GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

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API Salt Selection: A Classical but Evolving Approach in Modern Drug Development

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GSC Biological and Pharmaceutical Sciences, 2025, 33(01), 066-072

Publication history: Received on 31 August 2025; revised on 06 October 2025; accepted on 08 October 2025

Article DOI: https://doi.org/10.30574/gscbps.2025.33.1.0382

Abstract

For several decades, generating salt forms of the active pharmaceutical ingredients (APIs) has remained the preferred approach for the pharmaceutical industries. The salt form of the APIs provides the advantage of improving the solubility and stability, enhancing the dissolution rate, permeability, manufacturing robustness, taste masking, and life cycle management. The pharmaceutical salts are the ionic compounds of a drug and its counterion. The counterions can be classified as anionic, cationic, organic anions, and aromatic sulfonates. The salt form of the drug does not exhibit pH-dependent solubility. Developing a salt form of the drug will improve the bioavailability of poorly soluble drugs belonging to the biopharmaceutical classification system (BCS) class II and IV. Around 50% of the solid oral dosage forms in the market utilize the salt form of the drug. Identifying the suitable salt form right in the early stages of development will eliminate the need for complex formulation platforms such as amorphous solid dispersions. Despite various advantages, a few limitations must be addressed, such as hygroscopicity, polymorphism, and counterions. The salt screening can be integrated with artificial intelligence (AI) and computational tools to accelerate development. The review article summarizes the principles, benefits, limitations, and future outlook for pharmaceutical salts.

Keywords: Salt Form; Solubility Enhancement; Bioavailability; Artificial Intelligence; Counterion; Hygroscopicity

1. Introduction

Poor solubility is the central issue faced by the pharmaceutical industry, requiring exploration of advanced formulation platforms. Developing pharmaceutical salts is the most common strategy implemented by the pharmaceutical industry. The pharmaceutical salts are ionic compounds formed by a reaction between acidic and basic drug substances and suitable counterions [1–3]. The objective of developing pharmaceutical salts is to improve the physical and chemical characteristics without compromising the pharmacological action. Around 50% of the drug products within the market consist of the salt form of the drug. The pharmaceutical salts were introduced into the market from the time of Aspirin. Developing pharmaceutical salts will result in improved solubility of biopharmaceutical classification system (BCS) class II (Poor Solubility, High Permeability) and IV (Poor Solubility, Poor Permeability) drugs [4–8]. Evaluating the feasibility of salt form for improving the solubility during the early discovery phase of the development would save a lot of time for the pharmaceutical industry. Identifying a stable salt form is crucial to preventing serious problems in the future. In fact, developing salt form can be integrated within the active pharmaceutical ingredient (API) manufacturing process, eliminating the need for advanced formulation strategies [9–13].

Other solubility-enhancing approaches include cocrystals, co-amorphous systems, complexation, micronization, lipid-based formulations, and amorphous solid dispersions [14, 15]. Within the drug development process, evaluating salt form screening will be the first line strategy before assessing the feasibility of other approaches. Thus, pharmaceutical salts are essential within the industry and align with regulatory requirements [16–18]. Implementing salt forms also provides an opportunity for life cycle management and patentability in the industry. Once a suitable counterion is

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identified, conducting polymorph screening is essential for developing a stable salt form. The review article summarizes the principles, benefits, limitations, and future outlook for pharmaceutical salts.

2. Rationale for salt formation

Any oral medication should dissolve in the gastric environment and permeate through the biological membrane into the systemic circulation to reach the target site of action. Solubility and permeability are crucial for the drug to be bioavailable. Developing a salt form of the drug will improve the solubility and enhance the dissolution rate and permeability. The salt form of the drug will influence the lipophilicity, thereby promoting drug permeation [19–21]. Since most of the drug substances are either acidic or basic, the salt form of the drug will exhibit pH-independent solubility, eliminating the role of physiological pH in the solubility and performance of the drug. The salt form of the drug will also improve the stability by preventing hydrolysis, oxidation, and protecting the drug molecule from light. The salt form of the drug will also alter the melting point of the drug, thereby enhancing its stability [22–26]. The flow and compressibility of the salt form will be superior to that of the neat drug substance, facilitating improved processing for developing solid oral dosage forms. The salt form of the drug will mask the taste of bitter APIs, improving palatability for the patient population.

