

RESEARCH ARTICLE

In Situ Salt Screening—A Useful Technique for Discovery Support and Preformulation Studies

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ABSTRACT

The purpose of this paper was to present an in situ salt screening technique which is applicable to most basic compounds. The theoretical aspects, experimental details, applications, and significance of this technique are illustrated through in situ salt screening studies performed on GW1818, an α_{1A} adrenergic receptor antagonist intended for treatment of benign prostatic hyperplasia (BPH). Generally, the in situ salt screening technique includes (i) acid selection, (ii) a solubility study, (iii) characterization of residual solids, and (iv) calculation of the K_{sp} and solubility of the salts. Six acids were screened for salt formation with GW1818. Excellent agreement was found between the solubility results determined using the authentic salts and solubility results obtained through in situ screening. Additional evidence of salt formation and some solid state properties of the salts formed in situ were obtained through microscopic examinations, differential scanning calorimetry (DSC), and x-ray powder diffraction studies. Four salts of GW1818, the phosphate, succinate, mesylate, and hydrochloride, were crystalline and demonstrated adequate solubility. These were selected for further evaluation. Adequate solubility was also observed in the case of citrate and tartrate salts, but these were considered only as potential backup candidates because they were difficult to crystallize. The results of the in situ salt screening experiments also led to the development of an IV formulation for use in pilot toxicological studies and pharmacological studies. In conclusion, the in situ salt screening technique offers a time- and compound-conserving approach for prioritizing salt selection and for providing solubility and stability information useful for formulation development both in the research and the development stages.

KEY WORDS: Discovery support; In situ salt screening; pH-solubility profile; Salt selection; Solubility.

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INTRODUCTION

The involvement of pharmaceutical scientists in the drug discovery process has become increasingly important as the pharmaceutical industry searches for ways to accelerate drug discovery and development. With the help of formulation scientists, many studies in discovery stage can be carried out using suitable formulations rather than pharmaceutically unacceptable organic solvents. Understanding the physicochemical properties of a molecule in the early discovery stage can help chemists incorporate desirable properties into new molecules, and can also facilitate the selection of the "right" molecule(s) for development. This early choice of the right molecule will avoid many technical challenges that can slow the development process.

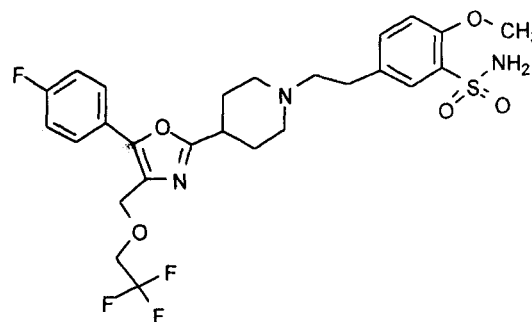
Traditionally, the pharmaceutical scientist does not have the opportunity to provide input as to which salt to use for biological, pharmacological, pharmacokinetic (PK), and toxicological evaluation in the discovery stage. The most common salt made is the hydrochloride salt which, in many cases, is not necessarily the most soluble salt (1-3). Having a compound in an insoluble salt form can make certain discovery stage studies such as toxicological studies very difficult and can also create unnecessary challenges for formulation development to support these studies.

The importance of selecting the correct salt form at the initial stage of drug development is well recognized (1-4). Changing the salt form in the middle of a developmental program may require repeating many of the toxicological, formulation, and stability tests that have already been performed. On the other hand, continuing the development of a nonoptimal salt form can lead to increased development and production time and even to product failure. Typically, the first step in a traditional salt selection process is the preparation of numerous salts (1-4). The subsequent solubility studies on these salts may demonstrate that some of these salts are very insoluble, and thus are excluded from further evaluation. A method which can provide solubility information without the need to make the salts can certainly avoid the preparation of these insoluble salts, and therefore, conserve time and resources.

Traditional preformulation studies to elucidate the physicochemical properties of drug molecules require gram quantities of material, quantities not often available during the discovery stage (5,6). Therefore, getting the maximum amount of information from the smallest amount of compounds is an essential part of the discovery support activities.

