How to Mitigate Disproportionation of API Salts in Pharmaceutical Formulations

Salt formation is a well-established strategy for improving the physicochemical properties of active pharmaceutical ingredients (APIs) containing ionizable groups. This approach is particularly effective in enhancing aqueous solubility, often leading to improved bioavailability for poorly soluble compounds[1]. Beyond solubility, salt formation can also provide advantages in process development and stability. Crystalline salts, for example, are generally easier to isolate and purify than amorphous free forms, while conversion to a more stable salt form can mitigate issues related to chemical instability. It is estimated that nearly half of all marketed APIs are formulated as salts[2]. Nevertheless, salt selection and development require careful consideration of potential liabilities, including the risk of disproportionation, counterion-related toxicity, and increased drug loading requirements[3].
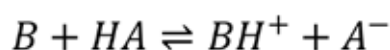
To provide a deeper understanding of salt disproportionation, this article examines the underlying reaction equilibria, key influencing factors, and potential mitigation strategies. The discussion focuses on salts formed between basic APIs and acids, which account for the majority of marketed salt forms[4]. However, the same fundamental principles apply to salts derived from acidic APIs and basic counterions.

Salt Formation and Disproportionation Equilibrium

Salt disproportionation describes the transformation of a highly soluble salt form into its poorly soluble, non-ionic free base or free acid. This process is governed by a series of equilibria that define both the formation of the salt and its dissolution behavior under varying pH conditions.

- **Salt Formation Equilibrium**

  For basic APIs, the salt formation equilibrium can be represented as:

$$B + HA \rightleftharpoons BH^+ + A^-$$

  The equilibrium constant (**K**) for this reaction is determined by the dissociation constants of the free base (**K_{ab}**) and the acid (**K_{aa}**), expressed as:

$$K = \frac{Kaa}{Kab}$$

  (Equation 1)

- **Dissolution Equilibrium of Salt and Free Base**
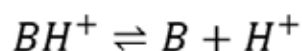
  The dissolution equation of the salt is given by:

  $$BHA \rightleftharpoons BH^+ + A^-$$

  The solubility of the salt (**S_s**) can be described by its solubility product (**K_{sp}**), ignoring common ion effects for simplicity:

  $$Ss = \sqrt{Ksp * \frac{Kaa + [H^+]}{Kaa} * \frac{[H^+] + Kab}{[H^+]}}$$

  (Equation 2)

  The dissolution equilibrium of the free base is given by:

  $$BH^+ \rightleftharpoons B + H^+$$

  The solubility of the free base (**S_b**) is expressed in terms of its intrinsic solubility (**S_0**, equivalent to **[B]**):

  $$Sb = S0 * \frac{[H^+] + Kab}{Kab}$$

  (Equation 3)

  By plotting **S_s** (Equation 2) and **S_b** (Equation 3) as functions of pH (i.e., $[H^+]$), two solubility curves are obtained, as illustrated in Figure 1.
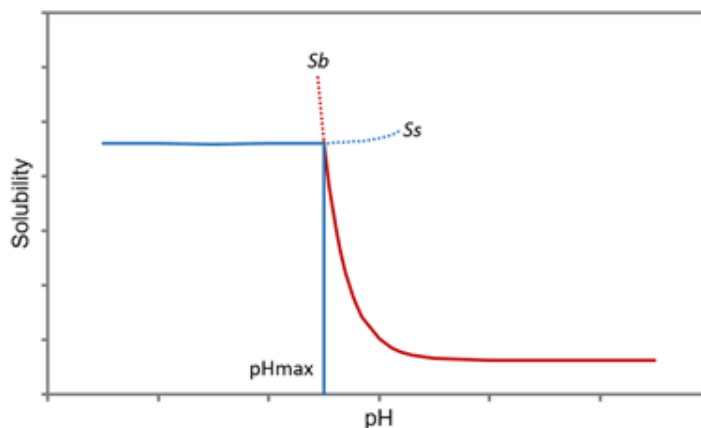

