Solid Dispersion of Pharmaceutical Ternary Systems I: Phase Diagram of Aspirin–Acetaminophen–Urea System

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Abstract □ The phase diagram of an aspirin–acetaminophen–urea system was constructed. The data obtained by the thermomicroscopic method showed that the binary systems of aspirin–acetaminophen, aspirin–urea, and acetaminophen–urea are simple eutectic mixtures with negligible formation of solid solutions or molecular compounds. The equilateral triangular phase diagram of the ternary system revealed that it forms, upon solidification, solid dispersions of the mechanical mixture type. The ternary eutectic corresponded to a composition of 60% aspirin, 20% acetaminophen, and 20% urea at 72°. The method of calculating the composition of finally solidified melts, lying within any area of the phase diagram, is presented. Use of the phase diagram in selecting the optimum ratio of components to enhance dissolution rates of these drugs may be possible.

Keyphrases □ Solid dispersions—aspirin–acetaminophen–urea ternary system, phase diagram constructed, physical properties evaluated □ Phase diagram—constructed for aspirin–acetaminophen–urea ternary system solid dispersion □ Analgesics—aspirin–acetaminophen–urea ternary system, phase diagram constructed, physical properties evaluated □ Dosage forms—solid dispersions, aspirin–acetaminophen–urea ternary system, phase diagram constructed, physical properties evaluated

Drug–drug and/or drug–adjuvant interactions in solid dosage forms have gained the interest of pharmaceutical research workers in the last two decades. A considerable change in physical properties of drugs such as dissolution rates, equilibrium solubilities, partition coefficients, and, consequently, bioavailability usually occurs if such interactions take place.

Thermal analysis has been used to construct phase diagrams from which interactions in the solid state can be identified. The cooling curve method (1), the thaw–melt method (2–4), the thermomicroscopic method (5–12), the zone-melting method (13), and differential thermal analysis (9, 14) are among the applied thermal techniques. Reviews of these methods were reported previously (3, 15).

BACKGROUND

Phase diagrams of pharmaceutical binary systems were first reported (16) to explain the obvious enhancement in dissolution rate of two sparingly soluble drugs *via* the solid dispersion technique. Since then, there have been other studies on phase diagrams of various drug–inert carrier binary solid dispersion systems (5–12, 15–22). Phase diagrams were used to study the physical nature of solid dispersions of some drug–carrier (8–11) as well as drug–drug (11, 12) binary systems. Phase diagrams of reported binary systems showed simple eutectic mixtures (5, 11, 12, 17, 19, 21), solid solutions (6–8, 18), glass solutions (20), or molecular compounds (9, 10, 22).

Almost all reported work on pharmaceutical solid dispersions is limited to binary systems. However, a solid dispersion may be composed of one or more active ingredients dispersed in one or more inert carriers to obtain ternary and quaternary systems. Although excellent work on ternary systems has been accumulated in metallurgy, geology, and chemistry (15, 23, 24), pharmaceutical solid dispersion ternary systems have not been studied extensively.

In the present study, the phase diagram of an aspirin–acetaminophen–urea system was constructed. Solid dosage forms of aspirin with acetaminophen are common. Trials to improve the dissolution rate of aspirin (25) or acetaminophen (5, 12) using solid dispersions were reported previously. Furthermore, urea is often used as an inert carrier in binary solid dispersion systems. The information from the constructed phase diagram might help explain the dissolution rate behavior of such a combination of drugs.

EXPERIMENTAL

Materials—Aspirin[1] BP (mp 135–136°), acetaminophen[2] NF (mp 167–168°), and urea[3] (GR) (mp 132–134°) were used as obtained.

Procedure—Phase diagrams of the binary systems aspirin–acetaminophen, aspirin–urea, and acetaminophen–urea were made using the thermomicroscopic method. Various combinations of binary mixtures were weighed and thoroughly mixed. Each mixture was carefully melted, resolidified with mild stirring, and then finely powdered.

Thaw and final melting points of each sample were determined using a hot-stage microscope[4]; the temperature was raised 4°/min. Phase diagrams were constructed by plotting both thaw and melting temperatures *versus* the ratio of components (percent weight per weight).

