replace a molecule from the crystal lattice of the second component.

In either type of solution the two components may not be miscible in all proportions. As in solid–liquid solutions, the solubility of one component in another in the solid state is often limited. Many different phase diagrams have been recognized for two-component systems exhibiting partial solution. Figure 2 (16) is of particular interest because of its close resemblance to a eutectic mixture phase diagram.

From this diagram it may be noted that solid B dissolves in solid A to form a solution (α region), which contains $X\%$ of B at saturation. Similarly, solid A dissolves in solid B to form a second solution (β region) which contains $Y\%$ of A at saturation. At the eutectic composition, crystals of saturated solid solution α and crystals of saturated solid solution β precipitate by alternate crystallization in a fixed ratio. There are no pure crystals of A or B in the system. In the regions labeled α and β, there exist solid solutions of continuously variable concentrations up to $X\%$ of B and $Y\%$ of A, respectively.

DISCUSSION OF THE LITERATURE

The increase in dissolution rate and in gastrointestinal absorption resulting from the use of eutectics has been attributed to the small particle size of the active ingredient in the eutectic mixture (7, 11). No consideration has been given to the possibility that a partial solid solution may be responsible for the increased dissolution rate. After an examination of the published data (7, 11) coupled with investigations in our laboratories, it was concluded that in at least two instances the existence of solid solutions rather than the reduced particle size of the

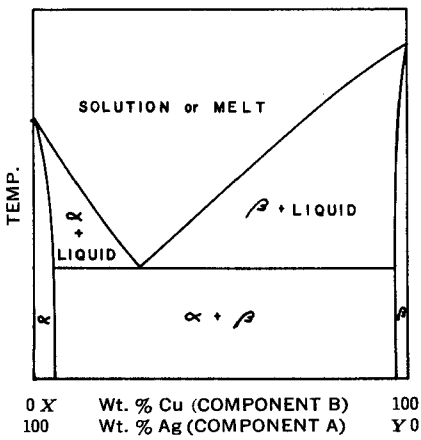

Fig. 2.—Phase diagram of Cu–Ag mixture showing partial miscibility of solid solutions. (From *Reference 16.*)

[1] The term "solution" will henceforth be used to refer to a solid solution.

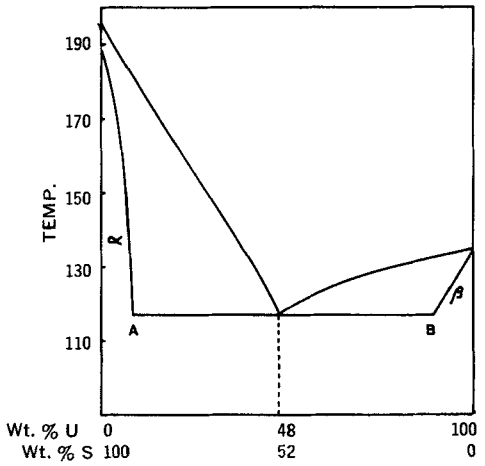

Fig. 3.—Phase diagram for mixtures of sulfathiazole (S) and urea (U). (From *Reference 7.*)

eutectic mixture was the determining factor in producing increased dissolution rates.

Sulfathiazole–Urea Mixture.—The phase diagram illustrated in Fig. 3 has been taken from the literature (Fig. 6 in *Reference 7*) where it was described as a eutectic diagram. An inspection of the diagram reveals a significant degree of solid–solid solubility rather than simple eutexia. Region α is a solution of urea in sulfathiazole. The maximum solubility (point A) is approximately 8% w/w urea. The saturated solution in the β region (point B) contains approximately 10% w/w sulfathiazole. At the eutectic point there is a mixture of the two saturated solutions present in a thermodynamically fixed ratio so that the mixture contains a total of 52% w/w of sulfathiazole. Using alligation or simultaneous equations, it may be calculated that the eutectic composition consists of about 51 parts of saturated α solid solution and 49 parts of saturated β solid solution. The former contains about 47 parts of sulfathiazole and 4 parts of urea, corresponding to a mole ratio of 3:1 sulfathiazole to urea. The 49 parts of β solid solution contains about 5 parts sulfathiazole.

On the basis of the composition of the eutectic mixture, one may predict it to be more rapidly soluble than pure sulfathiazole. When the mixture is placed in water, the urea contained in the β solid solution dissolves quickly leaving the sulfathiazole in a molecular state of subdivision. Thus, 10% of the sulfathiazole present in the eutectic mixture is almost immediately solubilized and available for gastrointestinal absorption.

The remaining 90% of the sulfathiazole is present in the less rapidly soluble α solid solution. It is reasonable to hypothesize that although this solution releases sulfathiazole at a slower rate than the β solid solution, it nevertheless would dissolve at a greater rate than pure sulfathiazole. There exists one molecule of urea for every three molecules of sulfathiazole within the crystal lattice of the α solid solution. It is proposed that the presence of these *soluble* defects greatly weakens the crystal lattice. Since both solubility and dissolution rate are a function of crystal lattice energy, it may be concluded that the α solid solution would dissolve somewhat more rapidly than the pure sulfa drug.

The over-all effect of these two separate dissolution mechanisms (proposed to exist in the urea–sulfathiazole eutectic mixture) is a significant increase in the dissolution rate of the sulfathiazole from the mixture as compared to its release from the pure crystal. This increased dissolution rate as well as more rapid gastrointestinal absorption has been confirmed (7). The underlying reason, however, is at least equally attributable to the formation of solid solutions rather than eutectic mixtures alone.

