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Review

Advance Methodologies for Pharmaceutical Salt Synthesis

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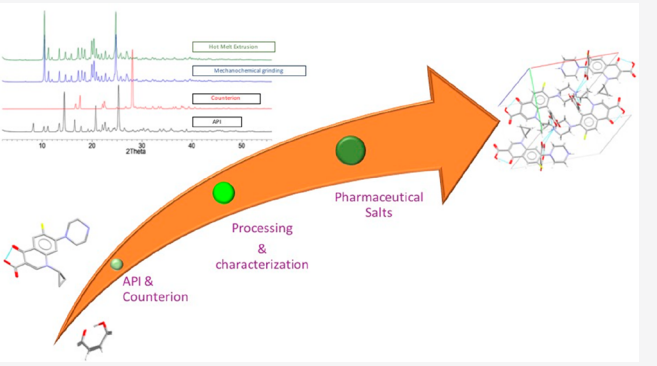
ABSTRACT: Pharmaceutical salt formation is the most preferred and effective method to enhance the physicochemical properties of an active pharmaceutical ingredient (API) such as solubility, bioavailability, stability, and processability. Salts are defined as crystalline materials composed of two or more different molecules, typically, drug and salt formers in the same crystal lattice, where the components in the crystal lattice are in an ionized state and interact via ionic interactions. Conventionally, the solvent-mediated process is used to manufacture the salts, where the use of a vast amount of solvent has a detrimental effect on the environment. Recently, there are very few methods that are being reported as solvent-free to manufacture the pharmaceutical salt. In this review, recent trends and advances in synthesis and manufacturing of salts are reviewed. Furthermore, the operational principles of commonly employed salt manufacturing technologies are discussed including their benefits and drawbacks in terms of purity, stability, throughput, and limitations in large-scale production. The final section is devoted to reviewing the regulatory issues in terms of the patent application for the salt form of an API compared to other multicomponent forms.



1. INTRODUCTION

Poor physicochemical properties prohibiting active pharmaceutical ingredients (APIs) from being readily utilizable in formulation development are a common drawback in the pharmaceutical industry. Currently, numerous drug substances suffer from low aqueous solubility, resulting in poor bioavailability,[1,2] while similarly, more than 60% of new drug molecules bear low solubility due to their increased size (molecular weight) and lipophilicity.[3−5] Newly introduced APIs in particular, commonly suffer from significant drawbacks pertaining to their physicochemical properties, namely, solubility, bioavailability, crystallinity, thermal stability, flow properties, etc. Such issues introduce additional risks of not attaining effective clinical outcomes and increasing associated costs, hence disfavoring investments in new drugs by pharmaceutical companies.[6,7] Efforts to tackle this challenge have been increasingly focused on the use of the salt forms of APIs, whereby the use of strong counterions for both anionic and cationic drugs has been exploited as a solution for more than three decades. A number of approaches including the synthesis of multicomponent drug products using pharmaceutically acceptable coformers/counterions are being actively studied by various research groups worldwide.[7,8] The APIs can exist in various solid forms, the nature of which is of eminent importance in relation to industrial scale-up and pharmacological activity.[9] As shown in Figure 1, the main forms are amorphous and crystalline with the latter being the preferred option for the pharmaceutical industry. Crystalline materials present better stability, and are easier to process and purify, but

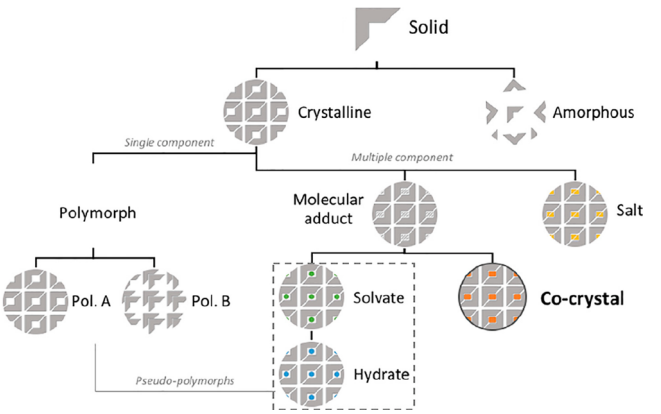


Figure 1. Diversity of solid forms in which an API can exist.[9] Adapted with permission from ref 9. Copyright 2012 American Chemical Society.

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in many cases the low water solubility is a major disadvantage. Nevertheless, different solid forms of APIs such as polymorphs, amorphous, hydrates, solvates, salts, cocrystals, and coordination compounds can improve the physicochemical properties of drug molecules[6] including water solubility and dissolution without affecting their pharmacological activity.[10]

The solid dosage forms, in particular, comprise the majority of common formulations (65−70%) in the pharmaceutical industry, due to being easily self-administered and thus highly patient compliant. The crystalline states of solid APIs are preferred, owing to their "relatively easy" synthesis, higher stability, and low levels of impurities.[7,11] Consequently, crystal engineering has become an emerging technology for drug development, having attracted the attention of a large body of researchers. Evidently, it is difficult to modify single-component crystals in order to attain the desired properties, as they are very much limited to polymorphs, wherein subtle changes in their physicochemical properties are only possible.[12,13] This is why the synthesis of multicomponent systems has become a preferred route to obtain sought-after properties in APIs, necessary to achieve required formulation attributes. While crystal engineering has indeed simplified the synthesis of multicomponent APIs including salts and cocrystals, determining which specific solid form of an API is suitable for further processing, scale-up, formulation, and clinical trials is critical.[7,9]

2. PHARMACEUTICAL SALTS TO IMPROVE SOLUBILITY

Pharmaceutical salts, which can be prepared using an appropriate counterion of an API, are undoubtedly the most common multicomponent systems, regularly used for improving the aqueous solubility of APIs. In cases wherein the salt formation is not feasible, cocrystal formation can be the best alternative to enhance the solubility and other physicochemical properties of the drug.[5−7]

According to IUPAC, a salt is a "chemical compound consisting of an assembly of cations and anions".[14] A pharmaceutical salt can be synthesized from an ionizable API (anionic, cationic, and zwitterionic) and an opposite charged ion, either molecular (acetate, mesylate) or atomic (sodium, bromide).[7] According to the FDA, salts are classified as "any of numerous compounds that result from replacement of part or all of the acid hydrogen of an acid by a metal or a radical acting like a metal; an ionic or electrovalent crystalline compound" (FDA guidelines 2018).[15]

In the last 60 years, salt formation has been employed as one of the most prominent methods to enhance drug properties. Notably, more than 50% of marketed drug products are in the form of salts.[7,16,17] The pharmaceutical industry has extensively utilized salt formation as an attractive approach to improve the solubility of poorly water-soluble drugs, due to the process simplicity and stability of salts resulting from ionizable drugs.[18] Moreover, salts enhance the dissolution rate rather than the solubility of the API itself, leading to improved bioavailability.[16,17]

The aqueous solubility of drugs, classified as weakly acidic or basic, is dependent on pH and governed by the ionization and dissociation constant as described by the Henderson−Hasselbalch equation.[17,19,20] The pH dependent solubility of a weak base can have two distinct profiles based on whether the free base or the salt is the equilibrium species except at the pH of the highest solubility (pH_{max}). The total solubility of a base can be presented as

$$S = [BH^+] + [B] \quad (1)$$

where S $[BH^+]$ and $[B]$ represent the total solubility, ionized and un-ionized base, respectively. The equilibrium for a monobasic base, when dissolved in water, can be written as

$$BH^+ + H_2O \overset{K_a}{\leftrightarrow} B + H_3O \quad (2)$$

Equation 2 can be rearranged to calculate the ionization constant (k_a):

$$K_a = \frac{[B][H_3O^+]}{[BH^+]} \quad (3)$$

As stated above, the solubility of the salts is greatly influenced by the pH of the dissolution media. The solubility of salt at pH higher than pH_{max} can be described as the solubility of the free base, as follows:

$$S = S_0(1 + [H_3O^+]/[K_a]) \quad (4)$$

where S_0 and S are the intrinsic (solubility of the un-ionized form) solubility and total solubility, respectively.

Similarly, the solubility at pH lower than the pH_{max} is defined as

$$S = \sqrt{K_{sp}}(1 + {[K_a]}/{[H_3O^+]}) \quad (5)$$

where K_{sp} ($[BH^+][A^-]$) is the solubility product of the salt.