In situ salt formation is a classical chemistry idea. Its application in the salt selection process was first reported by Shanker and colleagues (7). Good correlation between solubilities of in situ formed salt and solubilities of authentic salts were reported. However, the theoretical bases for the calculation of the solubility from in situ screening studies and the experimental details have not been published. The application of this technique in the formulation development area both for research compounds and development compounds as a screening tool has not been well documented.

The purpose of this report was to present the theoretical aspects, experimental details, and applications of the in situ salt screening method through in situ salt screening studies for GW1818, an α_{1A} antagonist for the potential treatment of benign prostatic hyperplasia (BPH). The structure of GW1818 is shown below. The pK'_a is 8.02, determined by potentiometric titration. The solubility of the free base is 0.0044 mg/ml in water.



MATERIALS AND METHODS

Materials

GW1818X (98% pure by HPLC) was synthesized by Glaxo Wellcome Medicinal Chemistry. Hydrochloric acid (0.1 M) was purchased from VWR Scientific (West Chester, PA). Phosphoric acid was purchased from J. T. Baker (Phillipsburg, NJ). Methanesulfonic acid (99%), citric acid (99%+), L-tartaric acid (99.5%), and succinic acid (99%) were purchased from Aldrich (Milwaukee, WI). Water was purified by a Milli-Qplus™ ultrapure water system (Millipore, Bedford, MA).

Methods

In Situ Salt Screening Technique

Generally, the in situ salt screening technique includes the following steps:

1. Acid selection. The pK_a of the acid should be at least 2 pH units lower than the pK_a of the compound (5). The acids screened with GW1818X are listed in Table 1.
2. Solubility study. The concentration of the acid used is generally 0.1 M. The amount of base added should be such that an excess amount of acid remains in solution after conversion of all of the base into its salt. If the solubility of the compound is higher than the concentration of the acid, a higher concentration of the acid should be used. The amount of base added should be recorded accurately because it affects the amount of acid that is converted to the salt. The solubility should be checked until equilibrium is reached. The pH of the final solution should be measured.
3. Characterization of the residual solids. The studies should include microscopic examination of the residual solid from the solubility samples including hot-stage microscopy; determination of the powder x-ray diffraction pattern of the residual solid from the solubility samples (both wet and dry); and characterization of the residual solid from the solubility samples by differential scanning calorimetry (DSC) and/or thermogravimetric analysis (TGA), provided enough sample is available.
4. Calculation of the K_{sp} and solubility of the salts. A spreadsheet can be set up according to Eqs. (10–15) (Appendix 1) to automate these calculations.

Solubility Determination

The solubilities of GW1818X were determined by equilibrating an excess of GW1818X in 500 μ L or 1 mL

of 0.1 M acids in temperature-controlled shaking water baths. Samples were drawn, filtered through a 0.22- μ m filter (Ultrafree-MC 0.22 μ m filter unit, Millipore, Bedford, MA), diluted using mobile phase, and assayed by HPLC after 1 and 2 weeks of equilibration.

Method of Quantitation

The concentration of GW1818X in solution was determined by reversed-phase HPLC using a Zorbax SB-phenyl column (250 $\times$ 4.6 mm, 5 μ m), and a mobile phase consisting of 60/40 0.05% trifluoroacetic acid (TFA) in water/0.05% TFA in acetonitrile, with a flow rate of 1 mL/min and detected at 263 nm. HPLC determinations were performed using Waters 510 HPLC pumps, a Waters 715 ultra WISP automatic sample injection system, a Waters 490E programmable multi-wavelength detector, and a Waters ExpertEase chromatography system.

Microscopy

Solid residues were taken from solubility samples and examined using crossed polars on a Nikon Optiphot-Pol polarized light microscope (Nikon Inc., Yokohama, Japan) with a red compensation filter. Photomicrographs were taken with a Polaroid camera attached to the Nikon microscope and controlled by a UFX-II shutter system. For hot-stage microscopy, a Mettler FP82HT/FP80 system was used on the Nikon microscope. Images were transferred to a Sony Trinitron monitor (PVM-1343MD), using a Sony DXC-151 CCD camera and recorded on a Panasonic AG7300 VHS VCR. Video prints were created with a Sony UP-5200MD video printer.