The phase equilibria of aspirin–acetaminophen–urea ternary systems were initially represented by a triangular prism, whose base was an equilateral triangle (composition triangle). Each vertical face of the prism depicted a two-component system. A number of ternary compositions, represented by points lying on lines connecting the apex of the composition triangle (representing urea) with the opposite side of the aspirin–acetaminophen binary system at 10, 20, 40, 50, 60, and 80% (w/w) of acetaminophen, were selected.

For the detection of the lines of intersections of the parts of the liquidus surface, additional compositions were taken on the lines joining the apexes of the triangle with the binary eutectic compositions on the corresponding opposite side. Thaw and final melting points of all selected ternary mixtures were determined as described. Perpendiculars were then erected at the selected points, and the critical points were plotted on these perpendiculars at the corresponding temperatures. Finally, the three binary and one ternary eutectic points, the curves joining them, and the different isothermal lines were projected on an equilateral triangle.

RESULTS AND DISCUSSION

Binary Phase Diagrams—Phase diagrams of aspirin–acetaminophen and aspirin–urea systems are shown in Fig. 1. Binary systems closely approximating theoretical eutectic mixtures were present. Moreover, the eutectic temperatures of aspirin–urea and aspirin–acetaminophen systems were 83 and 109°, respectively, while the eutectic composition was approximately 25% (w/w) aspirin in both systems. The eutectic composition for the acetaminophen–urea system, on the other hand, was 52% acetaminophen and 48% urea at 114°, which closely coincided with the values reported by Goldberg *et al.* (5). No solid solubility or molecular compound formation was evidenced in the three binary systems studied.

Ternary Phase Diagram—The phase equilibria in aspirin–acetaminophen–urea are represented by a triangular prism (Fig. 2). The three vertical faces of the prism depict the three binary systems aspirin–acetaminophen, aspirin–urea, and acetaminophen–urea. Points E_1, E_2, and E_3 are the binary eutectics. The liquidus of the ternary mixtures is formed by the three surfaces: $t_AE_2E_tE_1t_A$, $t_pE_3E_tE_1t_p$, and $t_UE_2E_tE_3t_U$.

Lines E_1E_t, E_2E_t, and E_3E_t are the intersections of the parts of the liquidus surface and correspond to the melting point of the binary eutectics

[1] Bayer, Leverkusen, West Germany.
[2] Courtesy of Alexandria Co. for Pharmaceutical and Chemical Industry, Egypt.
[3] E. Merck, Darmstadt, West Germany.
[4] Microheating table "Boetius," GDR.

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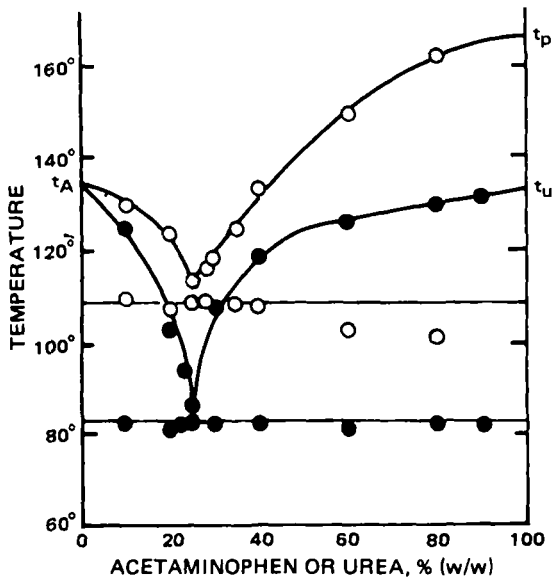

Figure 1—*Phase diagrams of aspirin–acetaminophen* (○), *and aspirin–urea* (●) *binary systems.*