Figure 1. Schematic diagram of solubility curves of basic APIs versus pH

At the intersection of these curves, the salt and the free base coexist in equilibrium, where S_s equals S_b. Under the condition where $K_{aa} \gg$ [H$^+$] $\gg K_{ab}$, the hydrogen ion concentration at this intersection point is:

$$[H^+] = \frac{Kab}{S0} \sqrt{Ksp}$$

This corresponds to a pH value known as pH_{max}[5], defined by

$$pHmax = pKab + log \frac{S0}{\sqrt{Ksp}}$$

（Equation 4）

Factors Influencing Salt Disproportionation and Mitigation Strategies

1) Impact of *pKaa* and *pKab*

According to the equilibrium constant in Equation (1), a lower K_{ab} (corresponding to a higher pK_{ab}) favors salt formation and reduces the risk of disproportionation. Literature surveys of approved salt-based drug products indicate that no marketed examples possess a pK_{ab} below 4.6. Consequently, it is generally recommended to prioritize candidates with a pKab greater than 5.0 for salt development[6]. Molecules with pK_{ab} values below this threshold should be considered with caution and evaluated on a case-by-case basis.

Additionally, based on the equilibrium defined in Equation (1), maximizing salt formation requires a sufficiently large ratio of K_{aa} to K_{ab}. A commonly accepted guideline is that the difference in pKa values (ΔpKa) should be at least 3 units. Salt formation is generally considered favorable when the $pKab$ of the basic API exceeds the $pKaa$ of the counterion acid by 3 or more units[7].

2) Solubility Considerations

As shown in Figure 1, for basic APIs, the total API concentration in solution remains relatively stable as pH increases—assuming pH is the only influencing factor and common ion effects are negligible. However, beyond a certain pH threshold, the concentration begins to decline. This critical point is defined as pH_{max}, and it plays a pivotal role in predicting the physical stability of the system[6]. When the system pH exceeds pH_{max}, the solubility of the salt surpasses that of the free base, leading to precipitation of the free base and the onset of disproportionation. A higher pH_{max} is generally favorable,

as it extends the pH range over which the salt remains stable and reduces the risk of disproportionation.

As indicated by Equation (4), a higher pK_{ab} results in an elevated pH_{max}, which is advantageous for minimizing the risk of salt disproportionation—consistent with the preceding analysis. Achieving a higher pH_{max} also depends on the relationship between the intrinsic solubility (S_0) of the free base and the solubility product (K_{sp}) of the salt. Specifically, S_0 should not be too low relative to K_{sp}, implying that salts with excessively high K_{sp} values (i.e., high solubility) may be more susceptible to disproportionation. Although enhanced solubility is often a key objective during salt screening to improve drug absorption, excessive solubility can potentially compromise physical stability. Therefore, when several salt candidates meet the desired solubility threshold for formulation, preference should be given to those with comparatively lower K_{sp} values. Such salts are inherently more resistant to disproportionation and may offer improved stability during development[6].

3) Microenvironment pH Control

Once a specific salt form of an API is selected, its corresponding pH_{max} is defined. To minimize the risk of disproportionation during formulation development, it is critical to control the pH of the excipient microenvironment. When the local pH remains below pH_{max}, the salt form is stable. However, if the microenvironment pH exceeds pH_{max}, the likelihood of disproportionation increases[6].

For salts derived from basic APIs, excipients with alkaline properties are particularly problematic, as they can elevate the microenvironment pH and promote conversion of the salt to the free base. Thus, excipients that contribute to a more acidic local environment are generally preferred. In cases where the use of high-pH excipients is unavoidable, incorporation of suitable pH modifiers may be necessary to maintain salt stability. Measuring the microenvironment pH in solid dosage forms remains technically challenging. Two commonly used approaches include: 1) Suspending the formulation in water and measuring the pH of the resulting saturated solution; 2) Mixing the formulation with a pH-sensitive indicator and determining the ionization state via diffuse reflectance spectroscopy[8].

4) Humidity and Moisture Management

Salt disproportionation is a solution-mediated process. Even in solid-state formulations, it is generally accepted that disproportionation can occur rapidly within localized aqueous microenvironments. Elevated humidity and moisture content promote this by enabling transient hydration at the particle level. Several studies have shown that high humidity exposure can trigger or accelerate disproportionation[9,10]. While a strong quantitative correlation is not always observed, high water content is broadly recognized as a contributing factor[11]. To mitigate this risk, moisture exposure should be minimized during formulation and processing. Dry granulation is often preferred over wet granulation to

avoid introducing water. For packaging, moisture-barrier materials and desiccants can limit water uptake. Hygroscopic excipients should also be avoided to reduce local moisture accumulation and the risk of disproportionation.