3. Criteria for salt selection

For developing a robust and stable salt form of the drug, the difference in the pKa of the drug and counterion should be at least 2-3 units. The salt form should exhibit satisfactory solubility across the pH range and remain stable at regular and accelerated storage conditions. The hygroscopicity of the salt form needs to be studied to avoid stability challenges [27–30]. It is advisable to select the counterion from the list approved by the Food and Drug Administration (FDA), which is non-toxic and safe for human administration. The in vivo performance of the salt form of the drug needs to be evaluated using an animal model or computational tools. The counterions that might cause gastric irritation need to be avoided. The compatibility of the salt form with other pharmaceutical excipients needs to be studied. The flow properties and compressibility must be assessed to ease drug product manufacturing. The regulatory history concerning the counterion needs to be examined beforehand to avoid any last-minute surprises [31, 32]. The ease of manufacturing the salt form API must also be verified and simplified if needed.

4. Commonly used salt-forming agents

Different types of counterions are available, which can be screened and selected based on the API's nature and the salt form's objective. For acidic APIs, usually cationic-based counterions are suitable for the formulation of salt form, whereas anionic counterions are needed for the basic drugs. Other types of counterions include organic and aromatic sulfonates. Each type of salt might provide different benefits. The salt form of amlodipine besylate has resulted in improved solubility, whereas the salt form of sertraline hydrochloride has aided bioavailability enhancement. The calcium salt form of atorvastatin has improved stability of the drug substance. A few of the counterions will provide a dual effect [33–37]. For example, citrate counterion can aid both solubility and buffering. Hydrochloride salt forms are suitable for basic drugs. Counterions such as perchlorates need to be avoided due to toxicity concerns. A detailed list of commonly used counterions for developing pharmaceutical salts is listed in **Table 1**.

Table 1 List of the most used counterions for the development of pharmaceutical salts**.**

Counterion Category	Examples
Cations	Sodium, potassium, calcium, magnesium
Anions	Hydrochloride, sulfate, phosphate, nitrate
Organic anions	Fumarate, maleate, citrate, tartrate
Aromatic sulfonates	Besylate, mesylate, tosylate

5. Advantages and success stories

Developing a salt form of the drug provides various advantages. Along with solubility enhancement, the salt form of the drug will also improve bioavailability and stability. The manufacturability of the drug product using salt form is superior to that of the neat APIs. The salt form of the drugs will have better flow and compressibility. The rate of dissolution can

be improved with the salt form, which thereby provides a rapid onset of action for short-acting drugs and for drugs with shorter half-life. Inclusion of a few counterions will reduce the hygroscopicity of the drug, thereby enhancing stability [38–42]. The salt forms of the drug also provide the flexibility of developing injectables. The injectable dosage form prefers the salt form of the drug for preparing high-concentration drug solutions, thereby reducing the dosing volume. The salt form of the drug can mask the bitter taste of APIs, thereby improving the palatability of the pediatric patient population. The salts can better control the polymorphic forms, resulting in a robust, stable, and safe API. Developing a salt form of the drug will allow life cycle management to extend the patient exclusivity [43–46]. The various advantages offered by pharmaceutical salts are shown in Figure 1.