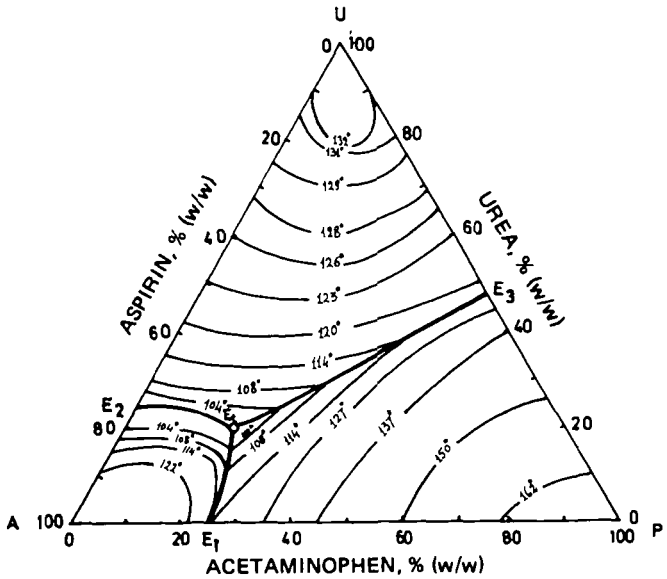

Figure 3—*Equilateral triangular phase diagram of aspirin (A)–acetaminophen (P)–urea (U) system showing isothermal lines.*

in the ternary system. These lines intersect at the common point E_t, which represents the eutectic aspirin–acetaminophen–urea of composition 60:20:20% (w/w) at 72°. This ternary system forms, upon solidification, solid dispersions of the mechanical mixture type (Fig. 2) (23). The solids aspirin, acetaminophen, and urea separate in the pure state, and there is no formation of compounds or solid solutions.

To obtain a convenient picture of the complete phase model, the three binary and the one ternary eutectic points and the curves joining them were projected on a horizontal plane, as shown by the equilateral triangular phase diagram (Fig. 3). Sections taken through the prism at a number of temperatures were projected on the triangle, and isothermal lines were presented as shown in Fig. 3. Eutectic lines E_1E_t, E_2E_t, and E_3E_t as well as lines AE_t, PE_t, and UE_t divide the phase diagram into six areas (24) (Fig. 4). From Fig. 4, it is possible to follow the solidification of any ternary melt having a composition within any of these six areas.

Calculation of the amounts of various solids deposited in such a crystallization process can be illustrated by the following example. On cooling a melt of composition h to a temperature at which the vertical line from h strikes the liquidus surface $t_UE_2E_tE_3t_U$, solid urea (in this case called the primary phase) begins to separate. As cooling proceeds, the composition of the residual liquid follows the linear extension of Uh to q.

On further cooling, solid acetaminophen as well as solid urea start to separate. At the same time, the liquid composition leaves q and alters its course to remain on E_3E_t. Eventually, the temperature of E_t is reached at which the liquid remaining solidifies completely to give the ternary eutectic mixture aspirin–acetaminophen–urea. While this occurs, the temperature must remain constant. The compositions of h, q, and E_t, determined from Fig. 4, are given in Table I.

Suppose that 100 g of the melt of composition h is gradually cooled and that x is the weight of urea deposited from h to q. Of the original 30 g of urea, there is now left in solution $(30 - x)$ g of urea but all of the original 45.5 g of aspirin. Therefore, in the liquid at q, the weight of urea/aspirin $= (30 - x)/45.5$, and this ratio equals 25.5/48 from the known composition of q. Solving for x gives 5.8 g of urea deposited by the time q is reached. The residual solution at q thus contains 45.5 g of aspirin, 24.5 g of acetaminophen, and $(30 - 5.8 = 24.2)$ g of urea.

By similar reasoning, if an additional y g of urea and z g of acetaminophen are deposited from q to E_t, y and z are found from the following equations, which are valid to E_t: weight of urea/aspirin $= 20/60 = (24.2 - y)/45.5$ and weight of acetaminophen/aspirin $= 20/60 = (24.5 - z)/45.5$. Solving for y gives 9.0 g of urea, and solving for z gives 9.3 g of acetaminophen deposited. Consequently, the residual solution now consists of 45.5 g of aspirin, $(24.2 - 9.0 = 15.2)$ g of urea, and $(24.5 - 9.3 = 15.2)$ g of acetaminophen. These are the amounts of the solid components that E_t gives on complete solidification. The finally solidified mixture of composition h, as well as any ternary mixture within area IV (Fig. 4), consists of the surplus component urea, the binary eutectic acetaminophen–urea,