The relationship between pH_{max}, pK_a, total solubility (S_0), and solubility product (K_{sp}) is represented by the following equations:

$$\text{Weak bases: } pH_{max} = pK_a + \log {S_0}/{\sqrt{K_{sp}}} \quad (6)$$

$$\text{Weak acids: } pH_{max} = pK_a - \log {S_0}/{\sqrt{K_{sp}}} \quad (7)$$

The pH_{max} value is essential for the determination of the pH at which the salt attains its maximum solubility, as well as to estimate the stability of the salt in comparison to the free base, as a function of pH (Figure 2). The pH_{max} and pK_a are directly proportional; hence, an increase of the pK_a leads to an analogous increase of the pH_{max} for a weak base. On the contrary, an increase of the salt solubility, or $\sqrt{K_{sp}}$, will result in a decrease of the pH_{max} due to their inverse relationship as presented in eq 7. Therefore, it is expected that the pH_{max} will change significantly based on the choice of counterions.[16,17,20]

The main prerequisite for salt formation is the ionizability of the API, to enable the interaction with the desired anion or cation. In general, salts are highly stable, but they can also exist as hydrates, which may compromise the stability and be proven problematic during secondary processing steps. The formation of hydrates can be difficult to monitor and control during wet massing, fluid bed drying, and aqueous film coating.[5,8,21,22] Similarly, it has been documented that salts containing chloride ions (54% of the salts approved between 1995 and 2006) might exhibit reduced dissolution rates due to the common ion effect, as gastric and intestinal fluids (jejunum) are rich in chloride.[8,16] Salts are an excellent way for enhancing the pharmacological properties of a drug, but the sole focus on the improvement of dissolution rate and solubility properties of drugs can sometimes be counterproductive. This is of

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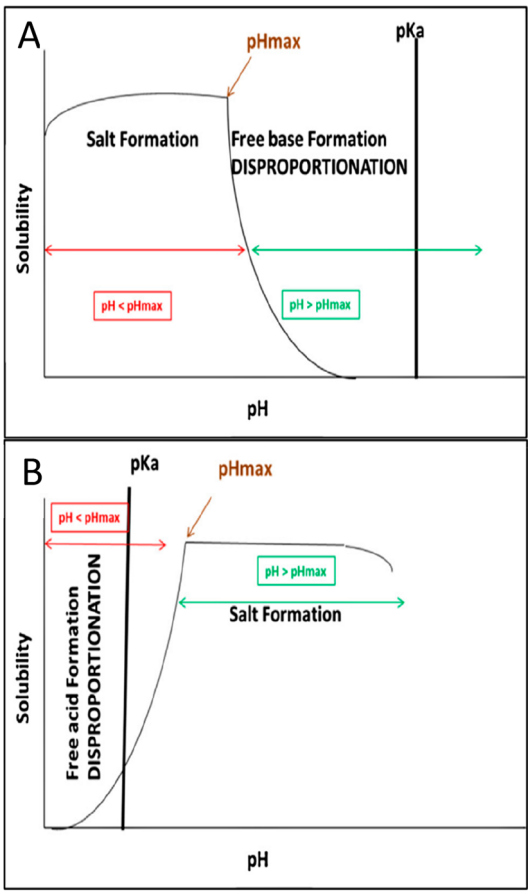

Figure 2. Schematic depiction of the pH−solubility profiles of (A) weakly basic drug, and (B) weakly acidic drug. In both the profiles, solubility may be expressed by two independent curves viz. when pH < pH_{max}, and when pH > pH_{max}. The point where these two curves meet is the pH_{max}. Sometimes a drop in solubility near the lower pH in curve "A" and a higher pH in curve "b" is observed due to the common ion effect.[16,17]

particular importance as this improvement can occasionally lead to adverse effects by increasing the accumulation of the drug beyond the equilibrium solubility, if not considered carefully.[23]

f3 Among numerous options, cocrystals (Figure 3) have opened a new door in relation to drug development as they are not limited, unlike salts, to ionizable drugs. Furthermore, cocrystals formation can be an effective approach to create new intellectual property in the pharmaceutical industry and thus prolong the life cycle of APIs.[25]

For nonionizable drugs and compounds, the salt formation of which is not possible, cocrystallization is a possible alternative for drug development. Although cocrystals have not yet gained a significant market share due to challenges related to their recognition as new APIs, the prospects are definitely promising.[7,24,26]

Albeit solubility is the predominant concern in drug development, a choice needs to be made between the highest solubility and the highest stability. This becomes a particular challenge in cases when the maximum soluble form suffers from stability issues due to, e.g., hydrolysis, which is a common degradation problem.[5,8,23]

Another common approach entails the application of amorphous solids in drug products; however, crystalline drug

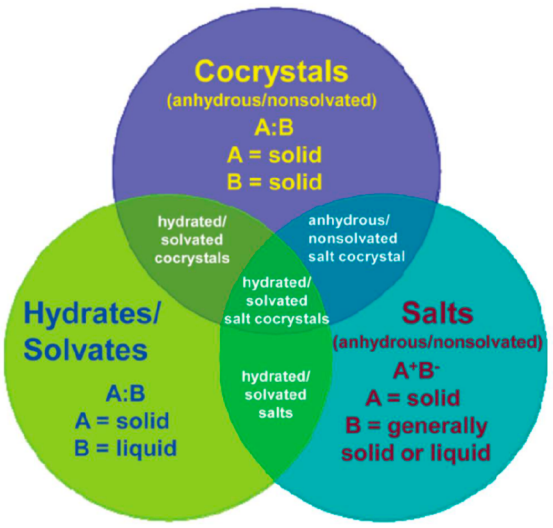

Figure 3. Different multicomponent formation: cocrystals, salts, hydrates/solvates.[24] Reprinted from ref 24 with permission. Copyright 2017 Elsevier.

materials are preferred to meet the requirements in terms of thermodynamic properties such as purity, stability, and means of processing.[12] Furthermore, for systems including solvates, hydrates, and inclusion compounds, physical stability is an important factor to consider since hydrates are considered a nemesis for crystal engineering due to the "promiscuity" of water.[27] Amorphous solids can show low thermal stability, and this often works against their desired use in drug materials. Solvates may show instability due to a rise in temperature and humidity that can possibly limit their selection as drug products.[12] Generally, hydrates/solvates are less soluble and more stable than the corresponding nonsolvated forms in a specified solvent. The solubility of hydrates or solvates decreases in relation to the increasing numbers of solvent molecules within the crystal lattice.[5,8,28] Therefore, salts are still the most recognized and widely accepted form of alteration to a drug molecule in the pharmaceutical industry, to obtain desired physicochemical properties leading to the development of formulations with optimal specifications. The critical factor in the development of salts is the choice of the salt former, which needs to be selected depending on the physicochemical properties and toxicological and pharmacological consequences of the counterion.

2.1. Pharmaceutical Salt Formers. The salt formation of an API largely depends on the acidity or basicity of the API itself, the safety of the salt former/counterion, the choice of dosage forms, the route of administration, and the drug indications.[29,30] The salt formers/counterions can be divided into two categories (Table 1) based on their purpose and t1 functionality.

In most cases, hydrochloride salts have been commonly employed to develop salts of weakly basic drug substances.[31] However, the use of hydrochloride salts had to be restricted due to the unacceptability of high acidity in formulations, the risk of corrosion, and poor stability of the acid labile and hygroscopic drugs.[29,31] The popularity of chloride as the counterion until the end of the 20th century in both oral and injectable dosage forms was high, although the growth in the usage of chloride salts clearly dropped since the beginning of the current century. Nonetheless, they still remain ubiquitous,

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Table 1. List of Counterions Used in Salt Formation[36]

acidic counterion	pK_{a1}	pK_{a2}	pK_{a3}
acetic	4.76		
benzoic	4.20		
citric	3.13	4.76	6.40
D,L-lactic	3.86		
fumaric	3.03	4.38	
glutamic	2.19	9.67	
hydroiodic	−8		
hydrochloride	−6		
hydrobromic	−6		
L-(+)-tartaric	3.02	4.36	
malic	3.40	5.03	
maleic	1.92	6.23	
methane sulfonic	−1.2		
nitric	−1.32		
oleic	5.02		
oxalic	1.25	4.28	
pamoic	2.51	3.1	
phosphoric	1.96	7.12	12.32
p-toluene sulfonic	−1.34		
salicylic	2.98	13.4	
succinic	4.19	5.48	
sulfuric	−3	1.92	
basic counterion	pK_{a1}	pK_{a2}	pK_{a3}
aluminum	5.0		
ammonium	9.27		
L-arginine	13.2	9.09	2.18
calcium	12.7		
chloroprocaine	8.7		
choline	13.9		
diethylamine	10.93		
diethanolamine	8.96		
ethanolamine	9.5		
ethylenediamine	9.69		
histidine	1.82	9.17	
L-lysine	10.79	9.18	2.16
magnesium	11.4		
meglumine	8.03		
potassium	14		
procaine	9.0		
sodium	14		
tromethamine	8.02		
triethylamine	10.75		
zinc	9[37]		

albeit succinates, acetates, and bromides have gained increasing acceptability.[31]

2.2. Prerequisites for Salt Formation. For a poorly bioavailable API, salt formation is often the first approach considered in industry, in view of the fact that salts are likely to be stable due to the presence of ionic bonds as well as be more soluble than the un-ionized form.[32,33] API crystallinity/solubility and whether solubility is the limiting factor are the primary criteria that need to be meticulously considered during the high-throughput multicomponent crystalline product (salt, cocrystal etc.) screening.[34]

Depending on the various stoichiometric molar ratios of API and counterion, multicomponent products such as salts can exhibit different physicochemical properties due to the distinct arrangements of molecules.[35] Moreover, different molecular entities consisting of different molar ratios of API and coformers can be treated as new products, yielding new patents. For this reason, increased attention should be paid to the molar ratio of API and counterion during the synthesis of multicomponent products.[18]

Salt formation occurs when an ionized compound forms a strong ionic bond with the oppositely charged counterions in a solution. The pK_a rule governs the development of multicomponent systems, and the difference between ΔpK_b and pK_α indicates whether the salt formation is possible. The respective equation is shown below:

$$\Delta pK_a = pK_b - pK_a \quad (8)$$

From the above equation, high ΔpK_a values provide a strong indication of salt formation.[8] It is known that at $\Delta pK_a < -1$, mostly cocrystals are formed, while salts are formed exclusively when $\Delta pK_a > 4$ (Figure 4).[38] The foregoing has been applied to various drug/coformer pairs; however, the outcome of a ΔpK_a at a range between 0 and 3 remains hard to predict.

