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Salt formation to improve drug solubility ☆

Abu T.M. Serajuddin *

Science, Technology and Outsourcing Section, Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ 07936, USA

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Abstract

Salt formation is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. In this article, physicochemical principles of salt solubility are presented, with special reference to the influence of pH–solubility profiles of acidic and basic drugs on salt formation and dissolution. Non-ideality of salt solubility due to self-association in solution is also discussed. Whether certain acidic or basic drugs would form salts and, if salts are formed, how easily they would dissociate back into their free acid or base forms depend on interrelationships of several factors, such as S_0 (intrinsic solubility), pH, pK_a, K_{sp} (solubility product) and pH_{max} (pH of maximum solubility). The interrelationships of these factors are elaborated and their influence on salt screening and the selection of optimal salt forms for development are discussed. Factors influencing salt dissolution under various pH conditions, and especially in reactive media and in presence of excess common ions, are discussed, with practical reference to the development of solid dosage forms.

Keywords: Salt; solubility; pH–solubility profile; Common-ion effect; Self-association; Dissolution rate; Salt selection; Counterion; Microenvironmental pH

Contents

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* Tel.: +1 862 778 3995; fax: +1 973 781 7329.
E-mail address: abu.serajuddin@novartis.com.

1. Introduction

Salts of acidic and basic drugs have, in general, higher solubilities than their corresponding acid or base forms. Salt formation to increase aqueous solubility is the most preferred approach for the development of liquid formulations for parenteral administration [1]. For solid dosage forms, Nelson [2,3] demonstrated as early as in 1950s that dissolution rates of salt forms of several weakly acidic compounds under gastrointestinal (GI) pH conditions were much higher than those of their respective free acid forms. He attributed the higher dissolution rate of a salt to its higher solubility (relative to the free acid form) in the aqueous diffusion layer surrounding the solid. Pronounced differences were observed in rates and extents of absorption of novobiocin [4] and tolbutamide [5] as compared to their respective sodium salts. Monkhouse and coworkers [6,7] reviewed physicochemical and biopharmaceutical advantages of salts over their free acid or base forms. The interest in salt formation has grown greatly over the past half a century and, in recent years, it has become the most commonly applied technique of increasing solubility and dissolution rate in drug product development.

The primary reason for the increased interest in salt formation is that with the progress in medicinal chemistry and, especially due to the recent introduction of combinatorial chemistry and high-throughput screening in identifying new chemical entities (NCE) [8,9], the solubility of new drug molecules has decreased sharply [10]. While a value of less than 20 μg/mL for the solubility of a NCE was practically unheard of until the 1980s, the situation has changed so much that in the present day drug candidates with intrinsic solubilities (solubility of neutral or unionized form) of less than 1 μg/mL are very common [11]. Lipinski [12] reported that 31.2% of a group of 2246 compounds synthesized in academic laboratories between 1987 and 1994 had solubility equal to or less than 20 μg/mL. According to the recent experience of the present author, approximately one-third of new compounds synthesized in medicinal chemistry laboratories have an aqueous solubility less than 10 μg/mL, another one-third have a solubility from 10 to 100 μg/mL, and the solubility of the remaining third is >100 μg/mL. With such a predominance of poorly water-soluble compounds, careful attention must be paid to identification and selection of optimal salt forms for development. In certain cases, salt formation may not be feasible due to physical and chemical properties of NCEs. In other cases, even though salts can be synthesized, they may not serve the purpose of enhancing dissolution rate and bioavailability. It is important that the reasons behind such situations are understood.

Despite major advantages of the use of salts, only limited attention has been paid historically to the selection of optimal the beginning of drug development programs, salts were often selected based on ease of synthesis, ease of crystallization, cost of raw material, *etc.*, and no systematic studies to evaluate their physicochemical properties, such as physical and chemical stability, processability into dosage forms, solubility and dissolution rate at different pH conditions, *etc.*, were conducted. If a salt was later found to be suboptimal for the desired formulation or if problems developed, it was often difficult to change the salt form without delaying the drug development program, since it required repeating most of the biological, toxicological, formulation and stability tests that had already been performed [14]. For most practical purposes, identification and selection of salt forms of NCEs still remain a trial and error process.

One major objective of the present article is to review the basic principles of salt formation and how salts influence solubility and dissolution rate in a comprehensive manner, such that they can be easily applied to the development of drug substances as well as dosage forms. Efforts will be made to indicate the application of such principles in screening various salt candidates for a NCE, identification of optimal salt form, and ultimately formulation of dosage forms using the selected salt. Wherever possible, advantages and disadvantages of salt forms relative to their respective free acid or base forms will be presented.

