PHARMACEUTICS OF SOLIDS AND SOLID DOSAGE FORMS

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Pharmaceutics of Solids and Solid Dosage Forms

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Preface

Everett Hiestand visited the School of Pharmacy at the University of Wisconsin in May 1975 and presented a series of lectures. After one of his illuminating presentations he commented, in response to a question from the audience, that aside from taking great pleasure in doing the solids research he had described, he had to ask himself why this work had not been done before. This question applies to many areas in the field of pharmaceutical solids, and the text that follows presents the state of this science on a somewhat basic level.

The area of pharmaceutical solids constitutes a fascinating field of knowledge that should impart great pride to those in the profession of pharmacy. It also constitutes an area of research that (strange as it may seem) still calls for much experimentation and validation. It is hoped that this text will aid other teachers of pharmacy and other researchers in the area of pharmaceutical solids.

JENS T. CARSTENSEN

Monona, Wisconsin
September 1976

Introduction

The text that follows is based on lectures presented at the School of Pharmacy at the University of Wisconsin in a required course in the pharmacy curriculum. Students enrolled in this course are in their second professional (fourth overall) year of study; the pharmacy program is of a five-year sequence, with three years at the professional level.

The purpose of this course is to give the student a sense of the importance of the basic scientific principles (taught in two prerequisite courses in pharmaceutics) on the manufacturing, formulation, and biopharmaceutical aspects of solid dosage forms. A set of laboratory experiments (Chapter VIII) accompany the course. It is *not* the intent to make the student a proficient pharmaceutical engineer or laboratory technician, but rather to make the students appreciate the impact of the basic concepts on the final dosage form and its effect. For this reason, each chapter is followed by a section denoted "Questions." Questions of this type are used in a six-week, a twelve-week, and a final exam and constitute minimum competency level (60% or D grade). Since the laboratory counts 10% and usually constitutes a good grade (mostly A), a student with even minimal mathematical comprehension can attain a C grade (70%) in the course, *and* (and this is more important than the grade) can acquire an appreciation of the factors that are of importance in the solid dosage form. For the more proficient students, mathematical examples should be mastered, and such examples are included in each chapter. Problems of this type constitute 20% of the grade allowing the great majority of students to obtain a B grade if they put forth sufficient effort. Finally, 10% of the grade is made up of deeper questions allowing the very proficient (honors-type) student to distinguish himself. In three years

of experience the grades have been about 10% A, 30% B, 55% C, and 5% D, with only very occasional failures.

The course consists of two weekly lectures of 50 minutes each and one three-hour laboratory experiment every second week for a total of three credits.

J.T.C.

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I. Fundamental Solids Concepts

I-1 CRYSTALLINE SOLIDS

Solids exist as amorphous and as crystalline solids. Amorphous solids have no periodicity, whereas crystals do. Figure I-1 shows (schematically) a periodic array and could be a substance such as an ionic crystal (Na^+Cl^-), a molecular crystal, or a hydrate ($M \cdot x H_2O$) (1, 2).

In pharmaceutical systems the substances encountered are usually either ionic (e.g., $CaHPO_4$), organic (and mostly hydrogen-bonded) (e.g., *p*-aminosalicylic acid), or amorphous. The hydrates comprise an important subgroup in the crystalline solids (e.g., lactose hydrate).

Molecular distances in crystals are of the order of angstroms (Å), $1\ Å = 10^{-8}$ cm; to measure such small distances, a measuring tool of the same order of magnitude is necessary. X rays have wavelengths of orders of magnitude comparable to the spacing in crystals; as shown in Fig. I-2, an X ray strikes the surface of the solid at an angle θ. The X rays are reflected from two planes d cm apart; the "lower" X ray will travel twice a distance of $d \sin \theta$ further than the other. If the two are in phase they will reinforce one another, so that this distance is a multiple of the wavelength λ:

$$n\lambda = 2d \sin \theta. \tag{I-1}$$

This is known as Bragg's law (3).

The angles in a crystal are not necessarily 90° (as implied in Fig. I-1), and a, b, and c (Fig. 1-1) are denoted crystal spacings and need not be equal. The crystal spacings can be used to evaluate molecular dimensions,

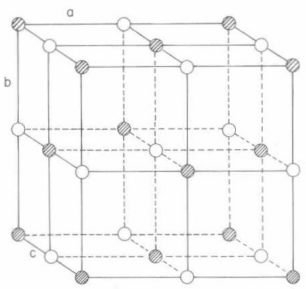

Fig. I-1 Arrangements of molecules or ions in a lattice.