Typically, the difference of the pK_a values gives an initial indication during multicomponent screening;[39] nevertheless, other factors such as particle size, solubility, potency, etc. should be also considered, as pK_a is usually evaluated with regard to water but not in the solid state, and it is temperature dependent.[7,32,33] Furthermore, pharmaceutical salt formation fully depends on proton transfer, so validating whether proton transfer between two components is possible is an essential prerequisite for salt screening. The proton transfer capabilities can be easily ascertained after calculating the difference between the acid dissociation constants for the hydrogen bond donors and the conjugate base of the hydrogen bond acceptor.[32,33]

A hydrogen bond will be formed without undergoing proton transfer if a negative value is returned from eq 8. However, proton transfer will take place along with a stronger double charge assisted hydrogen bond, if a positive value is obtained. Pharmaceutical salts can be mainly formed via hydrogen bonding[40] (Figure 5) in supramolecular synthons. Two types of supramolecular synthons are available: supramolecular homosynthons between the same complementary functional groups (e.g., carboxylic acid dimers) and supramolecular heterosynthons between different but complementary functional groups (e.g., carboxylic acid−amide). Different supramolecular homo- or heterosynthons include carboxylic acid−amide, carboxylic acid−aromatic nitrogen, alcohol−aromatic nitrogen, and alcohol−amine (Figure 6).[12]

Martin et al, 2013 reported the salt and cocrystal formation of a basic drug, ketoconazole, having a pK_a value of 7.47, formed cocrystals with fumaric acid, succinic acid, adipic acid, and a salt with oxalic.[10]

The pK_a difference between ketoconazole and oxalic acid is higher than 3, which, according to the pK_a rule, indicates that salt formation was expected. Furthermore, the pK_a difference of succinic and adipic acid with ketoconazole is less than 3 rendering salt formation unexpected, leading to the formation of the cocrystal. On the contrary, the pK_a difference between ketoconazole and fumaric acid was higher than 3 prompting the assumption that salt will be formed; however, the end product was a cocrystal due to the absence of proton transfer between the molecules. Hence, the pK_a rule is not applicable in all cases where proton transfer also depends on the availability of proton donor and acceptor.

In recent years, modern drug discovery and drug development tools have been employed to reduce the cost in this

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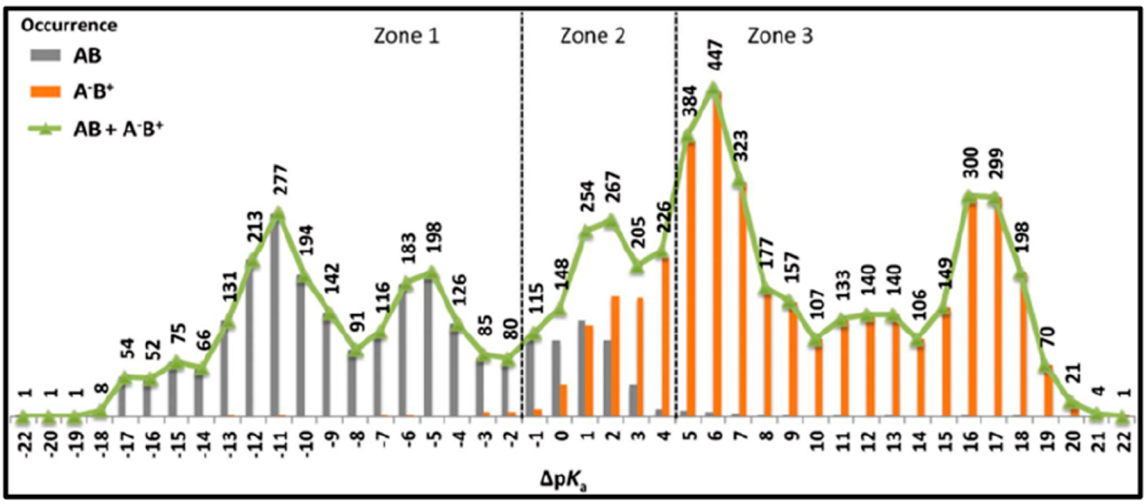

Figure 4. Occurrence of AB (gray) and A^-B^+ (orange) as a function of the calculated ΔpK_a, AB stands for acid base.[38] Reprinted with permission from ref 38.

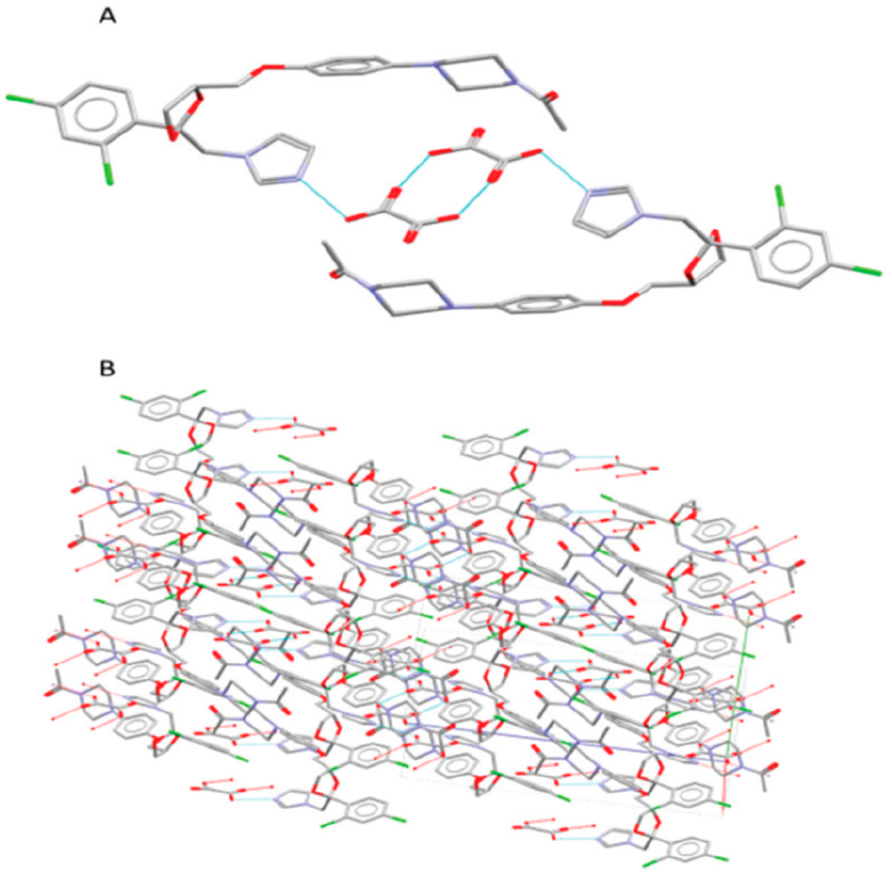

Figure 5. (A) Hydrogen bonds between oxalic acid (OA) dimers and imidazole ring of the ketoconazole (KTZ) moiety, (B) crystal packing projections for KTZ−OA salt (hydrogen bond). Other hydrogen and van der Waals bonds have been omitted for clarity.[40]

highly competitive environment. High throughput experimental salt screening became an integral part of the preformulating stages of drug development to narrow down the potential salt forming candidates. The selected salt candidate may then be promoted to the next stage of development such as scale up (Figure 7).[41,42] On the contrary, it is evident that, while high throughput screening on the basis of different criteria such as the difference of pK_a values provide advantages, it also suffers from the issue that many salt forms can be overlooked by the fixed protocols used.[41−43]

3. METHODOLOGIES OF SALT PREPARATION

Various techniques are used for the successful synthesis of salts, among which some are considered advantageous. Commonly applied techniques include solvent evaporation, solution crystallization, neat grinding, liquid-assisted grinding, slurrying, comelting, and vapor digestion. Other approaches

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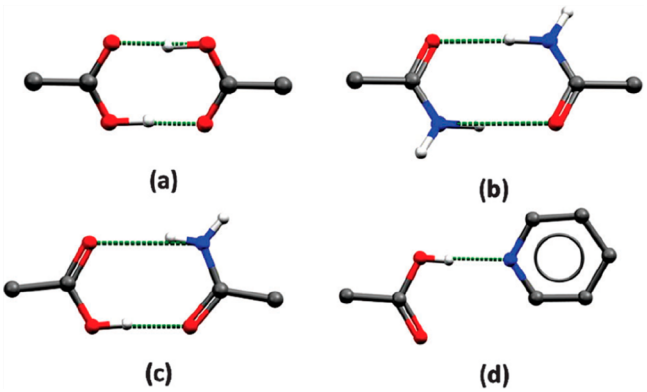

