Mechanism of Increased Rates of Dissolution and Oral Absorption of Chloramphenicol from Chloramphenicol–Urea Solid Dispersion System

WIN LOUNG CHIOU

Abstract □ The phase diagram of the chloramphenicol–urea binary system is reexamined using the differential thermal analysis and X-ray diffraction methods. It is concluded that the system is a simple eutectic mixture rather than a partial solid solution as previously proposed by other authors. The increased rates of *in vitro* dissolution and *in vivo* absorption of chloramphenicol solid dispersed in urea are explained mainly on the basis of a change of particle size of the chloramphenicol crystals.

Keyphrases □ Chloramphenicol–urea solid dispersion system—mechanism of increased dissolution, absorption rates of chloramphenicol □ Phase diagram, chloramphenicol–urea binary system—reexamined using differential thermal analysis, X-ray diffraction □ Dissolution, absorption, chloramphenicol solid dispersed in urea—mechanism of increased rates

In 1964, Sekiguchi *et al.* (1) showed that the rates of *in vitro* dissolution and *in vivo* oral absorption of chloramphenicol could be markedly increased by solid dispersions of the drug in urea at certain weight fraction (20% chloramphenicol–80% urea). They attributed such striking findings mainly to the particle-size reduction of chloramphenicol in the solid dispersed form as the eutectic grains of the chloramphenicol–urea mixture might be in the colloidal or micron range.

After reexamining the phase diagram (Fig. 1) reported by Sekiguchi *et al.* (1), Goldberg *et al.* (2, 3) proposed that the binary system of chloramphenicol–urea should be classified as a partial solid solution rather than a simple eutectic mixture. They further proposed that the attainment of supersaturation and the observed increase of dissolution and absorption rates were primarily due to the molecular dispersion of chloramphenicol in the carrier, urea, as they formed a solid solution. Their papers were cited by numerous authors (4–6).

A careful analysis of the differential thermal analysis (DTA) data of this binary system by Sekiguchi *et al.* (1) revealed, however, a possible error in their construction of the phase diagram. Additional X-ray diffraction studies of the system in these laboratories substantiated the DTA evidence. The following is a brief report of this study.

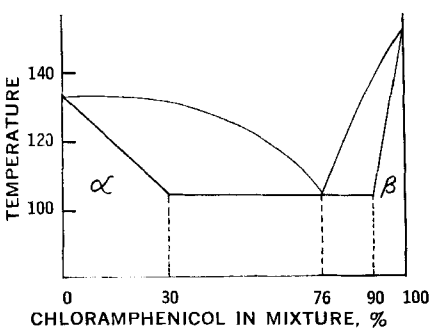

Figure 1—*Phase diagram for chloramphenicol–urea system (from* Reference 1).

EXPERIMENTAL

Materials—Chloramphenicol USP[1] and urea[2], reagent grade, were used without further purification.

Sample Preparation—The physical mixtures of various compositions of chloramphenicol–urea in suitable beakers were heated in an oil bath with stirring until melted. After solidification by shock cooling on a stainless steel plate, the masses were pulverized into fine powders.

X-Ray Diffraction Studies—The fine powders of samples were evenly laid as thin layers on glass slides with the aid of a small amount of Duco Cement[3]. The X-ray diffraction spectra of these preparations were obtained by scanning at 2°/min. in terms of a 2θ angle by a Norelco X-ray diffractometer.

DTA Study—The DTA thermograms of finely powdered samples were obtained from a Dupont 900 thermal analyzer attached with a standard DTA cell (500°). A sample size of 2–3 mg. of powders in a 2-mm. diameter sample tube and a heating rate of 5°/min. were employed. Glass beads were used as a reference.

RESULTS AND DISCUSSION

X-Ray Diffraction Studies—The X-ray diffraction technique was recently used to study the physical nature of polyvinylpyrrolidone–sulfathiazole coprecipitates (7). The crystalline precipitates of the sulfathiazole in the coprecipitates were easily detected by the presence of the typical spectra of the crystalline forms. Goldberg *et al.* (2, 3) suggested that an α-phase solid solution exists up to 30% chloramphenical in 70% urea and that a β-phase solid solution exists from 10% urea in 90% chloramphenicol. Therefore, to assess the validity of this postulate, the X-ray technique was used in this investigation to see if chloramphenicol crystals could be detected in the resolidified fused masses containing 2, 5, and 10% chloramphenicol.