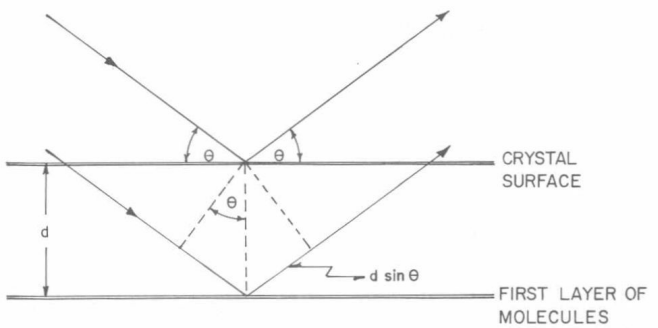

Fig. I-2 Schematic drawing of X-ray being reflected from surface and first molecular layer of a crystal.

a point of interest in dissolution kinetics. This is best illustrated by the following example.

Example I-1

Outin, Baenziger, and Guillory (4) give the following crystal dimensions for the α form of (monoclinic) sulfanilamide:

$$a = 9.04 \text{ Å}, \; b = 9.03 \text{ Å}, \text{ and } c = 10.06 \text{ Å}.$$

The monoclinic angles are 110°. If for simplicity it is assumed that the angles are perpendicular, what is the molecular volume of the sulfanilamide in the crystal?

Answer I-1

$$9.04 \cdot 9.03 \cdot 10.06 = 821.2 \text{ Å}^3.$$

Frequently (and not quite correctly, as we later see) the molecular

volume (V) is converted to an equivalent "radius," r, by assuming the volume to be a cube with the (assumedly spherical) molecule inscribed, that is,

$$(2r)^3 = V. \tag{I-2}$$

In the example above the molecular radius would have calculated out to be given by: $2r = (821.2)^{1/3} = 9.36$, so $r = 4.7$ Å.

A crystal form is not characteristic for a compound or vice versa, as we shall see in two sections hence.

I-2 GIBBS'S PHASE RULE

Assume that we are observing a binary system as shown in Fig. I-3, with two components, A and B. A is present in the liquid phase (l) in mole fraction x [B in $(1-x)$]. The total vapor pressure is P and the partial vapor pressure of A is P_A (i.e., that of B is $P - P_A$). The vapor phase is denoted v below and chemical potentials by μ. The temperature is denoted T (°K) and the gas constant is assumed to be $R = 2$ cal/deg-mole.

If the standard chemical potential of a substance is denoted $\mu°$, then the chemical potential of the substance, μ, is given by:

$$\mu^l = \mu° + RT \ln x$$

for a substance in solution and

$$\mu^v = \mu_v° + RT \ln P$$

for a substance in gaseous state. If, for instance, a substance is present in solution and in the vapor phase, then the chemical potentials μ^l and μ^v must be equal for equilibrium to exist. It is noted that the chemical potentials at a particular temperature would be a concentration- (or

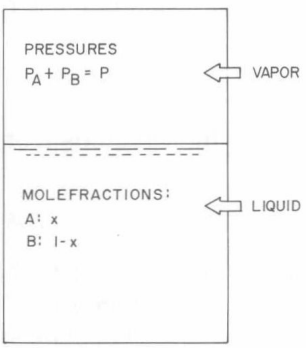

Fig. I-3 Binary liquid in equilibrium with gas phase.

pressure-) dependent number. To pinpoint which symbols represent variables and which do not (at a particular temperature), certain values have been arbitrarily assigned to the standard chemical potentials in the equations that follow. These equations refer to the situation in Fig. I-3 under equilibrium conditions at a given temperature.

$$\mu_A^l = 15 + 2T \ln x; \tag{I-3}$$

$$\mu_A^v = 23 + 2T \ln P_A; \tag{I-4}$$

$$\mu_B^l = 7 + 2T \ln(1 - x); \tag{I-5}$$

$$\mu_B^v = 9 + 2T \ln(P - P_A). \tag{I-6}$$

Since the system is in equilibrium, $\mu_A^l = \mu_A^v$ and $\mu_B^l = \mu_B^v$, so that by equating Eq. I-3 with Eq. I-4 and Eq. I-5 with I-6 we obtain:

$$15 + 2T \ln x = 23 + 2T \ln P_A \tag{I-7}$$

$$7 + 2T \ln (1 - x) = 9 + 2T \ln (P - P_A) \tag{I-8}$$

Equations I-7 and I-8 are two equations with four unknowns; if we decide on a pressure and a temperature (i.e., decide *two* variables), we can solve for the other two; we say that we have two degrees of freedom. We could have decided on x and P_A as well and found P, T, and other parameters. In general the degrees of freedom (df) are equal to the number of variables minus the number of equations.