Figure 6. Common supramolecular synthons formed via hydrogen bonding, (a) carboxylic acid homosynthon exists as a dimer (b) amide homosynthon exists as dimer; supramolecular heterosynthons (c) carboxylic acid−amide heterosynthon (d) carboxylic acid−pyridine heterosynthon.[12]

include sonication, sublimation, vapor digestion, and use of supercritical carbon dioxide.[7] Regarding traditional manufacturing methods of salts, solvent addition is required to facilitate the process.[20] Though solvents have been viewed as necessary catalysts for salt formation, their use is accompanied by a range of issues such as solvate formation, greenhouse gas emissions, and wastage.[12] Solvate formation is an undesirable byproduct in salt processing and potentially can cause uncontrollable changes to the physicochemical properties of the product reacting with the bulk constituents, leading to incomplete transformations and low purity batches and the creation of more industrial waste.[44,45] Furthermore, these require the implementation of extra waste disposal systems which can raise the risk of environmental hazards, while more volatile solvents can impose increased health and safety considerations.[46] These issues highlight the need to develop solvent-free processes for pharmaceutical manufacture. There are currently very few solvent-free methods being used for pharmaceutical salt preparation, such as mechanochemical neat grinding and extrusion.[40] Nevertheless, solvent processing techniques are frequently used due to their ease for salt formation and scale-up, the simplicity of configuration (e.g., equipment), and the possibility to couple with process analytical tools (e.g., NIR, Raman probes). Another advantage of solvent crystallization techniques is that are usually accompanied by phase diagrams and that are used to identify the salt formation mechanisms.

3.1. Solution Crystallization. Solution crystallization is the most common method used for the formation of single salt crystals after dissolution of specific amounts of API and salt former in a suitable solvent. In slow crystallization, the resulting solution is left undisturbed to form the single crystals within a time frame, the duration of which depends on the materials used (Figure 8).[32,33] In other cases such as crystal

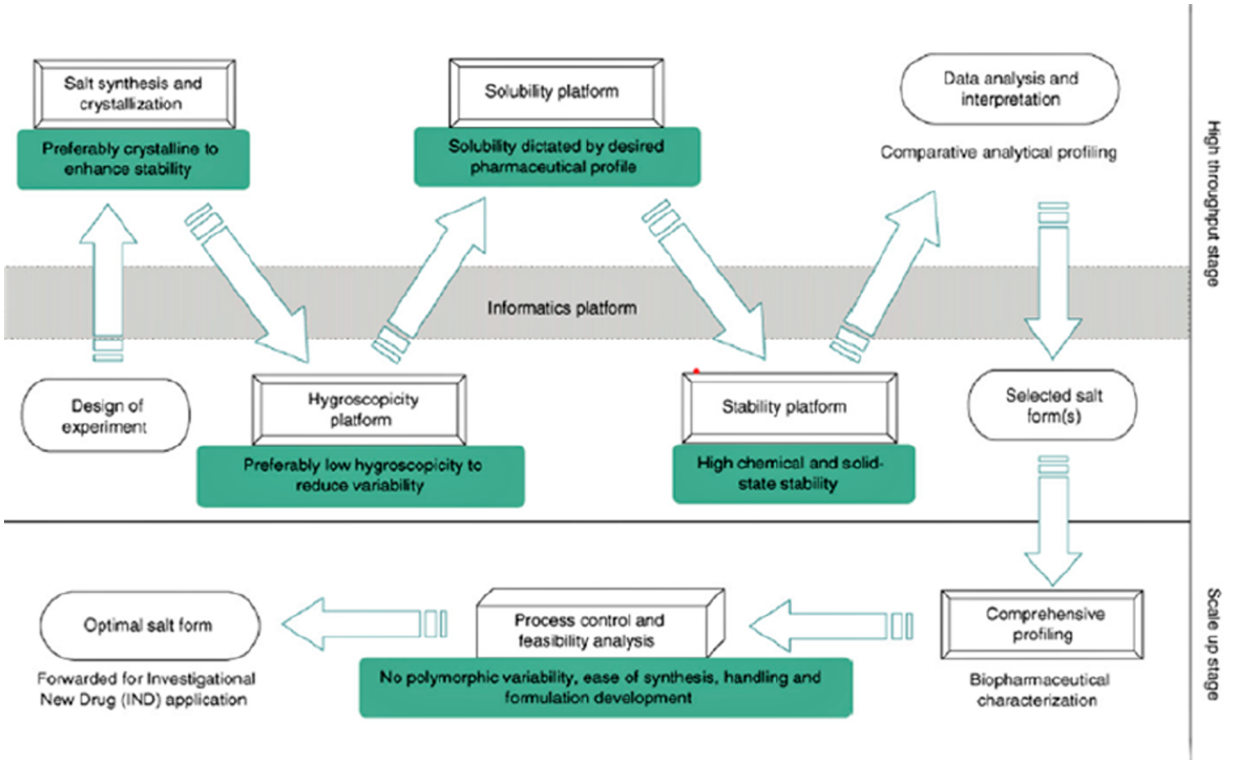

Figure 7. Stages of high-throughput salt selection showing an interface with the scale-up stage of salt screening. Each high-throughput stage is interlinked through the informatics platform. Stages depicted with double lined box indicate essential criteria, and the cuboidal box shows desirable criteria of salt selection, with the preferable parameters depicted in the underlying green shaded area. The informatics platform generates experimental design for crystallization, hygroscopicity, solubility, and stability platforms, and evaluates the analytical profile generated, to shortlist the potential salt(s). The initial "salt synthesis and crystallization" station includes a reaction platform for salt and counterion reaction, a crystallization platform for solvent recrystallization, and a solid form screening platform for initial solid form screening using X-ray diffraction, Raman, thermal, and chromatographic methods. Salt candidate(s) pass through the various stages of high-throughput salt selection (in the direction of the arrows indicated) to scale-up the stage for extensive biopharmaceutical characterization, proceeded by an assessment of desirable criteria to finalize the optimal salt form.[41] Reprinted with permission from ref 41. Copyright 2007 Elsevier.

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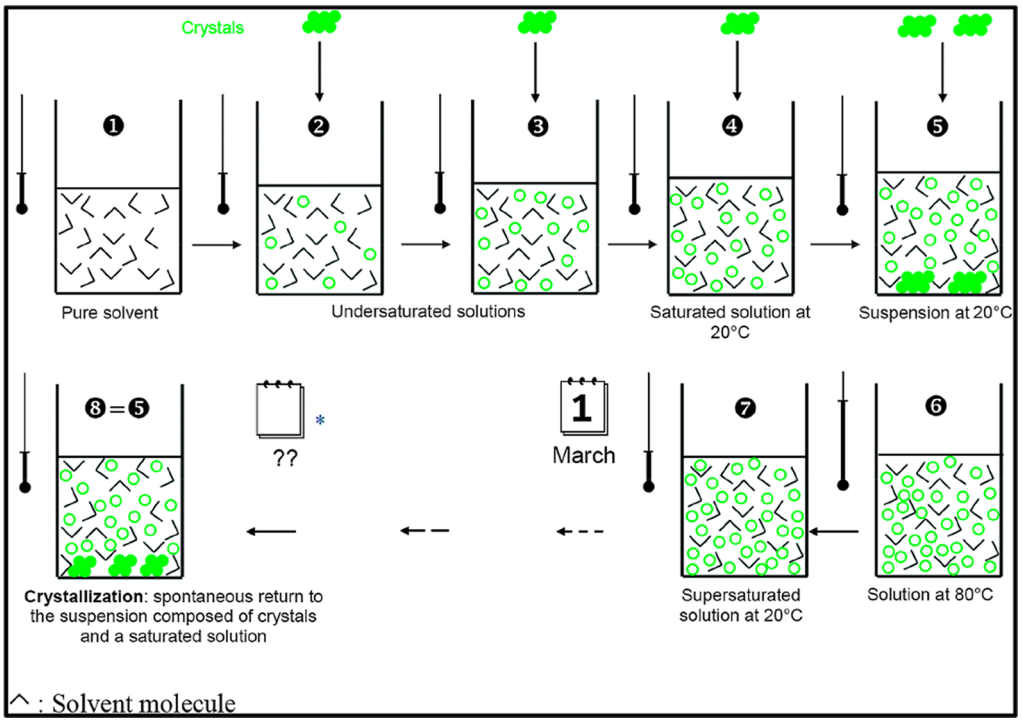

Figure 8. Cartoon illustrating an isothermal (e.g., 20 °C) dissolution process up to saturation of the solution (from ① to ④), the formation of a suspension (at 20 °C) point ⑥, the complete dissolution by heating: point ⑥ (e.g., 40 °C), the creation of a supersaturated solution after the return at 20 °C (point ⑦ out of equilibrium). Point ⑧ illustrates the return to equilibrium; i.e., the concentrations of the solution in ⑤ and in ⑧ are identical. (Solvent molecules are symbolized as ^, and amounts of crystals of a pure component are symbolized as ●). Reprinted with permission from ref 33. Copyright 2014 Royal Society of Chemistry.

seeding, rapid precipitation, solvent evaporation heat, or solvent is applied to swift the process.