5) Temperature Effects

Temperature influences both the thermodynamics and kinetics of salt disproportionation. In general, higher temperatures increase the likelihood of disproportionation occurring[12]. To reduce this risk, salt-form APIs and their formulations should be stored under controlled, lower-temperature conditions whenever feasible.

Case Studies

- **Disproportionation of Salts with Different Aqueous Solubility**

Thakral et al.[13] investigated the disproportionation behavior of three CRH-1 salt forms: hydrochloride, hydrobromide, and hemi-1,5-napadisylate. Among these, the hydrochloride exhibited the highest solubility, while the hemi-1,5-napadisylate showed the lowest, with differences attributable in part to their distinct stoichiometries (Table 1). Tablets were formulated using each salt in combination with excipients, and their propensity for disproportionation was evaluated. Under accelerated conditions (40 °C/75% RH/open), the hemi-1,5-napadisylate remained stable over an extended duration, whereas the hydrochloride displayed greater disproportionation than the hydrobromide. The corresponding K_{sp} values and pH_{max} data are summarized in Table 1 and shown in Figure 2. The hydrochloride, characterized by higher solubility (K_{sp}) and lower pH_{max}, was more susceptible to disproportionation—potentially exacerbated by hydrogen chloride volatility. In contrast, the hemi-1,5-napadisylate, with lower K_{sp} and higher pH_{max}, exhibited improved resistance to disproportionation.

Table 1. K_{sp} and pH_{max} of Different Salts of CRH-1

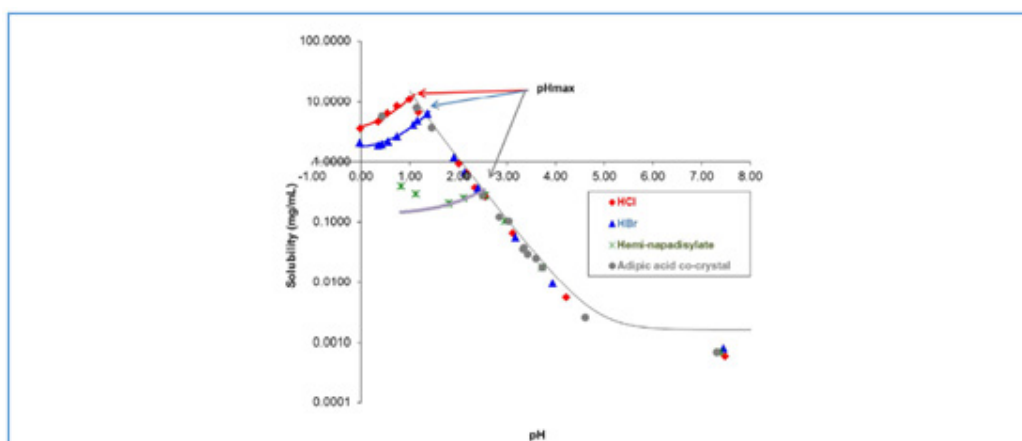| Salt	pH_{max}	K_{sp}
HCl	1.0	2.8×10^{-3} $[M]^2$
HBr	1.3	7.7×10^{-4} $[M]^2$
Hemi-1,5-napadisylate	2.5	8.0×10^{-10} $[M]^3$

Figure 2. Solubility curves of hydrochloride, hydrobromide, and hemi-1,5-napadisylate versus pH
(based on experimental data)

- **The Impact of pH Modifiers on Salt Disproportionation**

Koranne et al.[14] studied the impact of various organic acid pH modifiers on the disproportionation behavior of pioglitazone hydrochloride (PioHCl). Magnesium stearate and a range of organic acids (Table 2) were incorporated as excipients. Powder blends of the API and excipients were prepared and stored under accelerated conditions (40 °C/75% RH). The extent of free base formation was assessed using X-ray powder diffraction (XRPD), with results presented in Figure 3. The control formulation, lacking any acidifier, showed rapid disproportionation followed by a plateau. In contrast, formulations containing pH modifiers exhibited reduced levels of free base, indicating suppression of disproportionation. Notably, no disproportionation was observed in formulations containing maleic acid or oxalic acid. Comparison with the pK_a values of the acids listed in Table 2 suggests that stronger acids are more effective at mitigating disproportionation in PioHCl systems.