If there are C compounds and P phases, the number of equations is $(P - 1)$ equations per compound, in other words,

$$C[P - 1] \text{ equations.}$$

The number of variables is $C - 1$ composition variables per phase. Note that if one has three compounds, and one is present in a mole fraction 0.1, and one at 0.4, then by difference the last concentration is given (0.5), so there are only two composition variables (3-1) for three compounds. Temperature and pressure are also variables, so there are a total of $P[C - 1]$ composition variables from the P phases plus two more (temperature and pressure), hence an overall total of

$$P[C - 1] + 2 \text{ variables.}$$

The df is then obtained by subtracting the number of equations from the number of variables, then

$$df = P[C - 1] + 2 - C[P - 1] = C - P + 2 = df. \tag{I-9}$$

This is known as Gibb's phase rule. A well-known example of this is the triple point of water, where there are three phases (and one compound), that is, $df = 1 - 3 + 2 = 0$. If one variable (e.g., temperature) is changed, then a phase disappears.

Example I-2

An aqueous solution of dextromethorphan (an antitussive) is cooled. At a particular temperature T, crystals start forming; further cooling causes the temperature to drop further, while more and more crystals precipitate out. Can these crystals be both dextromethorphan and ice?

Answer I-2

Consider a particular temperature $T_1 < T$. If both ice and dextromethorphan are present as crystals, then there are two solid phases, one liquid and one vapor. There are two compounds, so $P = 4$ and $C = 2$, in other words, $df = 2 - 4 + 2 = 0$, so that if the temperature were increased or lowered, a phase would disappear, in contrast to the findings ("the temperature drops further while more and more precipitate out"). Hence the solid phase must be either ice or dextromethorphan.

I-3 POLYMORPHS

Most organic substances exist in more than one crystal form. For instance, the data by Outin, Baenziger, and Guillory (4) (quoted in Example I-1) give the crystal forms for sulfanilamide shown in Table I-1. The various forms in Table I-1 are denoted *polymorphs*. It should be noted that the molecule itself is the same in each form; only the packing of the molecules differs from one form to the next.

Three of the polymorphs in Table I-1 are of the same crystal system (monoclinic) and one is of a different system. There are eight crystal systems; these are not elaborated on here, but it is important to distinguish between crystal *system* and crystal *habit*. When a crystal grows, it has certain growth rates in the different crystallographical directions. A solvent may retard the growth in the a direction (Fig. I-4), in which case a "plate" is formed or the growth may be retarded in two directions (e.g., a

Table I-1 Polymorphs of Sulfanilamide (4)

Form	Crystal System	(a)	(b)	(c)	Monoclinic Angle	Molecular Volume
α	Monoclinic	9.04	9.03	10.06	110°42′	821.2 Å^3
β	Monoclinic	8.95	9.06	9.96	110°	807.6 Å^3
γ	Monoclinic	7.78	12.94	7.95	106°1′	800.4 Å^3
δ	Orthorhombic	14.81	5.65	18.46		(777.3 Å^3)

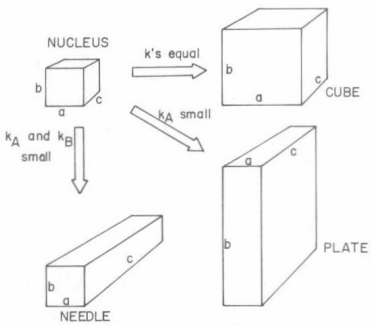

Fig. I-4 Growth patterns of nuclei leading to cubes, plates, and needles.

and b), in which case a "needle" results. The plate or needle may, however, be of the same crystal system (as is the case in Fig. I-4) (5). Table I-1 shows the fallacy of placing too much importance on molecular radii obtained from crystallographic data, since the four forms would give radii of 4.68 Å (α), 4.65 Å (β), 4.64 Å (γ), and 4.59 Å (δ). It is noted that with one significant figure, the figures correspond, so that with such a reservation the method has some merit.

It is instructive to view polymorphs with respect to a phase diagram. A phase diagram gives the vapor pressure of the compound as a function of temperature, and an example of a phase diagram is shown in Fig. I-5(A). At temperatures below T_t form I is stable, but if heated beyond this temperature form II is stable up to T_m, where it melts. If heated rapidly, the transition may not occur and I will melt at T'_m. It is noted that $T'_m < T_m$, so that the melting point of the polymorph stable at the higher temperature is the highest. Just as it is possible to heat I beyond T_t without conversion, so is it possible to cool II below T_t without conversion. In this state II is denoted *metastable.* It may stay in the more energetic state for indefinite periods, even though I would be the more stable form at the temperature in question (6).