Table 1
Results of GW1818X In Situ Salt Screening

Acid (0.1 M)	Amount of Solid Added X (mg)	Volume of the Solution V (mL)	pH of the Saturated Solution	Solubility in 0.1 M Acid S (mg/mL)	pK_a of the Acid	K_{sp}	Calculated Solubility of the Salt (mg/mL)	Appearance of Residual Material
Hydrochloric acid	2.9	0.5	1.40	0.06	–	9.44×10^{-6}	1.8	Crystalline (needles)
Methanesulfonic acid	10.9	0.5	1.79	2.28	–	2.63×10^{-4}	9.3	Crystalline (rods)
Phosphoric acid	9.6	1.0	2.23	8.38	2.12	8.08×10^{-4}	16.2	Crystalline (fine needles)
Citric acid	8.7	0.5	2.81	7.50	3.14	3.46×10^{-4}	10.6	Oily residue
Succinic acid	8.8	0.5	3.67	3.02	4.16	9.62×10^{-5}	5.6	Crystalline (rods)
Tartaric acid	11	0.5	3.11	10.80	2.98	8.72×10^{-4}	16.9	Oily residue

MW (free base) = 571.6

X-ray Powder Diffraction

The x-ray powder diffraction patterns were determined on a Scintag XDS 2000 theta-theta diffractometer (Scintag, Inc., Cupertino, CA) using -1500 volts on the detector, 45 kV and 40 mA on the x-ray tube, and slit widths of 2, 4, 1, and 0.3 mm. Samples were prepared by adding one drop of the suspension taken from the bottom of the solubility samples onto the center of quartz zero-background plates. Samples were spun during data acquisition. To screen for possible hydrates, samples were run wet and after being dried at 60°C under vacuum for 4 hr.

RESULTS AND DISCUSSION

Table 1 summarizes the in situ salt screening results for GW1818X. The differences between the solubility data determined after 1 and 2 weeks equilibration are less than 10%. The average of the two measurements is reported. Based on our experience, a tighter limit is more difficult to achieve and the additional effort would not significantly improve the interpretation of the results.

Four salts of GW1818X, the phosphate, succinate, mesylate, and hydrochloride, were crystalline and showed adequate solubility, therefore, these were first recommended to the medicinal chemists to prepare for further evaluation. The citrate and tartrate salts were not pursued because of the difficulty in obtaining crystalline materials. Because of their relatively high solubility, these two salts were reserved as back-up salts. Should none of the top four salts have the desired properties, the crystallization conditions for these two salts would be studied further.

The solubilities of the four authentic salts prepared by medicinal chemists were determined in water and 0.01 M of the corresponding acids. The results are summarized in Table 2. Because of the very poor solubility of the base (GW1818X) and the compound's weak basicity ($pK_a' = 8.02$), the use of 0.01 M acid in the solubility experiment was necessary to ensure that the solubility was not limited by the solubility of the base. This is illustrated in the case of phosphate salt. The solubility of the phosphate salt in water was 6.8 mg/ml and the pH of the saturated solution was 5.0. The solubility at this pH is limited by the solubility of the base as shown in the pH solubility profile (Fig. 1). It is only from a solubility experiment at a pH below pH_{max} (see Appendix 1) that the solubility of the salt can be estimated.