One particular issue with the use of salts in drug development is that, while salts are usually prepared from organic solvents, they are destined to encounter aqueous environment (water, humidity) during dosage form development and, in case of an orally administered tablet or capsule, at the time of dissolution in GI fluid. Therefore, a perfectly good salt isolated from an organic solvent may not behave well in an aqueous environment due to low solubility, conversion to free acid or base forms, poor stability, *etc.*, thus limiting its use in dosage forms.

2. Principles of salt formation and salt solubility

The aqueous solubility of an acidic or basic drug as a function of pH dictates whether the compound will form suitable salts or not and, if salts are formed, what some of their physicochemical properties might be [15]. pH–solubility interrelationships also dictate what counterions would be necessary to form salts, how easily the salts may dissociate into their free acid or base forms, what their dissolution behavior would be under different GI pH conditions, and whether solubility and dissolution rate of salts would be influenced by common ions [15,16].

2.1. pH–solubility interrelationship of free base and its salt

Kramer and Flynn [17] demonstrated that the pH–solubility

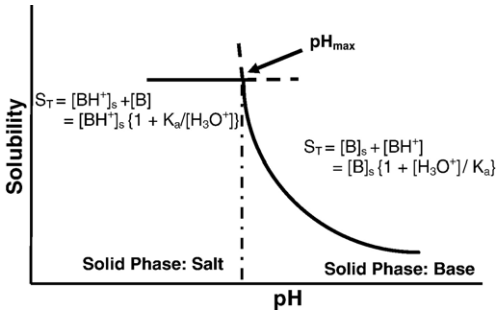


Fig. 1. Schematic representation of the pH–solubility profile of a basic drug indicating that the solubilities may be expressed by two independent curves and that the point where two curves meet is the pH_{max} (reproduced from Ref. [15] with permission).

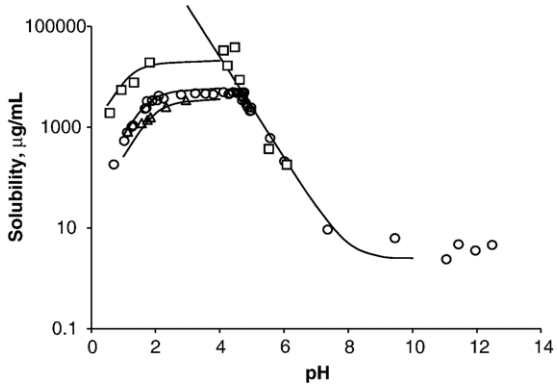


Fig. 2. pH–solubility profiles of haloperidol determined by using methanesulfonic (mesylic) (□), hydrochloric (○) and phosphoric (△) acids (reproduced from Ref. [24] with permission).

curves, one where the free base is the saturation or equilibrium species and the other where the salt is the equilibrium species. Essentially, the following equilibrium exists when a basic compound or its salt is dissolved in water:

$$BH^+ + H_2O \overset{K_a}{\Leftrightarrow} B + H_3O^+ \quad (1)$$

or

$$K_a = \frac{[B][H_3O^+]}{[BH^+]} \quad (2)$$

where BH^+ and B represent, respectively, protonated (salt) and free base forms of the compound. When the aqueous medium at a given pH is saturated with the free base, the total solubility (S_T) at that pH may be expressed as follows:

$$S_T, \text{base}(pH > pH_{max}) = [B]_s + [BH^+] = [B]_s\left(1 + \frac{H_3O^+}{K_a}\right) = [B]_s\left(1 + 10^{pK_a - pH}\right) \quad (3)$$

where the subscript "s" represents the saturation species. On the other hand, when the salt is the saturation species, the equilibrium solubility at a particular pH may be expressed by:

$$S_T, \text{salt}(pH < pH_{max}) = [BH^+]_s + [B] = [BH^+]_s\left(1 + \frac{K_a}{H_3O^+}\right) = [BH^+]_s\left(1 + 10^{pH - pK_a}\right) \quad (4)$$

The two independent curves mentioned above may be obtained by varying hydrogen ion concentrations (or pH) in Eqs. (3) and (4), and the point where the curves intersect is called pH_{max}, the pH of maximum solubility. This is shown schematically in Fig. 1, where the solubility profile at a pH higher than the pH_{max} is represented by Eq. (3), while Eq. (4) represents the solubility profile below pH_{max}. If the solid phase that is in equilibrium with a solution is analyzed, it would be the free base at pH>pH_{max} and the salt

only one point, can both the free base and salt coexist as solids. If the pH of a saturated solution with excess solid free base is lowered from above the pH_{max} to below the pH_{max}, the solid phase will convert to the salt, and it is important to note here that the pH will not drop below pH_{max} until enough acid is added to convert the entire excess free solid base into salt. The reverse is true for the conversion of a salt to the free base; no free base will precipitate out until the pH is raised above the pH_{max}.