Romanuk et al., 2009, reported the formation of saccharin (SAC) salts of fluoroquinolones (FQ), norfloxacin, ciprofloxacin (CIP), ofloxacin, and enrofloxacin to improve the low solubility and bitter taste.[48] Appropriate quantities of APIs and saccharin (molar stoichiometric ratio 1:1) were dissolved in water, and FQ−SAC salts were obtained.

Later, in 2010, they reported the formation of CIP−saccharinate polymorph II and found a new form along with the previously reported salts, where both forms were stable and pure. Similar to FQ-SAC, appropriate quantities of CIP and SAC were dissolved in hot water and were allowed to slowly cool down in the dark to obtain single crystals after 2−3 days (Figure 9).[47]

Figure 9. Single crystals of CIP-SAC II. Reprinted with permission from ref 47. Copyright 2010 Elsevier.

Chrzanowski and Ahmed, 2016, reported the formation of linogliride salts to obtain extended drug release, wherein seven acids were selected to attempt salt formation, but only four named pamoic, *p*-hydroxybenzoic, 3-hydroxy-2-naphthoic and 1-napysylic acids were capable of successfully forming the salt. pH solubility profiles of the newly formed salts were compared over the long pH range of 1.43−8.3, against the free base and the fast release linigloride fumarate salt. All the above-mentioned salts were prepared by solution crystallization as well as via the precipitation and vacuum filtration methods. Interestingly, all of the multicomponent systems of linigloride showed a slow dissolution rate compared to the fumarate salt, which is used for immediate drug release. Three salts, except *p*-hydroxybenzoate, were suggested as the potential candidate for the extended release dosage forms.[49]

Surov et al., 2015, reported the formation of three ciprofloxacin salts with dicarboxylic acid by solution crystallization after dissolving the solids in a mixture of aqueous and organic solvents. The crystalline salts of fumarate and adipate contained water molecules and formed hydrates, while maleate salt existed in anhydrous form. Ciprofloxacin is highly soluble in acidic conditions due to the piperazine ring in the structure; nonetheless, the salt showed enhanced dissolution in basic media compared to the bulk CIP.[50] Moreover, fumarate and adipate hydrates showed higher dissolution than marketed hydrochloride hydrate salt of ciprofloxacin. In continuation to this work, Surov et al., 2016, reported three polymorphic forms of ciprofloxacin maleate salts and one hydrate in the following year, prepared by solvent drop grinding combined with solution crystallization in different organic and aqueous solvents and mixtures of them. They discovered that the

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form III of ciprofloxacin maleate salt was unstable due to the possible kinetic instability and tendency to convert to the more stable form II. It was also found that changing the processing solvents had notable effects on the formation of different forms of the CIP salts, even if the employed method was the same.[44] Similar combinatorial methods were employed by Sarmah et al., 2018, where a series of olanzapine (OLZ) salts were formed using pharmaceutically acceptable salt formers, i.e., malonic, maleic, oxalic, succinic, glutaric, and adipic acid. Mechanochemical processing and solution crystallization were used for the formation of different olanzapine salts, and the success of this approach was established via a number of analytical techniques. Most importantly, hydration stability was studied at different % RH conditions, revealing that the length of the dicarboxylic acid chain in salt formation was correlated to their stability.[51]

3.2. Solvent Evaporation. Although it is difficult to find a suitable solvent to dissolve poorly soluble drugs, solvent evaporation is still a commonly used preparation method for salts. Hence, a mixture of organic and aqueous solvents is typically employed to synthesize salts using this method, wherein the solvent is removed by applying heat to the solution until the solvent is evaporated[52] (Figure 10). Reddy et

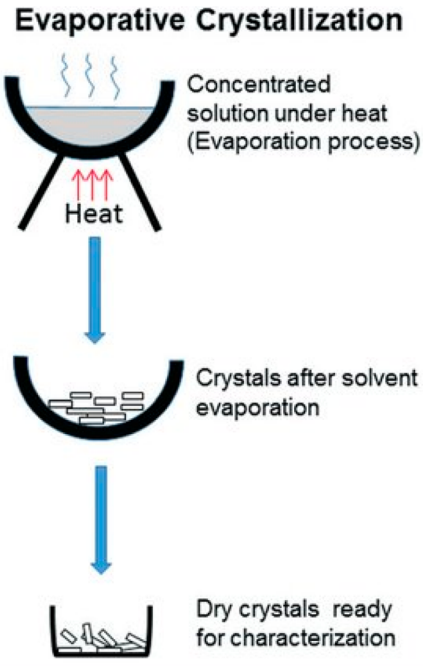

Figure 10. Traditional crystallization techniques: single droplet crystallization and evaporative crystallization. Reprinted with permission from ref 52. Copyright 2016 Royal Society of Chemistry.

al., 2011, reported the formation of six different forms of norfloxacin (NFX) and CIP salt with five different carboxylic acid salt formers. The preparation method included slow evaporation of the solution in aqueous and organic solvents and mixtures. NFX formed hydrates with all three carboxylic acids which had a higher aqueous solubility than anhydrous forms. CIP formed one anhydrous and other two hydrate salt forms with enhanced properties in comparison to the bulk API.[53]

Similarly, Hiendrawan et al., 2017, prepared salts of the antihypertensive drug carvedilol, with the four different GRAS listed salt formers oxalic, fumaric, benzoic, and mandelic acid, using the solvent evaporation method. Several different organic solvents and water, either separately or in combination, were used to enable salt formation between the API and the salt formers. Salts prepared using this approach were endowed with a higher aqueous solubility compared to the API itself.[54] Moreover, salts prepared with mandelic acid led to the formation of two polymorphs where the form I was found to be more stable than the other. Solvent evaporation in combination with grinding has also been commonly used in salt preparation. For example, Fulias et al., 2015, reported the formation of a ketoprofen (KTP) salt with the amino acid cysteine (CYS).

A physical mixture of the drug and amino acid was homogeneously blended in an agate mortar for a predetermined time, prior to making the respective solution that was subjected to slow solvent evaporation to obtain the salt.[55] Similar studies on salt preparation using a combination of KTP and LYC were also reported by other researchers Panerai et al., 2012[56] and Stigliani et al., 2013.[57] Along the same lines, multicomponent solid forms of ethambutol (ETH) were reported by Diniz et al., 2017, using four different pharmaceutically acceptable salt formers (oxalic acid, maleic acid, terephthalic acid, and trichloroacetic acid) to avoid rifampicin-induced degradation during combination therapy for the treatment of tuberculosis. The salts reported in this study were prepared by solvent evaporation except for the ETH-oxalate, which was formed by mechanochemical grinding process. The developed salts had higher thermal stability than the free base without the presence of any phase transition. ETH-oxalate salts were observed to be non-hygroscopic, whereas the other three salts retained the hygroscopic nature of the free base.[58]

Recently, Cvetkovski et al., 2017, reported the formation of two new pharmaceutical salts of pyridoxine (PYR), prepared with syringic acid and ferulic acid via slow solvent evaporation, after dissolving the drug and salt formers in individual solvents or mixtures (1:1 stoichiometric ratio). Hirshfeld surface analysis was used to explore the intermolecular interactions between the API and the salt former and indicated the robustness of the pyridine/carboxylic acid as supramolecular synthons.[59] Ainurofiq et al., 2018, described the first multicomponent crystal formation of desloratadine (an antihistamine drug) with benzoic acid, where both components were first dissolved in methanol, and the resulting solution was evaporated at 50 °C using a rotavapor. The obtained salt was characterized by various analytical techniques to confirm the salt formation, and successful proton transfer between the API and salt former was reported. This work also included comparison with other salt formation methods including neat grinding, liquid assisted grinding, and slurry conversion, but successful salt formation occurred only with solvent evaporation. The resulting salt exhibited enhanced tabletabilty and plasticity profiles compared to the parent compound, while showing improved solubility profiles in water and acidic media.[60]

Solvent evaporation has also been used in combination with other methods for the successful preparation of salts. Wang et al., 2017, reported the formation of four different salts of diphenhydramine (DPH), a first-generation H-receptor antagonist, using four different salt formers: hydrochloride acid (HCL), citric acid, saccharin (SAC) and acesulfumaric acid (ACS). The crystalline salts of DPH-SAC and DPH-ACS were prepared through the anion exchange reaction between

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DPH-HCL with Na-SAC and K-ACS, respectively. On the other hand, DPH-HCL and DPH-citrate single crystals were obtained by slow evaporation of a solution prepared by dissolving the solids in a suitable solvent. The correlation between energy framework and crystal structures were studied to find the optimal mechanical properties and tabletability of the prepared salt crystals. This study provided insights and enabled the prediction of the tableting performance of crystalline products, based on crystal structures and mechanical properties.[61]