Excellent agreement was found between the solubility results determined by using the authentic salts and the solubility results obtained by in situ screening as shown in Table 3, except for the succinate salt. The larger difference observed for the succinate salt may be due to a combination of several factors. The succinate salt prepared by medicinal chemists was proven to be a stable hydrate(s). The x-ray diffraction pattern of this hydrate was different from the x-ray diffraction pattern of the residual material from the in situ salt screening study. These results suggest that the solubility data from these two different studies are for different crystal forms, and therefore, are not directly comparable. Additionally, the pH of the suspension (3.67) in the in situ screening is very close to the pK_a (4.16) of the succinic acid. Small error in pH measurement and/or ionic strength effect on the ionization of the acid could cause rather significant error in the estimation of the concentration of the anion, $[A_{ionized}]$ (see Appendix 1). Despite

Table 2
Solubility of GW1818 Salts at 25°C

Salt	Medium	pH of the Saturated Solution	Solubility (mg/ml)	Solubility After Correction for the Common Ion Effect (mg/ml)
Phosphate	0.01 M phosphoric acid	3.4	13.5	15.7
	Water	5.0	6.8	
Succinate	0.01 M succinic acid	4.3	2.6	3.5
	Water	4.8	2.9	
Mesylate	0.01 M methanesulfonic acid	2.8	7.7	10.2
	Water	4.6	9.2	
Hydrochloride	0.01 M hydrochloric acid	2.0	0.4	1.6
	Water	5.6	1.2	

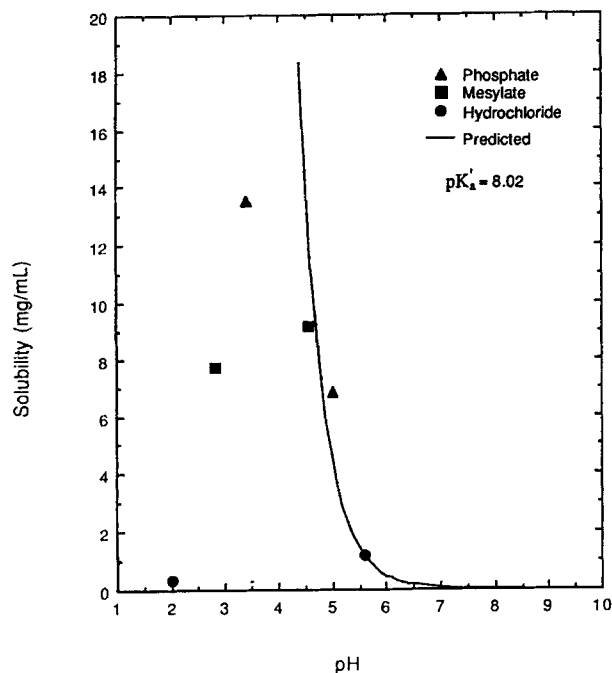


Figure 1. Solubilities of GW1818 salts. The free base solubility of 0.0044 mg/ml and the compound's pK_a' of 8.02 were used to calculate the predicted solubility curve.

this difference, the results were still useful in guiding the salt selection process.

Figure 2 shows the photomicrographs of GW1818X (free base) and residual solids from solubility studies in 0.1 M hydrochloric acid, methanesulfonic acid, and phosphoric acid. The morphology changes provided additional evidence of the salt formation.

The hot-stage microscopic examination performed on the residual material from 0.1 M hydrochloric acid showed that the material lost some volatile content, pre-

sumably water, near 45°C and melted at approximately 185°C. This was confirmed by the DSC of the authentic hydrochloride salt (8).

Figures 3 and 4 compare the powder x-ray diffraction patterns of the base with residual material from the solubility study and the pattern of the authentic hydrochloride salt using water as final crystallization solvent. The x-ray pattern of residual material from the solubility study differs from the pattern of the free base, but matches the pattern of the hydrochloride salt, suggesting the conversion of the free base to the hydrochloride salt in the solubility sample. The differences seen between the patterns of wet and dry samples suggest that the material might form hydrates. This was later confirmed by studying the authentic hydrochloride salt (8). The XRD pattern of the hydrate (Form IV) matches the pattern of the wet residual sample from the solubility study.

Although the in situ screening provided much useful information as showed above, it should be pointed out that this technique would not replace traditional salt selection methodologies. Instead, this technique should be used to screen a large number of possible salts in order to eliminate those with inadequate solubility prior to synthesizing the salts. In addition, the screen could also be used to prioritize the evaluation of the promising salts as shown in the case of GW1818.