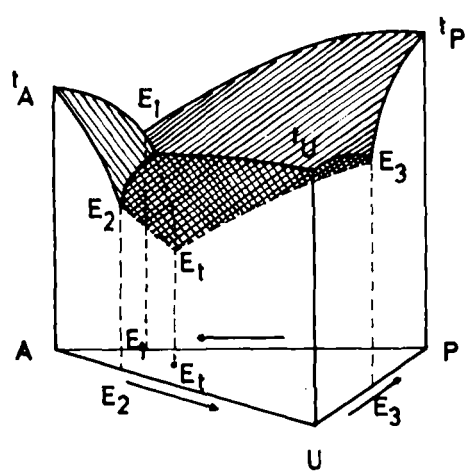

Figure 2—*Model phase diagram of aspirin (A)–acetaminophen (P)–urea (U) system. Key: E_1, aspirin–acetaminophen eutectic; E_2, aspirin–urea eutectic; E_3, acetaminophen–urea eutectic; and E_t, ternary eutectic.*

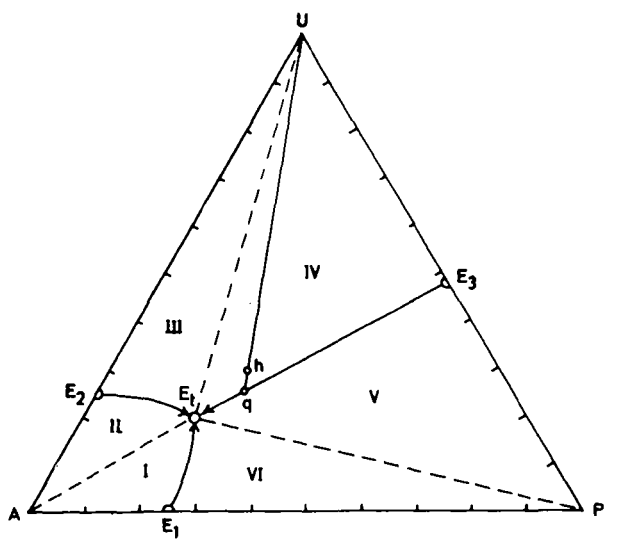

Figure 4—*Phase diagram of aspirin (A)–acetaminophen (P)–urea (U) system showing the final composition of solidified melts of the various areas I–VI. Key: I, A + AP + APU; II, A + AU + APU; III, U + AU + APU; IV, U + PU + APU; V, P + PU + APU; and VI, P + AP + APU.*

Table I—Compositions of h, q, and E_t Determined from Fig. 4

Sample (Melt)	Composition, % (w/w)		
	Aspirin	Acetaminophen	Urea
h	45.5	24.5	30.0
q	48.0	26.5	25.0
E_t	60.0	20.0	20.0

and the ternary eutectic aspirin–acetaminophen–urea. Similarly, the composition of other solidified ternary mixtures within the areas (I–VI) can be estimated (1).

On the other hand, ternary mixtures of compositions along line E_1E_t, E_2E_t, or E_3E_t consist of the binary eutectic aspirin–acetaminophen, aspirin–urea, or acetaminophen–urea, respectively, as well as the ternary eutectic aspirin–acetaminophen–urea when completely solidified. Ternary mixtures of compositions along lines AE_t, PE_t, and UE_t contain no binary eutectics but only the surplus component aspirin, acetaminophen, or urea, respectively, and the ternary eutectic. The ternary mixture of the composition corresponding to point E_t consists only of the ternary eutectic when completely solidified (23).

Information about the composition of solidified melts is useful in explaining dissolution patterns of drugs from binary solid dispersion systems (11, 14). It is hoped, therefore, that the knowledge obtained from the ternary phase diagram of the aspirin–acetaminophen–urea system will help in selection of the optimum ratio of these components (within therapeutic doses) for enhancement of their dissolution rates and improved bioavailability. Dissolution studies on this ternary system will be presented in Part II.

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