3.3. Slurry Conversion. The slurry method, another widely employed technique for the development of salts, involves the preparation of a suspension by adding a small amount of solvent to the physical mixture of API and salt former. Hiendrawan et al., 2015, used this method to obtain salts of antifungal agents, namely, ketoconazole with the GRAS listed salt former, oxalic acid. Studies performed at accelerated stability conditions of 40 °C/75% RH over the period of 1 month confirmed no changes to the prepared multicomponent system. Also, an *in vitro* activity assay showed that the prepared salt demonstrated equally effective antifungal action when compared to the bulk ketoconazole.[62] Derdour et al., 2017, reported the development of a reactive slurry crystallization method for salt formation to tackle issues pertaining to scalability, low yield, and undesirable API powder properties associated with a potent oncology drug available in industry. The newly introduced slurry crystallization process was developed based on the solubility behavior of both the base and the salt, utilizing the base as a seed in the process, to achieve supersaturation. The parent crystalline solvate was crystallized first, and then the nonsolvated crystalline salt was prepared from a slurry which contained the crystal of solvate. A significant yield of around 90% with narrow particle size was achieved using this process. This work also assessed the potential of the process to be upscaled, where 50 g of crystallites was produced without any significant difference in comparison to 3 g. Although the scaled-up method was essentially the same, few parameters such as mixing effects and potential hold points needed to be investigated beforehand.[63]

In a recent review, Fernandez et al., 2015, investigated three salt screening methods: the *in situ* salt formation, the saturated solution method, and the cooling-evaporation method. The outcome of this study highlighted that all the aforementioned carry significant advantages as well as disadvantages. It was reported that the choice of the salt screening process mostly depended on the physical properties of the drug substances. Hence, aripiprazole and desvenlafaxine were used as the APIs along with 17 pharmaceutically acceptable acids to investigate the relationship between the physical properties of the drug and the salt screening process. Three different salt preparation methods as mentioned earlier were evaluated aiming at creating guidelines on their suitability in salt formation of the APIs in question. The authors concluded the saturated solution method to be the ideal choice, due to its cost-effectiveness, efficiency, and highest hit-ratio among the three methods tested in this study. However, the cooling-evaporative method was suggested in cases wherein the API is possible to "oil out", hereby rendering high-throughput screening necessary. The study also underlined difficulties in obtaining salts using APIs that may be soluble in aqueous media. For the screening of water-soluble APIs, the antisolvent-based crystallization process was recommended to induce the production of crystalline salts by precipitation, which is further discussed in the following section.[64]

3.4. Vapor Diffusion with Antisolvent. During the crystallization process, a second liquid or solvent can be added to enhance the supersaturation process, termed as antisolvent. Aqueous solvents such as water along with organic solvents can be used as an antisolvent in various cases. In the vapor diffusion process, the solute is dissolved in a solvent in a vial and kept in an outer container which is filled with an antisolvent. After the outer container is closed, an equilibrium condition is established between the two liquids in a closed environment resulting in crystallization. An appropriate choice of solvent (should moderately solubilize the solute) and antisolvent (should desolubilise the solute) should be used to facilitate the vapor equilibration process.[65] Chadha et al., 2016, reported the formation of ciprofloxacin hippurate (CP-HA) salt by solvent-assisted grinding; a combination of solution creeping and vapor diffusion with antisolvent was used to obtain the single crystals of the salt. The slow diffusion of antisolvent vapors reduced the solubility in the preferred solvent, thereby facilitating the crystal formation due to supersaturation followed by precipitation. Different solvent combinations such as methanol−hexane, acetone−hexane, dimethoxyethane−hexane, acetonitrile−tetrahydropyran, and tetrahydrofuran−cyclohexane were used in the crystallization process. The processes containing hexane resulted in block-shaped crystals in all cases, in contradiction with others not involving hexane. An appropriate volume of a saturated solution of CP-HA salt was put into small test tubes, which were thereafter placed in larger test tubes, containing another solvent which operated as the antisolvent. The formed salt was found to be stable and demonstrated an improved aqueous solubility and intrinsic dissolution rate, in comparison to the bulk ciprofloxacin.[1]

3.5. Freeze-Drying Method. Freeze-drying is the removal of ice or other frozen solvents from a sample through sublimation, whereby bound water molecules are extracted from the system through the desorption process. Elshaer et al., 2013, reported the preparation of a ciprofloxacin (CIP) salt with two amino acids, L-glutamic and L-aspartic, from the aqueous solution of the drug and salt-former that was filtered and freeze-dried for 42 h. The authors also attempted salt formation using L-lysine, L-arginine, and L-histidine, without any success. The role of inter- and intramolecular interactions between CIP and amino acids in salt formation was studied using molecular dynamic simulation, to justify the inability of cationic amino acids to induce CIP salt formation. It was concluded by experimental and theoretical investigation that both ionic and hydrophobic interactions are essential for salt formation. More explicitly, it was revealed that the ionic interaction and/or hydrophilic interactions between CIP and amino acids molecules should be greater than hydrophobic interactions between CIP molecules. Furthermore, the successfully formed glutamate and aspartate salt of CIP was found to exhibit a higher dissolution rate compared to bulk CIP.[66]

3.6. Supercritical Fluid Processing. The use of supercritical fluid (SCF) in pharmaceutical product formation and processing has gained enormous attention in recent years in the fields of particle engineering, as well as for the development of drug delivery systems.[67,68] The ability of SCF to act as solvent and antisolvent can be utilized effectively in the salt formation of pharmaceutical actives. The SCF has been

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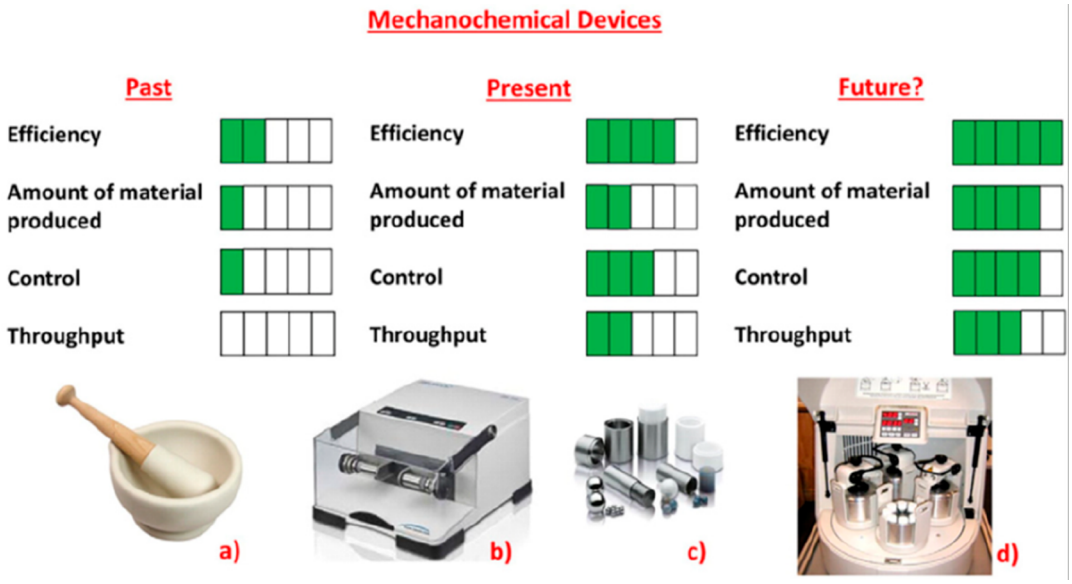

Figure 11. Top: summary of the main characteristics of past, present and possible future mechanochemical devices. Bottom: pictures of (a) mortar and pestle, (b) a modern vibrational mill with (c) a set of jars and grinding media having different volumes and composition (for more details visit www.Retsch.com) and (d) a multisampling planetary mill (for more details, visit www.automaxionltd.com).

commonly employed as a medium in cocrystallization,[69,70] and yet studies on salt formation via SCF processing are rare in the literature. However, similar fundamental principles as to cocrystallization can also be effectually used in SCFs-aided salt formation. For example, *in situ* diastereomer salt formation was reported by Bansaghi et al., 2012. The study attempted the salt formation between racemic ibuprofen and (*R*)-(1)-phenylethylamine, wherein supercritical fluid extraction from the process was implemented, in order to separate the unreacted enantiomers from the formed salts. The effects of pressure, temperature, and reaction time were studied in detail. It was discovered that when the pressure was increased, the reaction rate and the resolution efficiency at equilibrium also increased, while a rise in temperature resulted in the improvement of the reaction rate and optical purity of ibuprofen in the carbon dioxide phase.[71]

3.7. Spray Drying Processing. Spray drying has been employed successfully in the formation of pharmaceutical products to produce pharmaceutical dry powders, granules, microspheres, coatings, amorphous formulation, cocrystals, etc.[72] It is a commonly used technique in industry due to its processing simplicity and cost-efficiency. During the spray drying process, a liquid solution, suspension, or emulsion of the compound is atomized into fine liquid droplets, which are then dried by hot air maintained in the drying chamber.[73,74] Jensen et al., 2016, prepared coamorphous drug-amino acid salts using spray drying of indomethacin and three amino acids, namely, arginine, histidine, and lysine, which were previously prepared by vibrational ball milling. The coamorphous form of indomethacin-arginine showed improved dissolution behavior in simulated intestinal fluid compared to the crystalline form of the drug, which was not the case for other drug-amino acid pairs. This was owed to indomethacin recrystallization during dissolution, an event that affected the dissolution behavior in the case of indomethacin−lysine and indomethacin−histidine pairs.[74]

Chitosan (CH) is generally regarded as safe (GRAS) excipient and drug carrier and forms salts with organic and inorganic acids. Cervera et al., 2011, reported the formation of chitosan salts with three different organic acids, lactic acid, citric acid, and acetic acid, by the spray drying process, after the development of the aqueous solutions of chitosan-organic acid mixtures. The effects of spray drying on chitosan-acid salts were studied by different analytic methods, which revealed that the prepared salts were amorphous.[75]

3.8. Mechanochemical Grinding. Mechanochemical grinding has gained popularity as part of the screening process for the development of different multicomponent pharmaceutical products.[76,77] Previously, grinding was performed using mortar and pestle, while at the present time, different highly efficient devices are being used for the purpose (Figure 11).[76−78] In the future, the efficiency of the instrument and the amount of output can be possibly increased using advanced technology. Neat grinding is currently widely used, as it omits the use of solvents and is cost-effective.[79] In view of several unfruitful attempts to form salts by neat grinding, a small amount of solvent was introduced during grinding, with the aim to synthesize salts by a process known as solvent drop grinding or liquid assisted grinding.[79] The reduced cost and environmentally friendly nature of this method make it attractive among researchers.