Traditionally, a series of salts in relatively large quantity (e.g., 100 mg) are made by chemists as a first step in the salt selection process. Subsequent solubility studies often find that several of those salts do not possess an adequate solubility, and therefore, will not be considered for further evaluation. If an in situ salt screening technique was used, those insoluble salts would be detected using only a few milligrams of material. The saving in time, material, and resources from this technique would be tremendous considering the number of compounds we need to evaluate.

Table 3

Comparison of Solubility of GW1818 Salts Determined by In Situ Screening and by Using the Authentic Salts at 25°C

Salt	Solubility by In Situ Screening (mg/ml)	Solubility of the Authentic Salt (mg/ml)
Phosphate	16.2	15.7
Succinate	5.6	3.5
Mesylate	9.3	10.2
Hydrochloride	1.8	1.6

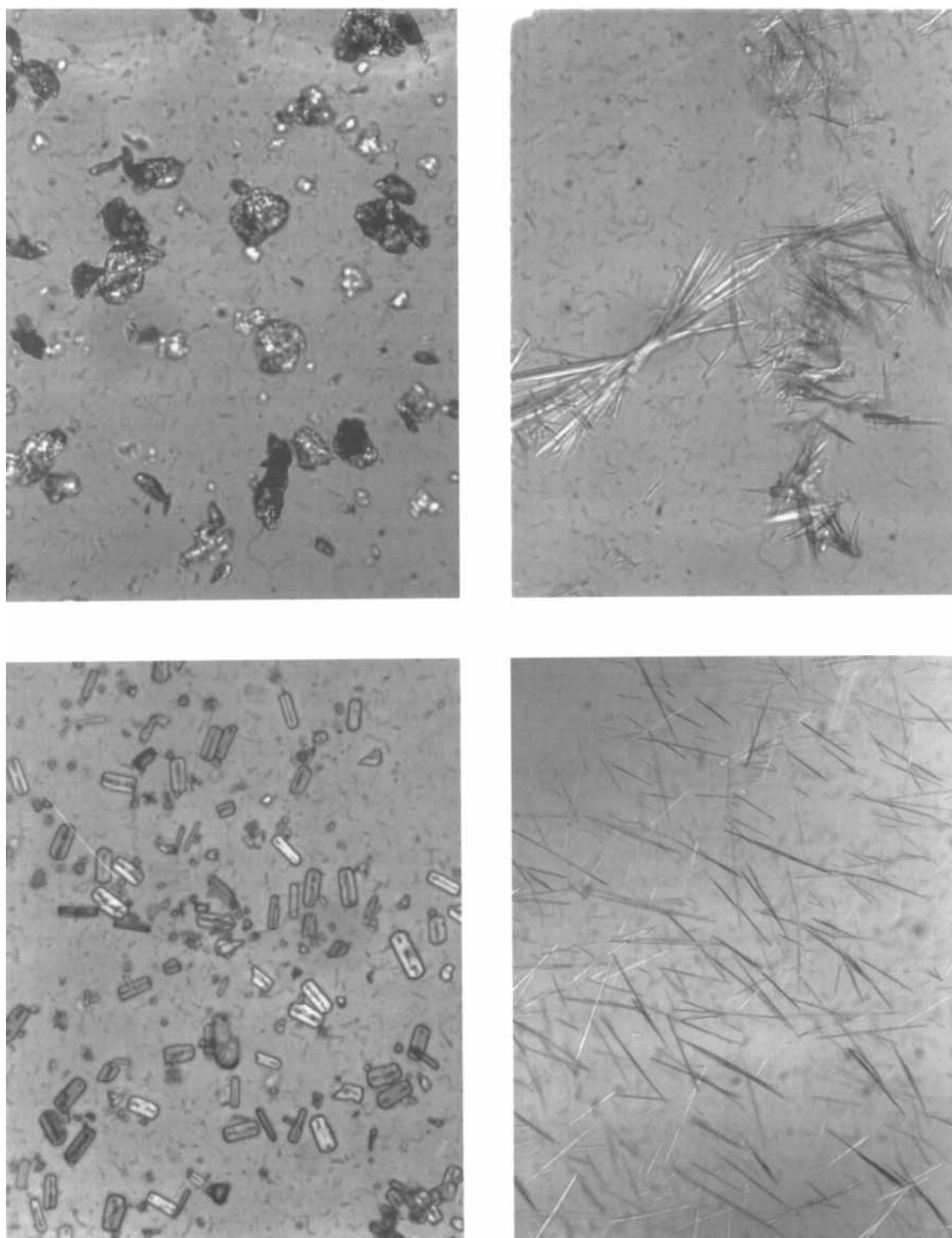