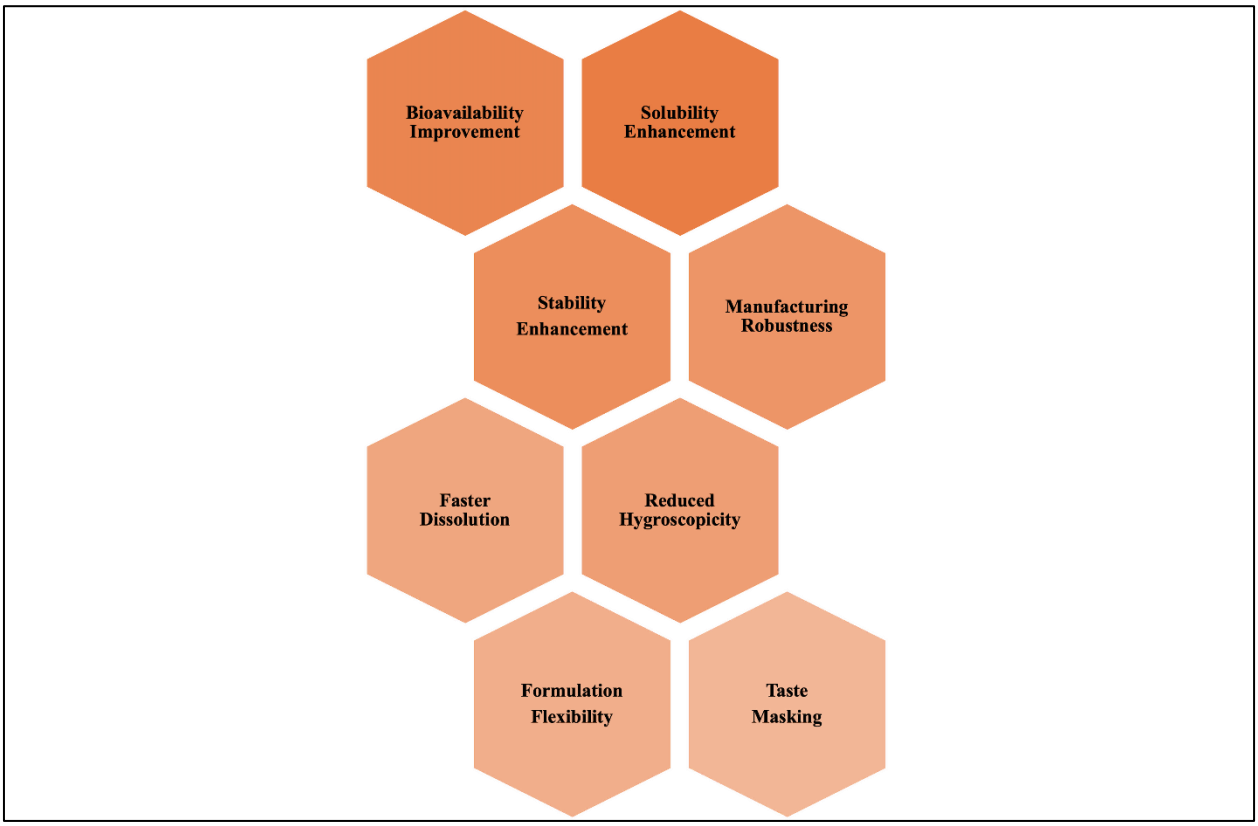

Figure 1 Various advantages offered by pharmaceutical salts

6. Limitations and challenges

A few salt forms will limit the solubility of the drugs, making them suitable for controlled-release dosage forms but not for immediate-release medications. The pKa rule will not produce a stable salt form in all situations. A few salt forms might be hygroscopic and require additional control measures to preserve stability [47–49]. A few counterions might aid in solubility enhancement, but need to be avoided due to toxic concerns. The risk of polymorphism exists for the salt form of the drug and requires a thorough screening before a stable form is identified. The salt form might not address the permeability challenge in all situations, especially for BCS class IV drugs [50–54].

7. Future perspectives

To accelerate the screening of suitable counterions for generating stable salt forms, computational tools with artificial intelligence (AI) must be integrated [55, 56]. More counterions that are safe for human administration need to be screened. The manufacturing process needs to be optimized to reduce the use of solvents and promote green chemistry [57–61]. The feasibility of the salt form of the drug for developing orally disintegrating tablets needs to be evaluated. The salt form of the drugs can be used within additive manufacturing techniques to create patient-centric medications [62].

8. Conclusion

Salt forms of the APIs are the most preferred approach by the pharmaceutical industry for improving the solubility and stability of the medications. In situations where developing a salt form of the drug is not feasible, alternate solubility enhancement techniques will be evaluated. Along with the advantage of solubility and stability enhancement, the salt form also provides the opportunity for life cycle management. A few limitations, such as the toxicity of the counterions, hygroscopicity, and polymorphism, exist but can be addressed by implementing thorough screening techniques. The future lies in the computational tools, novel counterions, and integration with the advanced drug delivery. However, the salt form of the APIs will dominate the development of solid oral dosage forms while next-generation approaches are developed and implemented.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflict of interests

Author's contribution

All aspects of this work, including literature review, analysis, and manuscript preparation, were solely conducted by the author

Funding source

The review article has received no external funding.

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