The X-ray diffraction spectra of the pure chloramphenicol and urea [melting point and DTA thermograms of both compounds used in this study are almost identical to those reported by Sekiguchi *et al.* (1)] are shown in Fig. 2. The diffraction spectra of the mechanical (or physical) and dispersed mixtures of 10% chloramphenicol–90% urea are shown in Fig. 3. By comparing these spectra with the diffraction spectrum of pure chloramphenicol, the peaks, due to chloramphenicol crystals in the physical mixture, can be readily identified, as shown by checkmarks in the spectrum. The presence of these identical chloramphenicol diffraction peaks in terms of diffraction angles in the spectrum of the resolidified fused mass unmistakably show that the mass contains some separated chloramphenicol crystallites. From a theoretical point of view, if the chloramphenicol dissolved completely as a minor component in the urea at the solid state, *i.e.*, solid solution formation, one should not be able to find these typical chloramphenicol diffraction peaks. On the contrary, the lattice parameters, such as diffraction peak angles of the solvent crystal, can be either increased, unchanged, or decreased in the formation of a solid solution (8, 9). No noticeable change in the urea crystalline lattice could be detected in the resolidified fused

[1] Supplied by Parke, Davis and Co.
[2] Mallinckrodt Chemical Works.
[3] Dupont Co.

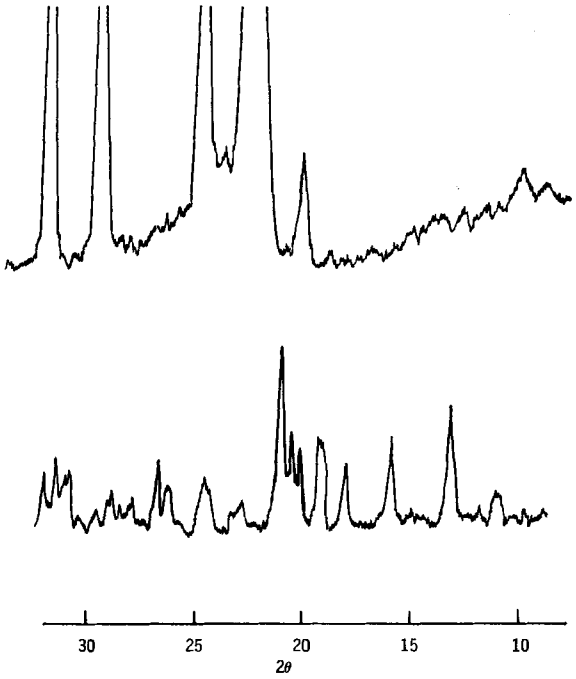

Figure 2—*X-ray diffraction spectra of pure chloramphenicol (bottom) and resolidified pure urea (top).*

mixture, as indicated by the same diffraction peaks of the urea present in the mixture as in the pure urea sample.

The aforementioned diffraction peaks of chloramphenicol are also present in the 5 and 2% resolidified samples, but with a decreasing intensity. These diffraction spectra were run within 2 hr. after the resolidification of the melt by the rapid cooling process. It is well known that a supersaturated solid solution can be often obtained at room temperature by the quenching method, as employed in this study (10). Based on these data, one can, therefore, conclude that the solid solubility of chloramphenicol in this binary system at the eutectic temperature is probably less than 2% w/w, and its solid solubility at ambient temperatures (less than 30°) is certainly less than 2% w/w.

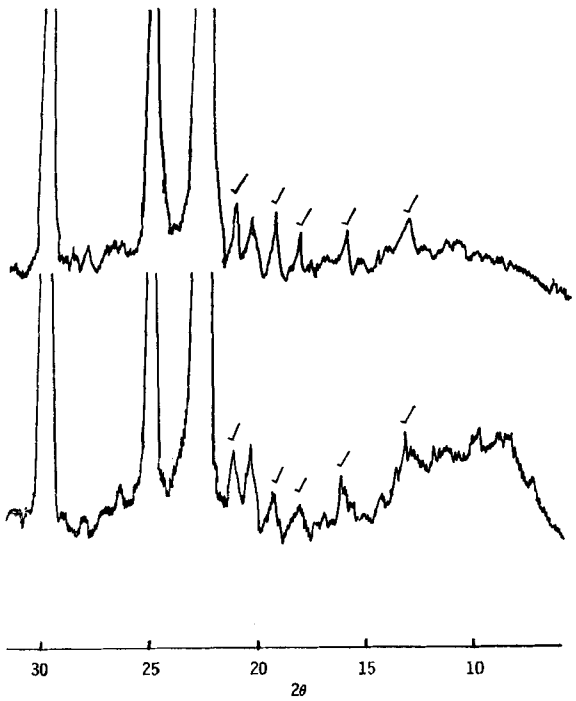

Figure 3—*X-ray diffraction spectra of physical mixture of 10% chloramphenicol–90% urea (bottom) and resolidified fused mixture of 10% chloramphenicol–90% urea (top). Arrows indicate diffraction peaks due to the presence of chloramphenicol crystallites.*