Figure 2. Photomicrographs of GW1818X (top left) and residual solid from solubility studies in 0.1 M HCl (top right), 0.1 M methanesulfonic acid (bottom left), and 0.1 M phosphoric acid (bottom right).

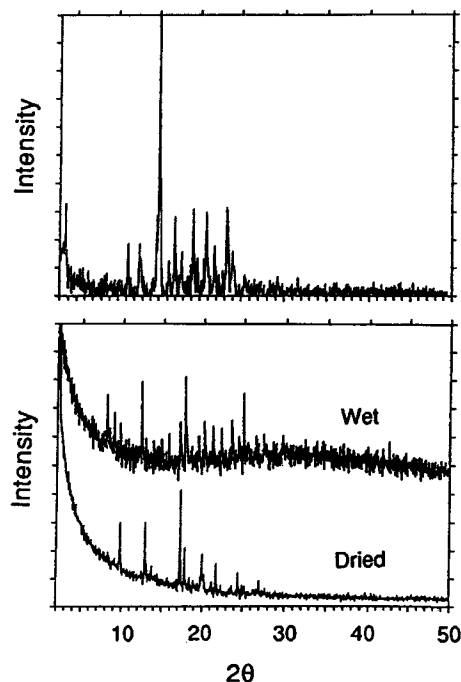


Figure 3. Comparison of the XRD pattern of GW1818X (top) with the patterns of the residual material from solubility studies of GW1818X in 0.1 M HCl (bottom).

The solubility results clearly indicate that the phosphate salt is the most soluble salt among those studied. Based on these data, the following formulation was developed for the pilot toxicological studies and pharmacological studies: 10 mg/ml in 0.025 M phosphoric acid with 5% dextrose. The concentration of the phosphoric acid was chosen so the pH of the formulation would be low enough (below pH_{max}), yet the common ion effect would not reduce the solubility to <10 mg/

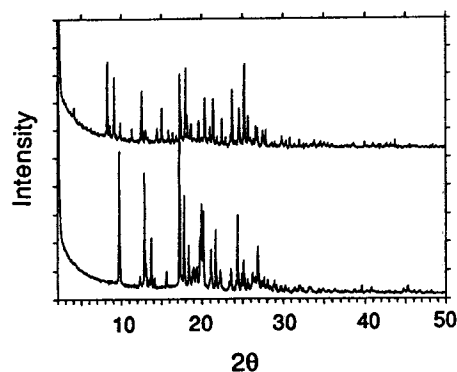


Figure 4. The XRD patterns of the authentic hydrochloride salt (GW1818A). Top: hydrate (Form IV), bottom: Form II.