Table 2. Organic acids used as pH modifiers

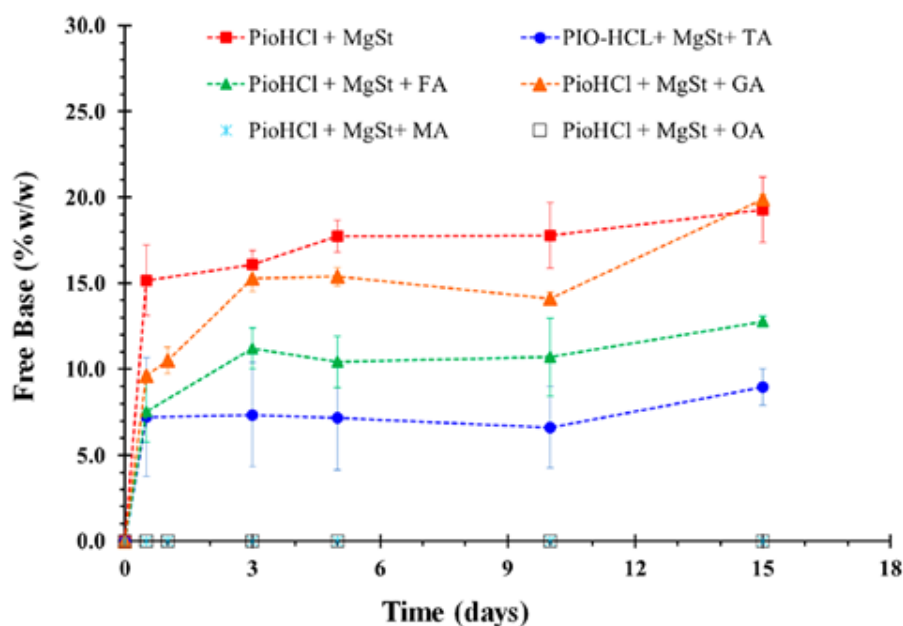| Organic acid	Chemical structure	pKa (pKa1, pKa2)	Aqueous solubility (mol/L), 25 °C
Oxalic acid/OA		1.2, 4.2	1.56
Maleic acid/MA		1.9, 6.2	4.05
Tartaric acid/TA		3.0, 4.3	8.66
Fumaric acid/FA		3.0, 4.3	0.05
Glutaric acid/GA		4.3, 5.4	4.77

Figure 3. Content of pioglitazone free base over time for different systems after storage at
40 °C/75% RH (mean ± SD; n=3)

- **Impact of Ambient Relative Humidity and Moisture Content on Disproportionation**

Weldeab et al.[3] examined the effect of excipients with varying water content—trisodium phosphate dodecahydrate (TSPD) and anhydrous trisodium phosphate (TSP)—on the disproportionation behavior of Compound 1 tartrate salt. Binary mixtures of the API with each excipient were prepared and stored under both open and closed conditions to evaluate the extent of disproportionation. As shown in Figure 4, for a given type and amount of excipient, disproportionation occurred more readily under open conditions at 40 °C/75% RH compared to closed conditions at 40 °C, highlighting the role of ambient humidity in promoting salt instability. Figure 5 further demonstrates that at an excipient-to-API molar ratio of 0.36:1, the TSPD-containing system—due to its higher water content—exhibited greater disproportionation (i.e., increased free base formation) than the system with anhydrous TSP. These findings confirm that formulations with higher moisture content are more susceptible to salt disproportionation.
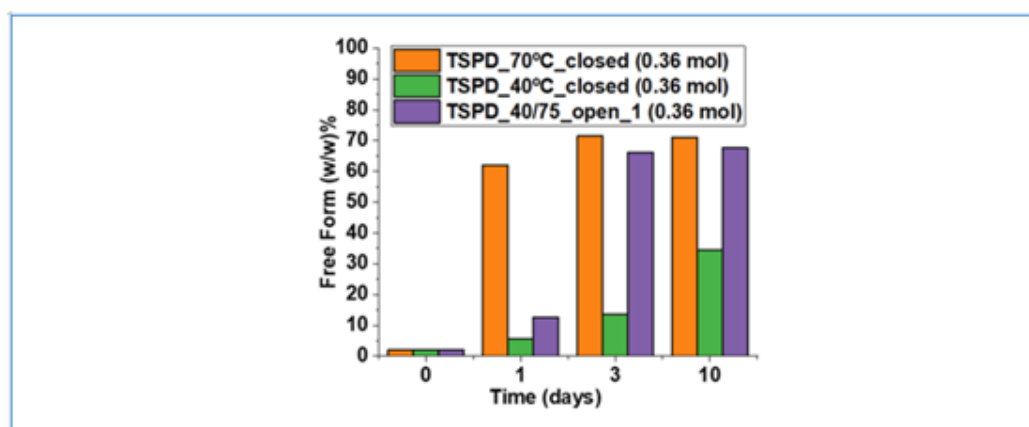