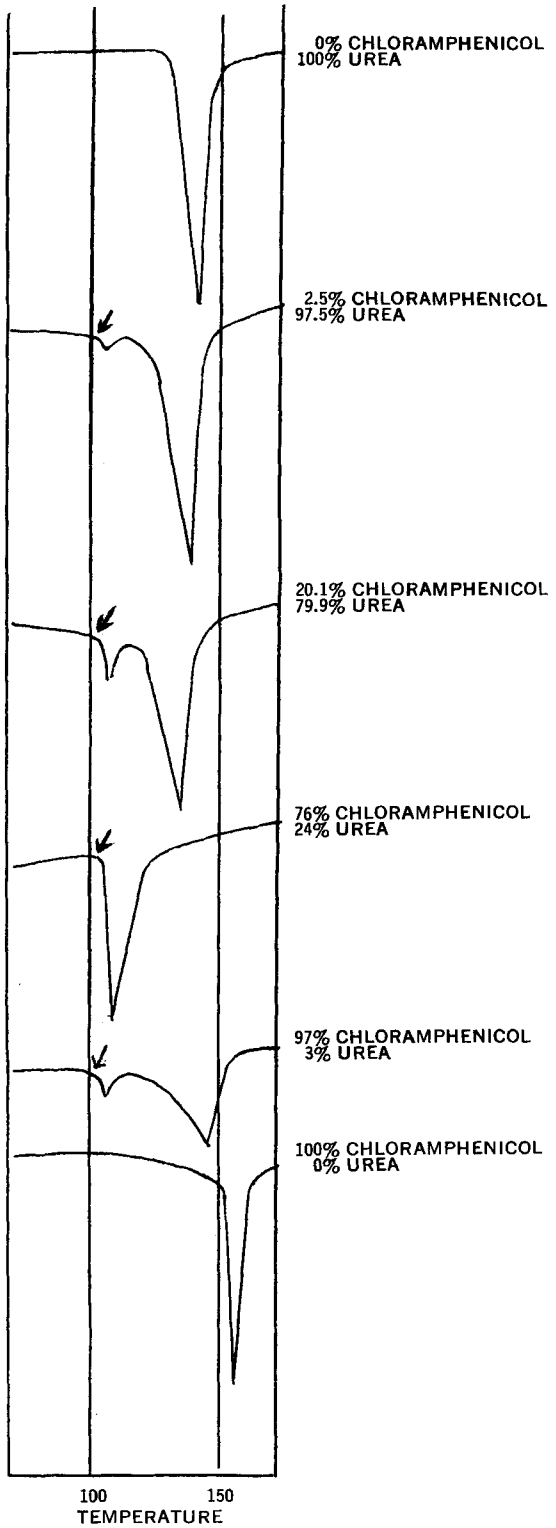

Figure 4—*DTA thermograms of chloramphenicol–urea mixtures redrawn from* Reference 1.

DTA Studies—Figure 4 includes a modified drawing of the original DTA data of Sekiguchi *et al.* (1) for the fused mixtures of chloramphenicol–urea. The top and bottom curves represent the DTA data on the pure compounds. The four intermediate curves are on the respective mixtures noted to the right of the curves. All four of these curves show clear evidence of a eutectic peak (e.p.)

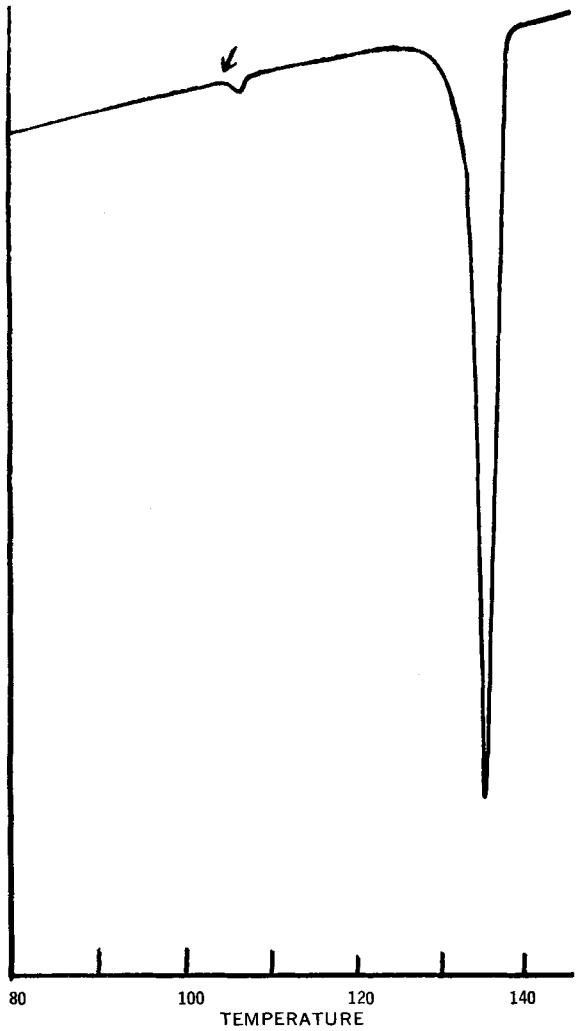

Figure 5—*DTA thermogram of 2% chloramphenicol–98% urea physical mixture run at 5°/min. (arrow indicates the thaw point of the mixture which is equal to the eutectic temperature).*