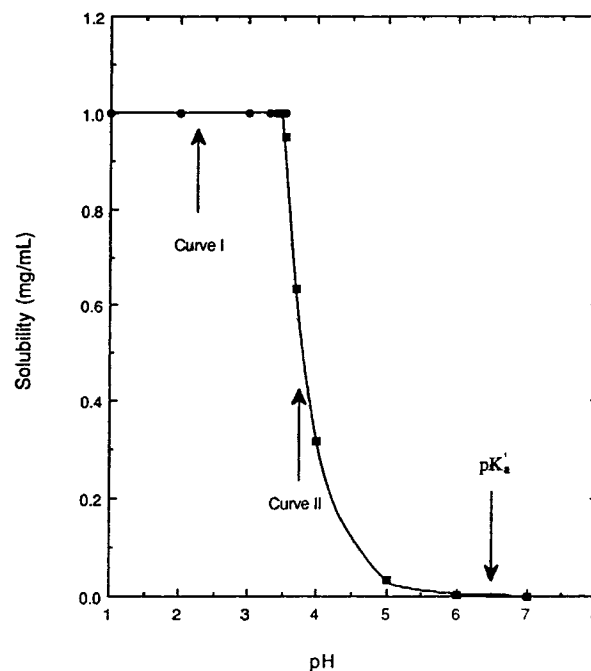


Figure 5. pH-solubility profile of an ideal compound BH^+Cl^- , assuming $[\text{BH}^+]_s = 1 \text{ mg/ml}$, $[\text{B}]_s = 0.001 \text{ mg/ml}$, and $\text{pK}'_a = 6.5$.

ml. This formulation made it possible to conduct the toxicological studies at the dosing level of 100 mg/kg/day.

The solubility results from in situ salt screening also provide useful information for buffer selection of an IV formulation. For an IV formulation of the hydrochloride salt, it is clear that the phosphate and citrate buffers should be compatible with the compound in an IV formulation.

Since the HPLC method used for the solubility determination is stability indicating, assaying solubility samples at different time intervals also provided evidence for the stability of the compound in the solubility samples. No significant degradation was detected in any of the solubility samples, suggesting that the salts studied are stable in the acidic media for at least 2 weeks (the equilibration time for the solubility samples).

CONCLUSION

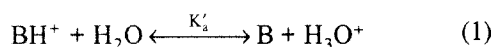
The application of an in situ salt screening as an important tool in research support and preformulation was described. With very small amounts of material (from <20 mg to 50 mg, depending on the solubilities

of the compound and its salts), the method provides very important information for the development of IV and oral formulations for in vivo efficacy studies, pharmacological studies, PK studies, and toxicological evaluations; for the solubility estimation as the first step in the salt selection process; and for the buffer selection for the solution formulations in the preformulation studies. Results from in situ salt screening studies can also provide information on the solid state properties of the potential salts and the solution stability of the drug substance.

APPENDIX I: THEORETICAL CONSIDERATIONS

pH Effects on the Solubility of Organic Bases: pH-Solubility Profile (9,10)

The equilibrium for the dissociation of a salt may be expressed by:



where BH^+ is the protonated species, B is the free base, and K'_a is the apparent dissociation constant of BH^+ , which is defined as follows:

$$K'_a = \frac{[\text{H}_3\text{O}^+][\text{B}]}{[\text{BH}^+]} \quad (2)$$

Generally, the relationships drawn in Eqs. (1) and (2) must be satisfied for all weak electrolytes in equilibrium, irrespective of pH and the degree of saturation. At any pH, the total concentration of a compound, S_T , is the sum of the individual concentrations of its respective species:

$$S_T = [\text{BH}^+] + [\text{B}] \quad (3)$$

In a saturated solution of arbitrary pH, this total concentration, S_T , is the sum of the solubility of one of the species and the concentration of the other necessary to satisfy the mass balance.

At low pH where the solubility of BH^+ is limiting, the following relationship holds:

$$S_{T, \text{pH} < \text{pH}_{\text{max}}} = [\text{BH}^+]_s + [\text{B}] = [\text{BH}^+]_s \left(1 + \frac{K'_a}{[\text{H}_3\text{O}^+]} \right) \quad (4)$$

where pH_{max} refers to the pH of maximum solubility and the subscript $\text{pH} < \text{pH}_{\text{max}}$ indicates that this equation is only valid for pH values less than pH_{max} . The subscript

s indicates a saturated species. A similar equation can be written for solutions at pH values greater than pH_{max} where the free base solubility is limiting:

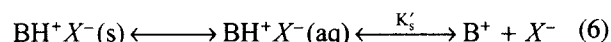
$$S_{T, \text{pH} > \text{pH}_{\text{max}}} = [\text{BH}^+] + [\text{B}]_s = [\text{B}]_s \left(1 + \frac{[\text{H}_3\text{O}^+]}{K'_a} \right) \quad (5)$$

Each of these equations describes an independent curve which is limited by the solubility of one of the two species: curve I for Eq. (4) and curve II for Eq. (5), as shown in Fig. 5.