Figure 4. Bar graph showing the extent of disproportionation for Compound 1 tartrate + TSPD mixtures
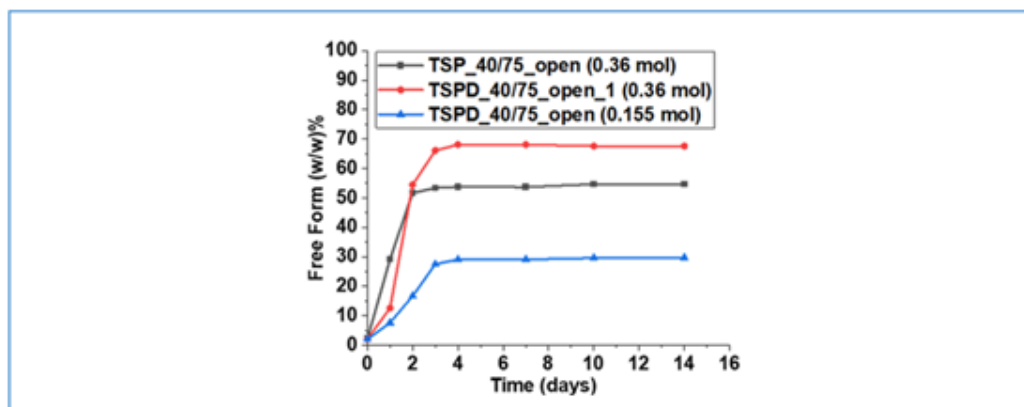at different time points under various conditions

Figure 5: Disproportionation curves for Compound 1 tartrate + TSP or TSPD mixtures
at different time points under various conditions

Conclusion

Effective mitigation of API salt disproportionation requires a comprehensive understanding of both the intrinsic properties of the salt and the characteristics of its surrounding environment.

From the perspective of intrinsic salt properties, basic APIs should possess a high **pK_{ab}**, ideally exceeding the **pK_{aa}** of the counterion acid by at least three units to favor salt formation and stability. Additionally, the selected salt should exhibit appropriate solubility; when bioavailability requirements are met, salts with comparatively lower solubility are generally preferred due to their reduced susceptibility to disproportionation. From an environmental perspective, minimizing the risk of disproportionation involves selecting excipients that maintain a lower microenvironmental pH, avoiding exposure to elevated temperature and humidity during storage, and carefully controlling the moisture content within the formulation.

Crystal Formulation Services (CFS) provides clients with comprehensive salt-form screening and formulation evaluation services, delivering integrated solutions and end-to-end support throughout drug development. At the salt screening stage, the Crystal Pharmatech technical team—leveraging over a decade of practical experience—conducts a systematic and scientifically rigorous screening process to identify the most suitable salt form for further development. During formulation development, we conduct a thorough assessment of salt disproportionation risk and apply a data-driven approach to excipient selection, formulation design, and process optimization. When the potential for disproportionation is identified, targeted controls—such as tailored packaging strategies and storage condition recommendations—are implemented based on stability data. In cases where disproportionation occurs in solid dosage forms, the appearance of the free base is typically detectable via distinct X-ray powder diffraction (XRPD) patterns. Our specialized instrumentation and expertise in solid-state characterization ensure effective monitoring and evaluation of such transformations, supporting robust and stable drug product development.

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