starting approximately at the same eutectic temperature, as indicated by an arrow (equivalent to e.p. used in the original reference) (11). The data of these samples, ranging from 2.5 to 97% chloramphenicol (w/w), indicate that they all start to thaw at the eutectic temperature. In other words, the eutectic isothermal line in Fig. 1 should extend to at least the 2.5% chloramphenicol–97.5% urea on the left and to at least the 97% chloramphenicol–3% urea on the right (12). Therefore, the solid solubility for chloramphenicol at the eutectic temperature is less than 2.5% w/w, and that for urea is less than 3% w/w in this binary system on the basis of the DTA data.

The original Sekiguchi *et al.* (1) chloramphenicol–urea phase diagram was the result of a thaw–melt study utilizing capillary melting-point tubes. It may have been a difficult task to detect visually the thaw point at the extreme ends of the curve by this method. However, the DTA apparatus is extremely sensitive to endothermic and exothermic reaction, and minute amounts of impurities in samples can be detected by this method (12). The average thaw points from capillary studies reported by Sekiguchi *et al.* (1) for 10 and 5.6% chloramphenicol physical mixtures are 107 ± 1.5 and 113 ± 3°, respectively. The thaw point for 2% chloramphenicol physical mixture might then be expected to be much higher than 113°. Nevertheless, the thaw points of 2, 5, and 10% chloramphenicol physical mixtures are all at 104 ± 1° according to the DTA studies conducted in this laboratory. The value, 104°, is in good agreement with the reported eutectic temperature. The thermogram of 2% chloramphenicol–98% urea run at 5°/min. is shown in Fig. 5.

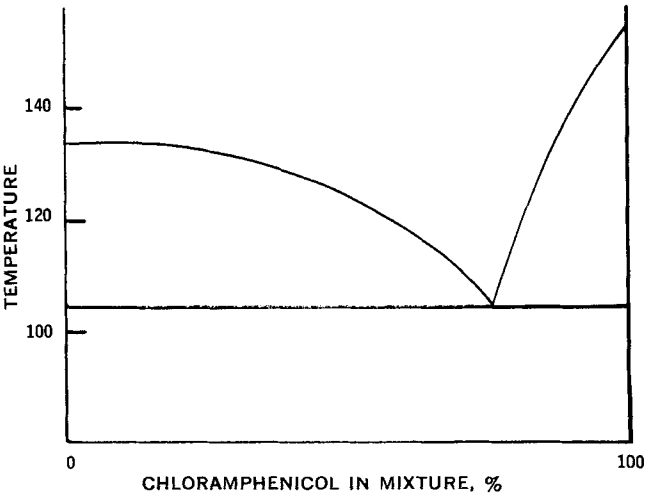

Figure 6—*Phase diagram of a simple eutectic mixture of chloramphenicol–urea system. Negligible solubilities at solid state are not shown in the diagram.*

Mechanisms of Increased Rate of Dissolution—From the DTA and X-ray diffraction evidence, one can conclude that the mutual solid solubility of chloramphenicol and urea is very limited and such a binary system can be more correctly described as a simple eutectic mixture with negligible solid solubility (Fig. 6). Goldberg *et al.* (2, 3) based their postulate on the extremes of the phase diagram, which are clearly not in accord with the DTA or X-ray spectral data reviewed here. It would appear that the original suggestion of Sekiguchi *et al.* (1) of a particle-size effect in increasing rates of dissolution and absorption of chloramphenicol is more in accord with the physical–chemical facts discussed here.

There is little doubt that a solid solution of a poorly water-soluble drug in a rapidly dissolving matrix would result in a rapid availability and absorption of a drug such as chloramphenicol. However, no data are available at present to allow a comparison of a solid solution *versus* a dispersion system as represented by chloramphenicol–urea.

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ACKNOWLEDGMENTS AND ADDRESSES

Received June 19, 1970, from the *College of Pharmacy, Washington State University, Pullman, WA 99163*

Accepted for publication April 13, 1971.

The author thanks the Department of Soils, Washington State University, for permission and help in conducting X-ray diffraction studies.

Present address: School of Pharmacy, University of Illinois at the Medical Center, Chicago, IL 60680