Figure 5 is the pH-solubility profile of compound BH^+X^- calculated using salt and free base solubilities of 1 mg/ml and 0.001 mg/ml, respectively, and a pK'_a of 6.5.

Solubility Product and Common Ion Effect (9,10)

Without assuming anything about the actual step-by-step mechanism of the solubility process, the following model for the equilibrium system of a 1:1 salt (BH^+X^-) in contact with its saturated solution may be proposed:



where s is for solid and aq is for aqueous.

The solubility product, K_{sp} , is defined as the equilibrium expression that relates the concentrations of the final dissociated ions to the solid substance. For the above simple case, if the material is pure, then its molar concentration $X_{\text{BH}^+\text{X}^-(s)}$ is 1:

$$K_{sp} = \frac{[\text{BH}^+][\text{X}^-]}{X_{\text{BH}^+\text{X}^-(s)}} = [\text{BH}^+][\text{X}^-] \quad (7)$$

The solubility of the salt (S_{salt}) can be calculated from the K_{sp} :

$$S_{\text{salt}} = (K_{sp})^{1/2} \quad (8)$$

When the solution contains some other solute that can contribute X^- to the system, the dissociation of BH^+X^- will be partly depressed, and the concentration of BH^+ and X^- will not be equal. The solubility product itself, however, is still valid, and therefore, we may write:

$$[\text{BH}^+] = \frac{K_{sp}}{[\text{X}^-]_T} = \frac{K_{sp}}{[\text{BH}^+] + [\text{X}^-]_A} \quad (9)$$

where $[\text{X}^-]_T$ is the total concentration contributed both by the dissociation of BH^+X^- ($[\text{BH}^+]$) and by the second source of X^- ($[\text{X}^-]_A$). The solubility of the salt is

inversely proportional to the equilibrium concentration of the X^- .

In Situ Salt Screening

If free base (B) is added to a certain concentration of acid, the base will form the corresponding salt with the acid. If the acid concentration is chosen so that there is excess amount of acid in the solution (ensuring that the pH of the solution is lower than pH_{max}), the solubility of the compound will be limited by the solubility of the salt ($[\text{BH}^+]$), as expressed in Eq. (4). Knowing the amount of drug in solution, the volume of the solution, the solution pH, and starting acid concentration, the K_{sp} and the solubility of the salt formed in situ can be calculated.

The amount of the compound precipitated, X_p , can be calculated as follows:

$$X_p \text{ (mg)} = X - S \cdot V \quad (10)$$

where X (mg) is the amount of solid base added, S (mg/ml) is the solubility in the acid solution which is determined by the solubility studies, and V (ml) is the volume of the solution.

The concentration of the acid remaining in solution, $[A_s]$, can then be calculated:

$$[A_s] = [A] - \frac{X_p}{V \cdot \text{MW}} \quad (11)$$

where $[A]$ is the concentration of the acid used and MW is the compound's molecular weight.

Knowing the ionization constant of the acid, $\text{p}K'_a$, and the pH of the saturated solution, the concentration of the acid in its ionized form, $[A_{\text{ionized}}]$, can be calculated based on Eq. (2):

$$[A_{\text{ionized}}] = \frac{[A]_s}{1 + [\text{H}^+]/K'_a} \quad (12)$$

The molar concentration of the compound in solution is

$$[S] = \frac{S(\text{mg/ml})}{\text{MW}} \quad (13)$$

The K_{sp} of the salt can then be calculated:

$$K_{\text{sp}} = [S] \cdot [A_{\text{ionized}}] \quad (14)$$

Finally, the solubility of the salt, S_{salt} (mg/ml), is calculated as follows:

$$S_{\text{salt}} = (K_{\text{sp}})^{1/2} \cdot \text{MW} \quad (15)$$

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