Despite its popularity for multicomponent synthesis due to not involving solvents, grinding suffers from a number of limitations. For instance, the final product occurring from grinding is usually a microcrystalline powder, and single crystals are hard to obtain via this process. Mechanical energy generated during the process can intensify crystalline disorder, whereby products have a lower degree of crystallinity compared to the solution methods.[78] Furthermore, scale-up using mechanochemical techniques is also troublesome and often unfeasible. The choice of solvent for cogrinding is a critical factor, as the solvent, which behaves as a catalyst, should dissolve at least some of the original components.

In the cases of cocrystal formation, grinding has been extensively used.[80,81] Trask et al., 2006, used neat grinding and solvent drop grinding as a screening method for crystalline salt preparation. Two structurally similar weak nitrogen bases, trimethoprim and pyrimethamine, were employed as model

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drugs along with seven well-known, pharmaceutically acceptable acids to form salts.[79]

The efficiency of both types of the grinding method was explored, revealing that neat grinding provided about 40% screening efficiency, whereas a remarkable 100% was achieved through the solvent drop grinding method.[79] Hence, neat grinding, albeit having been associated with several advantages, can be an inefficient method in cases such as the one discussed. Ledeti et al., 2016, reported the multicomponent formation of desipramine, an antidepressant, with three pharmaceutically acceptable dicarboxylic acids: glutaric, malonic, and succinic acid. As tricyclic antidepressant materials have low water solubility, improvements were necessary to enhance their pharmacological properties. The API and salt formers were mixed in an agate mortar and pestle with the addition of a few drops of organic solvent. The mixing procedure was repeated for each API-acid pair, and the resulting samples were dried in an oven to obtain salts. Various spectroscopic and diffraction analyses confirmed the formation of new crystalline products by identifying the proton transfer between the materials.[82]

Kasten et al., 2017, reported the formation of crystalline and coamorphous salts of indomethacin with lysine using mechanochemical methods. Dry ball milling or neat grinding was used to form the coamorphous salt. On the other hand, liquid assisted grinding (LAG) was applied to develop the crystalline form, using very small amounts of ultrapure water as solvent and drying the resulting sample in a desiccator. This study claimed to present the first direct comparison between the crystalline and coamorphous forms of indomethacin salts, highlighting the significance of the salt physical forms with respect to stability and solubility. The coamorphous form of the salt showed better physical stability and improved dissolution rate compared to the crystalline form.[83] Recently, Bolla et al., 2018, reported the development of novel pharmaceutical salts of an antihelmintic drug, albendazole, formed with different carboxylic acids and other salt forming agents. Different stoichiometric ratios of API and salt former were ground together, with the addition of a few drops of solvent. The resulting ground mixtures were solubilized in a suitable solvent for crystallization. The resulting crystallized solid salts forms were analyzed, and salt formation was confirmed by single crystal diffraction and other analytic techniques.[84]

The mechanochemical grinding process has also been used along with the aforementioned solvent evaporation technique. Braga et al, 2013, described the formation of lidocaine salts with four different dicarboxylic acids, namely, oxalic, malonic, succinic, and fumaric acid, by evaporation and mechanochemical grinding. All the formed salts showed enhanced thermal stability compared to the free base or chloride salt of lidocaine. Additionally, the dissolution rate of the formed salts was higher compared to the free base but lower compared to chloride salt.[85] Mechanochemical grinding also enables the formation of drug−drug salts such as ciprofloxacin fumarate/adipate hydrated and ciprofloxacin, with diflunisal and indoprofen, as reported by Surov et al., 2015[44] and Bag et al., 2014.[86] To achieve this, three different methods were investigated: neat grinding, solvent drop grinding, and fast evaporation. The neat grinding method was found to be unsuccessful, and new salts were formed only through the other two methods. The efficiency of the fast evaporation technique as a screening method was also discussed. Single crystals of the forenamed drug−drug salt were formed by the solution crystallization method.[86] Zhang et al., 2016, used solvent drop grinding (SDG) along with solvent evaporation as a salt screening process, for the combination of ciprofloxacin along with three different salt formers: fumaric, citric, and maleic acid. The solubilities of all salts formed showed marked improvement compared to bulk ciprofloxacin and fumarate salt (molar stoichiometric ratio 1:1) and were 50-fold more soluble.[18]

3.9. Extrusion Processes and Continuous Manufacturing. Twin screw extrusion (TSE) is an emerging processing technology for different types of pharmaceutical product formulation.[26] During the process, the materials are fed through a feeder into the extruder, in certain feeding rates and then extruded applying a predetermined optimum thermal profile, screw speed, and screw configuration (Figure 12).

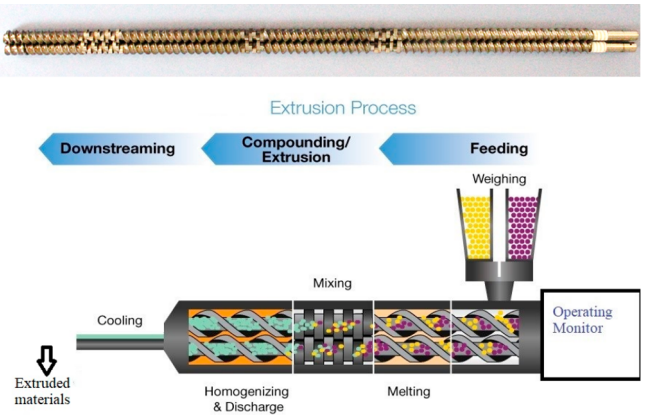

Figure 12. Representation of a complete extrusion system and screw used in extruder.

A significant amount of research work on TSE recently involves cocrystal formation,[87,88] while salt formation has not yet been fully explored. TSE has gained abundant attraction as a salt formation technique since it is similar to cocrystallization. For example, Lee et al., 2017, reported the continuous preparation of haloperidol-maleic acid salt by TSE.[89] This was the first reported continuous salt preparation method by extrusion.

The effect of operating temperature and screw configuration on salt formation were investigated. It was found that the temperature had a significant effect on crystallinity, with salts produced at higher temperatures being less crystalline than the ones at lower temperatures.

With regard to screw configuration, two different configurations (A and B) were used, where six mixing zones screws were used in configuration A, and only three mixing zones screws were used in configuration B. The conversion to salts was directly related to the degree of mixing and shear intensity applied, and hence screw configuration B resulted in low conversion, as confirmed by broad peaks and low peak intensities in powder X-ray diffraction (PXRD) analyses of the formed salts. The effect of the screw configuration is a very well-known phenomenon and has also been previously mentioned during the cocrystal preparation via TSE methods.[90]

The TSE results were also compared with salts prepared by various other methods such as solution crystallization, liquid assisted grinding, and heat assisted grinding, deducting that highly crystalline materials with identical enthalpies of melting

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Table 2. Advantages and Disadvantages of Pharmaceutical Salt Preparation Technologies[24]

method	advantages	disadvantages
Solvent mediated methods (solution crystallization, solvent evaporation, slurry conversion)	• High purity	• Not easy to scale-up
	• Wide range of drug-coformer pairs	• Use of organic solvent
	• Accurate process control	
Antisolvent crystallization	• High purity	• Time consuming
	• Wide range of drug-former pairs	• Not easy to scale-up
	• In-line process monitoring	• Relative low yields (65−80%)
	• Accurate process control	
Spray drying	• High purity	• Use of organic solvent
	• Particle engineering	• Low yields (40−45%)
	• Easy to scale up	• Limited number of studies on salt formation
	• Small footprint	
	• Fast processing	
	• Wide range of drug-former pairs	
Freeze-drying	• High purity	• Time consuming
	• Suitable for thermolabile materials	• Not easy to scale-up
	• Accurate process control	• Costly
	• Relative high yields	• Solvent residues
		• Limited number of studies
Supercritical fluid processing	• High purity	• Time consuming
	• Suitable for thermolabile materials.	• Limited number of studies
	• Accurate process control	• Solvent residues
	• Use of low processing temperature	
Mechanochemical neat grinding	• Good purity salts	• Low yield
	• Wide range of drug-coformer pairs	• Scale-up issues
	• Particle size reduction	• Time consuming
	• Environmentally friendly, no solvents	• Every time not in a reproducible manner
	• Isolate polymorphs of same salt	
	• Use different stoichiometric ratios	
Liquid assisted grinding	• High purity	• Use of solvents
	• Wide range of drug-coformer pairs	• Scale-up issues
	• Broader range of synthesized salts and cocrystals	
	• Particle size reduction	
	• Fast processing	
	• Isolate polymorphs of same cocrystals	
	• Use different stoichiometric ratios	
Extrusion	• High purity	• Only one polymorph of the same cocrystal
	• Continuous process	
	• Easy to scale-up	
	• Small footprint	
	• Environmentally friendly, no solvents	
	• Short residence time	
	• In-line process monitoring	
	• Wide range of drug-coformer pairs	

were formed by both solution crystallization and melt extrusion.