Chloramphenicol–Urea Mixture.—The phase diagram depicted in Fig. 4 was originally described in the literature as a eutectic mixture (Fig. 1 in *Reference 11*). Here, too, inspection of the diagram reveals the existence of solid solutions. This interpretation greatly aids in explaining the rather unusual results obtained by Sekiguchi *et al.* (11) in determining dissolution rates of various compositions of this chloramphenicol and urea mixture.

The studies conducted by these authors are summarized in Table I. In all cases the particles were screened to approximately the same size (150–300 μ) before each dissolution experiment, and the sample size was adjusted so as to contain 1 Gm. of chloramphenicol. The dissolution rates of samples *1*, *2*, and *3* were virtually identical. Sample *2*, a fused mixture containing the two components at the eutectic composition (76% chloramphenicol and 24% urea) displayed the same dissolution characteristics as the pure chloramphenicol. This finding raises some questions regarding the proposed basic concept and general applicability of this technique of particle size reduction. Sekiguchi *et al.* proposed that although fine-grained crystals of chloramphenicol were present in the eutectic mixture, variable factors which occurred during sample preparation

Table I.—Dissolution Studies of Chloramphenicol in Fused and in Physical Mixtures with Urea[a]

Sample	% (w/w) Compn.	Mixing Method	Amt. (Gm.) of Chloramphenicol Dissolved in 100 ml. Water from Powdered Samples	
			10 min.	30 min.
1, Chloramphenicol (recrystallized)	100	...	0.24	0.37
2, Chloramphenicol	76			
Urea	24	Fusion	0.24	0.39
3, Chloramphenicol (recrystallized)	76			
Urea	24	Physical mixture	0.22	0.37
4, Chloramphenicol	20			
Urea	80	Fusion	0.46	0.53
5, Chloramphenicol (recrystallized)	20			
Urea	80	Physical mixture	0.32	0.46

[a] Data obtained from *Reference 11.*

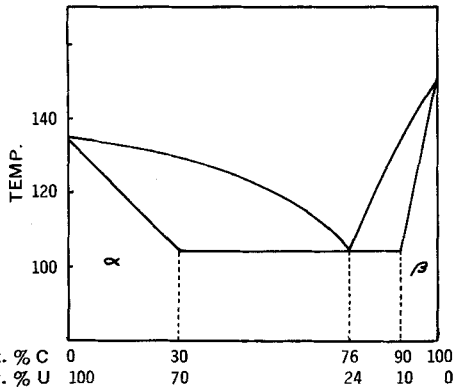

Fig. 4.—Phase diagram for mixtures of chloramphenicol (C) and urea (U). (From *Reference 11.*)

may have led to hardening of the eutectic crystals during cooling.

The results obtained with sample *5* are explained by the authors (11) on the basis of solubility. Previous experiments indicated that urea increased the water solubility of chloramphenicol. The solubility of the drug is approximately 1.33 times greater in a 5% aqueous solution of urea than in water. In view of the large excess of urea present in sample *5*, the dissolution rate would be expected to be higher.

Sample *4* showed the greatest dissolution rate. The presence of excess urea does not satisfactorily explain the results. Although samples *4* and *5* contain the same amount of urea, sample *4* was observed to dissolve significantly faster than sample *5*. A reasonable interpretation of the results can not be made on the basis of a simple eutectic system. However, if the phase diagram (Fig. 4) is interpreted as being that of a solid solution, a more plausible explanation may be postulated.

At the eutectic point the mixture contains 76% chloramphenicol which is present as part of two distinct saturated solid solutions. The α solid solution contains 30% chloramphenicol, while the β solution contains 90% of the drug. The eutectic mixture is composed of 23 parts of α and 77 parts of β solid solutions. The β solid solution accounts for 69 parts of chloramphenicol, while the α solution contains 7 parts of chloramphenicol. On the basis of our previous discussion, this mixture should show a greater dissolution rate than the pure drug. The discrepancy between theoretical expectations and experimental results may possibly be accounted for by the existence of a strong crystal lattice in the β solid solution, the form which accounts for over 90% of the total chloramphenicol. The possibility of a strong solid state interaction between urea and chloramphenicol is heightened by the existence of an interaction between the two components in aqueous solution as evidenced by solubility determinations. Studies are presently being conducted to resolve this question.

Sample *4* contains 20% chloramphenicol and 80% urea. Since this amount of chloramphenicol does not exceed the saturation solubility (30%) of the drug in urea, the entire sample exists as the rapidly soluble α solid solution. Thus, the results obtained with sample *4* are predictable. Upon dissolution of the urea, the chloramphenicol would be released in a state of molecular subdivision, and the dissolution rate of the drug would be expected to be enhanced considerably. It should be noted that despite the encouraging experimental results, the dissolution rate was below theoretical expectations. This may indicate solid state interaction resulting in a stronger crystal lattice.

CONCLUSIONS

The interpretations presented in this report represent a concept of solid–solid interaction that has heretofore been neglected in the pharmaceutical literature. Solid solutions and perhaps eutectic mixtures provide a unique approach for increasing dissolution rates and suggest a fertile area of biopharmaceutical research. The approach is limited, of course, by such factors as thermal degradation, sublimation, and polymorphic transitions. There exists, however, a sufficiently large number of poorly soluble drugs and highly soluble carriers to warrant extensive experimentation. Investigation of a number of factors discussed in this communication is in progress.

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