It is instructive to apply Gibb's phase rule to the phase diagram. Points have zero *df.* Lines have one *df.* Planes have two *df.* For instance, a point below C is in a plane, is one phase (gas), and has two *df.* Point B (on a line) consists of melt and vapor (i.e., two phases) and one *df* (e.g., one can vary the temperature without loss of a phase). C, however, contains three phases (two solid and one vapor phase), so *df* are zero, and temperature cannot be changed without loss of a phase.

All three curves in Fig. I-5A (i.e., DC, CE, and EB) adhere to a Clausius-Clayperon type equation, that is,

$$\log P = \nu \frac{1}{T} + \sigma, \tag{I-10}$$

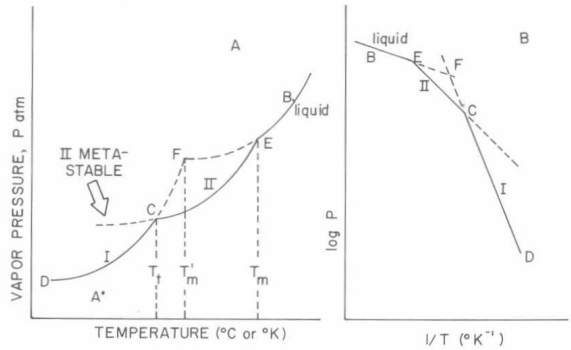

Fig. I-5 Phase diagram of substance existing in two polymorphic forms. **A**: Linear representation, **B**: Clausius–Clapeyron representation.

where ν and σ are constants. If P is plotted semilogarithmically versus $1/T$, where T is the absolute temperature (see Appendix A), then straight lines such as those shown in Fig. I-5B result.

Two polymorphs of a substance will have different solubility. When the logarithm of the solubility is plotted versus reciprocal absolute temperature, two intersecting lines will result, and the intersection occurs at the transition temperature (i.e., at $1/T_t$). This is best illustrated by Example I-3.

Example I-3

Milosovich (7) reported the solubilities of forms I and II (two polymorphs) of sulfathiazole in 95% ethanol as shown in Table I-2. What is the transition temperature for the two polymorphs?

Table I-2 Solubility of Sulfathiazole in 95% Ethanol (7)

Temperature (°C)	1000/T (°K^{-1})	Solubility (g/1000 g) I	II
59.1	3.00	31.5	—
48.8	3.10	19.8	28.1
39.4	3.19	14.0	21.4
29.6	3.30	—	16.7
24.1	3.36	—	14.2

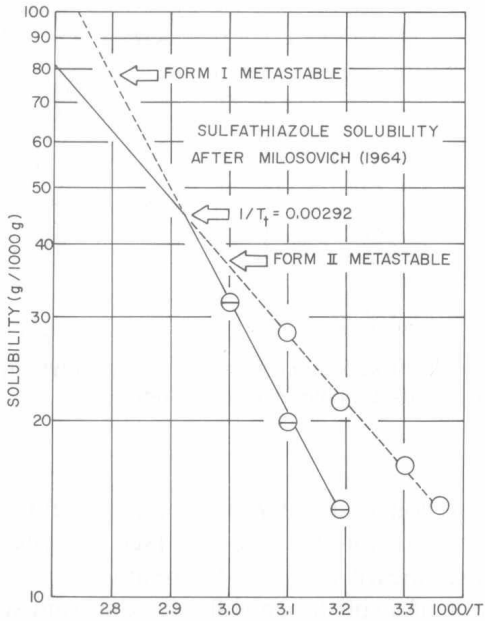

Fig. I-6 Graphical determination of transition point using solubility data. After Milosovich (7).

Answer I-3

The temperatures (°C) are converted to °K by adding 273 to them. $1000/T$ is then obtained from the table in Appendix A. $1000/T$ values appear along abscissas on semilogarithmic paper and solubility, along ordinates. Figure I-6 shows the results; the two lines intersect at $1000/T = 2.92$ (or $1/T = 0.00292$); in other words, $T = 1/0.00292 = 342.5°K = 69.5°C$.

Polymorphism is pharmaceutically important due to the solubility implications involved. If a metastable form is used in a solid dosage form, then its solubility is higher than if the stable form were used and hence, as we shall see, the dissolution rate will be higher. In biopharmaceutical aspects we are concerned with the solubilities at body temperature (i.e., 37°C).

I-4 SALT PAIRS AND RELATIVE HUMIDITY

Figure I-7 shows a conventional vapor-pressure diagram of Na_2HPO_4, which exists as anhydrous salt, as dihydrate, as heptahydrate, and as