After the previous report, Bookwala et al., 2018, reported the preparation of a crystalline salt of indomethacin and tromethamine using hot melt extrusion (HME).[91] Samples from different zones were collected, aiming at monitoring the progress of salt formation, and the finished salt form was compared with the salts prepared via the solvent evaporation method. The salt formation was studied at various stoichiometric ratios of API and salt former, determining that only the 1:1 ratio successfully resulted in a salt. The melt enthalpy for the salt prepared by the two methods suggested that the salts obtained by solvent evaporation had higher conversion (99% instead of 95% with HME) and crystallinity than the salt formed by extrusion.

The salt formation had a notable effect on the dissolution profile of bulk materials, where 100% of the drug of the salts was released within 5 min, regardless of their method of preparation. On the basis of the collected data, it was concluded that HME can result in uniform mixing of the materials, that helps to accomplish content uniformity. The drug content of extruded materials was determined to be approximately 98%, to which the optimization of screw configuration during the extrusion process had a significant contribution.

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Recently, a ketoconazole oxalate (Figure 5) and ciprofloxacin maleate salt were manufactured through thermomechanical twin-screw extrusion, reported by Mithu et al., 2019. Salts prepared by extrusion were compared with the respective salt produced by mechanochemical grinding, and notably, the purity of the salts produced by both techniques was identical. The progress of salt formation in different extrusion zones was determined by analyzing the sample collected from different zones. The analyses illustrated that the rate of salt formation depends on the availability of the proton donor and acceptor in the API-salt former mixture, along with other extrusion parameters.[40]

All the aforementioned technologies employed for the synthesis of pharmaceutical salts, including their advantages and disadvantages, are presented in Table 2.

4. SALT CHARACTERIZATION TECHNIQUES

Techniques such as crystallography single crystal X-ray diffraction (SCXRD), powder X-ray diffraction (PXRD), thermal analysis such as differential thermal analysis (DTA), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and others are commonly used to analyze the newly synthesized pharmaceutical salts.[7]

PXRD is a fast-analytical technique, mainly used for phase identification of a crystalline material, and it can provide detailed information on unit cell dimensions of the solid materials. The pattern detected by PXRD is unique to the polymorphic form and also allows verification of whether the material is crystalline/amorphous, as amorphous materials will generate a featureless halo.[92]

The appearance of the peaks can provide detailed information on the uniformity, where broadened peaks indicate a lack of crystallinity, including the information related to particle size. SCXRD is used to determine the new diffraction pattern of a single crystal, in order to identify the new crystalline materials. Recently, along with SCXRD, X-ray photoelectron spectroscopy (XPS) was also used to identify the proton transfer during the salt formation.[93]

Solid-state nuclear magnetic resonance (SSNMR) can be used to identify the structure of salts, crystal packing, hydrogen bond environments, and the number of independent molecules in molecular complexes, although it requires an experienced person to interpret the obtained data.[94] Fourier transform infrared spectroscopy (FTIR) and Raman spectroscopy are readily available and can be used to evaluate interactions in the solid state, particularly by supporting PXRD data for chemical structure identification by pointing out functional groups/phases, and hydrogen bond analysis based on bond stretching and bending frequencies.[95,96] During the salt formation, interaction occurs between the functional group of the APIs and salt former, and this can be identified by studying peak shift of the major functional group of the materials with the help of FTIR and Raman spectroscopy analysis.

Thermal analysis including differential thermal analysis (DTA), differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA) are easy to perform and are readily available in most laboratories to attain information regarding melting, glass transitions, crystallization, decomposition, and solid-state transitions.[97] These techniques can be extremely helpful in predicting solubility and stability through the analysis of the melting endotherm sharpness, which can provide an indication of the purity and crystallinity of the sample. Complex thermograms may also reveal polymorphism, which can be vital in the search for the most stable form. Furthermore, TGA can detect the measure of the weight change either at a constant temperature or as a function of the changing temperature, by which hydrates and solvates can generally be separated from anhydrous forms due to the nature of the endotherm associated with the weight change of samples. Hot stage microscopy (HSM) or thermomicroscopy can provide invaluable information on the physical characterization of pharmaceutical materials in relation to temperature.[98] These microscopy techniques provide valuable visual information pertaining to polymorphic transitions, thermal behavior displayed by materials, and thermal inhomogeneities of the sample surface (Figure 13) that are not detected by DSC.[91] Other routine characterization methodologies based on microscopy such as scanning electron microscopy (SEM) are intended to examine visual attributes of the pharmaceutical salts related to particle size, crystal habits, and morphology.[40]

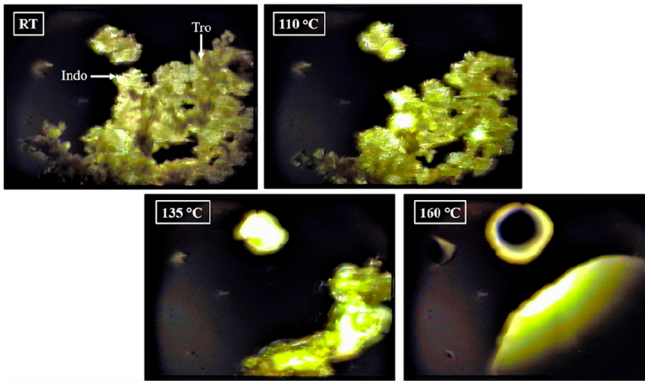

Figure 13. Hot stage polarized light microscopy of a 1:1 indomethacin and tromethamine physical mixture. Reprinted with permission from ref 91. Copyright 2018 Elsevier.

5. REGULATORY PERSPECTIVES

Pharmaceutically relevant salts have been manufactured for a long time, and regulatory bodies have published clear corresponding guidelines. Salts are always considered as new entities, and this can be advantageous compared to cocrystals, from the perspective of regulatory framework and issue of patents. In 2013, the FDA published a set of directives for pharmaceutical cocrystals: "Cocrystals are crystalline material composed of two or more molecules within the same crystal lattice" (FDA guidelines, 2013).[99] Recently, in 2018, the FDA revised the latter, redefining cocrystals as "Crystalline materials composed of two or more different molecules, one of which is the API, in a defined stoichiometric ratio within the same crystal lattice that are associated by non-ionic and noncovalent bonds" (FDA guidelines 2018).[15] According to the guidance provided by the FDA, salt formation and cocrystal formation can be differentiated by the pK_a difference between the API and the coformers. If the ΔpK_a between the API and the coformer is greater or equal to 1, there must be ionization owed to proton transfer, and the process will be referred to as salt formation. However, if the ΔpK_a is less than 1, the chance of proton transfer minimizes and cocrystals can be formed due to a nonionic reaction. According to the FDA, cocrystals are not new APIs as they were classified as drug product intermediates (DPIs) in 2013. If the cocrystals are formed by two or more APIs with or without a coformer, they are also

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not treated as a new API, unlike salts, but only as a fixed dose combination product.

According to the European medicines agency (EMA), as like as FDA, salts are considered as new entity, and cocrystals are defined as "homogenous (single phase) crystalline structures made up of two or more components in a specific stoichiometric ratio where the arrangement in the crystal lattice is not based on ionic bonds".[100] The current regulatory framework considers each new salt as a new API, even if it is produced using the same drug. Hence, unlike cocrystals, salts still present an interesting potential for the pharmaceutical industry with regard to generating novel IPs.

6. CONCLUSIONS

Because of the lack of favorable physicochemical properties that would accommodate pharmaceutical applications, APIs are being modified to form multicomponent compounds to achieve better clinical performance. Pharmaceutical salt formation is the first choice among various approaches when it comes to improving the properties of APIs. Moreover, the availability of various methods to produce salts along with the longevity of these systems in the pharmaceutical industry makes them a confident choice when looking for an approach to improve the physicochemical properties of pharmaceutical actives. In this review, we discussed a wide range of methods applied for the preparation of pharmaceutical salts in order to improve poor physical properties of APIs. Recent advances in processing technologies have led to the manufacturing of scalable, high-quality pharmaceutical salts by using green chemistry approaches. Although various approaches have shown promising results for salt preparation, only a handful of techniques are being repeatedly used, due to the ease of production with appropriate specifications. From the regulatory perspective, pharmaceutical salts are well accepted; however, there are several challenges including salt former selection, physicochemical characterization, and formulation. Nonetheless, different current methodologies of salt formation along with newly introduced methods make salt preparation more efficient and viable for the pharmaceutical industry.

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Notes

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