There are numerous reports in the literature confirming interrelationships of solubilities of bases and their salt forms as per the schematics in Fig. 1 [17,18–23]. An example of typical pH–solubility profiles is given in Fig. 2, where solubilities of haloperidol and its methanesulfonate (mesylate), hydrochloride and phosphate salts as a function of pH are shown [24].

2.2. pH–solubility interrelationship of free acid and its salt

Fig. 3 shows a schematic diagram for the pH–solubility interrelationship of a free acid and its salt form. The free acid would be the equilibrium species at a pH below pH_{max}, and it would convert to a salt only if it is equilibrated with a solution at a pH above pH_{max} by adding a sufficient quantity of an alkali or

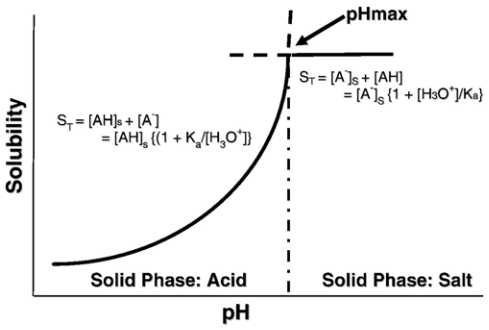


Fig. 3. Schematic representation of the pH–solubility profile of an acidic drug indicating that the solubility may be expressed by two independent curves and

organic counterion. The relevant equations below and above pH_{max} are given below [25]:

$$S_T, \text{acid}(pH<pH_{max}) = [AH]_s + [A^-] = [AH]_s\left(1 + \frac{K_a}{[H_3O^+]}\right) = [AH]_s\left(1 + 10^{pH-pK_a}\right) \quad (5)$$

$$S_T, \text{salt}(pH>pH_{max}) = [A^-]_s + [AH] = [A^-]_s\left(1 + \frac{[H_3O^-]}{K_a}\right) = [A^-]_s\left(1 + 10^{pK_a-pH}\right) \quad (6)$$

As indicated in Fig. 3, the solid phase in equilibrium with a saturated solution at $pH<pH_{max}$ is the free acid and the solid phase at $pH>pH_{max}$ is the salt; only at pH_{max}, both forms coexist. Interconversion from the salt to the free acid form or *vice versa* may occur if the pH shifts from one side of the pH_{max} to the other. There are numerous reports in the literature indicating that Eqs. (5) and (6) are, in general, followed for solubilities of free acids and their salts, respectively [22,23,26–29]. In all cases, salts had higher solubilities than their corresponding free acids, although solubilities of different salt forms of a particular acid could vary.

2.3. Effect of counterion on salt solubility

Salt-forming agents used to prepare salts, such as acids to form salts of basic drugs and bases to form salts of acidic drugs, exert influences on salt solubility by exerting common-ion effects in solution. This may be seen in Fig. 2, where solubilities of methanesulfonate, hydrochloride and phosphate salts of haloperidol decreased gradually at pH below 2.5. This is due to the common-ion effect since the acids used to lower pH generated excess counterions.

The common-ion effect may be explained by the following equilibrium that exists below pH_{max} for the salt of a basic drug:

$$(BH^+X^-)_{solid} \Leftrightarrow [BH^+]_s + [X^-] \quad (7)$$

where $(BH^+X^-)_{solid}$ denotes undissolved solid salt that is in equilibrium with solution, $[BH^+]_s$ is the salt solubility, and $[X^-]$ is the counterion concentration. The apparent solubility product (K'_{sp}) can be derived from Eq. (7) as follows:

$$K'_{sp} = [BH^+]_s[X^-] \quad (8)$$

In the absence of excess counterion, $[BH^+]_s = [X^-]$, and therefore, solubility = $\sqrt{K'_{sp}}$. Under such a condition, the solubility of a salt remains unchanged as seen in the flat region of salt solubility in Fig. 2. On the other hand, if a significant amount of excess counterion is used either to lower pH or as a formulation adjuvant in dosage form (*e.g.*, in adjusting ionic strength, tonicity, *etc.*), a major decrease in solubility may be observed, according to:

Streng et al. [30] studied the combined effect of the addition of NaCl and HCl on aqueous solubility of the HCl salt of a basic drug; the solubility in the relatively flat region of the pH–solubility profile (pH 3 to 6) decreased by a factor of 3 when 0.05 M NaCl was added to the solution, while at pH below 3 the solubility further decreased due to the effect of Cl^- ion associated with HCl added to adjust pH. Similarly, in developing a liquid formulation for the sodium salt of an acidic drug, Serajuddin et al. [31] observed a decrease in solubility from 7.8 mg/mL to 1.1 mg/mL with the addition of 0.1 M NaCl to adjust the ionic strength of solution. The common-ion effect also has a major influence on solubility and dissolution rates of salts in the GI tract, where the solubility of HCl salts are particularly sensitive to the presence of chloride ion [24].

The overall impact of counterions on salt solubility depends on the magnitude of K_{sp} value. According to Eq. (9), for an equal change in $[X^-]$, the common-ion effect will be less pronounced in a salt of higher K_{sp} (*i.e.* higher solubility) than in a salt with lower K_{sp} (*i.e.* lower solubility). For example, the aqueous solubility of tiaramide HCl at 37 °C remained practically constant around 200 mg/mL (~0.5 M) during the lowering of pH from 4.0 to 1.6 by the addition of HCl, since, as compared to the drug concentration, changes in the chloride ion concentration during the pH adjustment were negligible. Further, the solubility of tiaramide HCl decreased by just 25% to ~150 mg/mL at pH 1. In contrast, there are numerous reports in the literature indicating drastic common-ion effects on salts having relatively low aqueous solubilities [18,21]; three such examples demonstrating major impacts of maleate and chloride ions on solubilities of a maleate salt [32] and two hydrochloride salts [33,34], respectively, at low pH are shown in Fig. 4. Since, as mentioned earlier, most compounds currently synthesized in drug discovery laboratories have poor aqueous solubilities and, as a consequence, their salt forms are also found to have relatively low aqueous solubilities, an investigation of potential impacts of common ions is critically important in salt selection and during dosage form development.

2.4. Effects of solubility, pK_a and K_{sp} on pH_{max}

The concept of pH_{max} is an important one in the physical chemistry of salts. It is apparent from Figs. 1 and 3 that pH_{max} plays a major role in determining whether a salt would be formed or not, and, in case it is formed, whether it would remain 'as is' or would convert to the corresponding free acid or base form. As mentioned previously, it is only at the pH_{max} that both forms could coexist. Therefore, at the pH_{max}, both Eqs. (3) and (4) can be valid for the solubility of a basic drug and, similarly, both Eqs. (5) and (6) can be valid for the solubility of an acidic drug. Bogardus and Blackwood [18] proposed that, for a basic drug, the saturation solubilities of free base and its salt form may be set equal at pH_{max}, and solving the relevant equations for pH_{max}, they derived the following relationship:

$$[B]_s$$

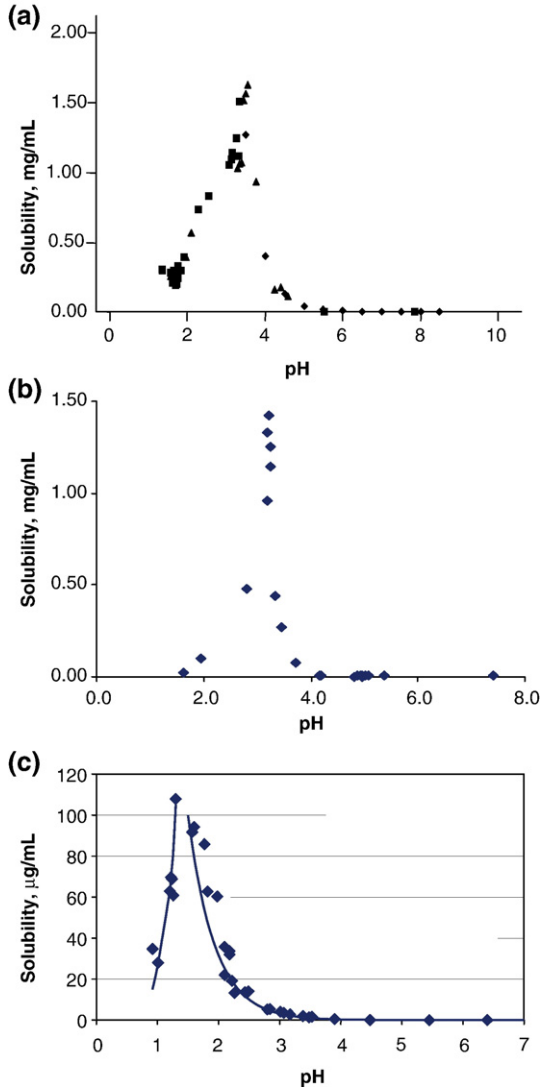


Fig. 4. Typical pH–solubility profiles of poorly water-soluble basic drugs: (a) the solubility profile of a compound with intrinsic solubility (S_0) of 2 μg/mL and a pK_a of 6.3, for which a pH_{max} of ~3.4 and a common-ion effect below pH_{max} were observed when the pH was lowered using maleic acid (reproduced with permission from Ref. [32]); (b) solubility profile of a compound with S_0 of 3.4 μg/mL and pK_a of 5.7, for which pH_{max} of 3.2 and common-ion effect below pH_{max} were observed when the pH was lowered using HCl; and (c) the solubility profile of a base having S_0 of <0.0001 μg/mL (below detection limit) and estimated pK_a in the range of 5.5 to 6.0, for which the pH was adjusted by HCl and the hydrochloride salt did not have acceptable properties for further development due to low pH_{max} (~1.5), low salt solubility (0.1 mg/mL at pH_{max}) and strong common-ion effect (reproduced with permission from Ref. [34]).

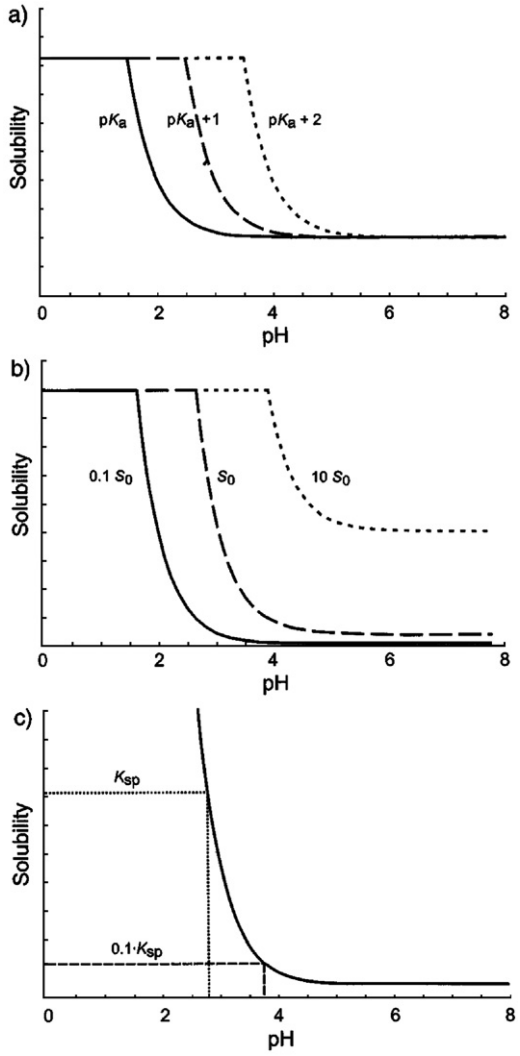
Pudipeddi et al. [16] depicted the influence of S_0 (or $[B]_s$), pK_a and K_{sp} on pH_{max}, according to Eq. (10), by using Fig. 5, where:

a) an increase in pK_a by one unit increases the pH_{max} by one unit;
b) an increase in intrinsic solubility, S_0, of the base by one order of magnitude increases pH_{max} by one unit; and
c) a decrease in salt solubility (K_{sp}) by one order of magnitude

It is evident from Fig. 5 that a stronger basicity (higher pK_a), a higher intrinsic solubility and a lower salt solubility will favor salt formation for a basic drug by increasing pH_{max}. Analogous relationships may also be derived for the salt formation of an acidic drug where an increase in S_0 and decreases in pK_a and salt solubility will decrease pH_{max} and, therefore, favor salt formation.

2.5. Deviation of pH–solubility interrelationship from ideality

Organic compounds often undergo self-association in solution because of their amphiphilic nature [35,36]. Indeed, bile salts are great examples of how organic compounds exhibit surface activity and undergo self-association in aqueous solutions because of their amphiphilic properties [37]. It has been reported that salt forms of many drug molecules undergo similar aggregation in solution [38–41]. Because of self-aggregation, activities of saturated solutions of many salts and even non-salts are lower than their measured concentrations in solution, resulting in non-ideal pH–solubility behavior. An example of



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