Review article / https://doi.org/10.15446/rcciquifa.v53n1.112981

Organic salts as a tool for pharmaceutical ingredient purification: Bibliographic review

Juan Carlos Ortiz Lara

Sintenovo, S.A. de C.V. Calle 13 Este nº 3 62578 Civac, Jiutepec, Estado de Morelos, México.

E-mail: jcortiz@sintenovo.com.mx

Received: October 12, 2023
Corrected: January 31, 2024
Accepted: January 31, 2024

Summary

Introduction: Medicines aims to improve the health of the population; for this reason, pharmaceutical ingredients with a high purity level are necessary. In this context, the impurity content is one of the premises in the manufacture of the pharmaceutical ingredients; to comply with this parameter several unit operations can be implemented. In this regard, the pharmaceutical salts can be used as an alternative in the purification process to generate pharmaceutical ingredients with a high purity. **Purpose:** This review will discuss in first instance, the importance of the impurities in the regulated environment (known, unknown impurities, genotoxic, residual solvents, and elemental impurities). Continuing with the basis of the pharmaceutical salts including functional groups that can form salts, basis of generation and hydrolysis and the main characteristic: the change in the solubility properties due to the formation of the ionic bond. This part also includes general references of previous works and compilations. The next part involves two methodological approaches to purify pharmaceutical ingredients. The first approach is based in salt formation extractions followed by salt hydrolysis. The second tactic is based on salt formation and the solubility properties. **Results:** Some examples will demonstrate the advantages of these tools. One interesting input is the compilation of several synthetic method to form salts, including examples and alternatives for sensitives cases (water, solid form, ion interchange, etc.). Finally, the salt structure determination will be commented on including the main characterization methodologies.

Keywords: Pharmaceutical salts, impurity content, salt formation, salt hydrolysis, purification, extractions, solubility change, synthesis.

Resumen

Sales orgánicas como herramienta para la purificación de ingredientes farmacéuticos: revisión bibliográfica

Introducción: Los medicamentos tienen como objetivo mejorar la salud de la población; por este motivo, son necesarios ingredientes farmacéuticos con un alto nivel de pureza. En este contexto, el contenido de impurezas es una de las premisas en la fabricación de los ingredientes farmacéuticos; para cumplir con este parámetro se pueden implementar varias operaciones unitarias. **Objetivo:** En este sentido, las sales farmacéuticas se pueden utilizar como una alternativa en el proceso de purificación para generar ingredientes farmacéuticos con una alta pureza. Esta revisión discutirá en primera instancia la importancia de las impurezas en el ambiente regulado (impurezas conocidas, desconocidas, genotóxicas, solventes residuales e impurezas elementales). Continuando con la base de las sales farmacéuticas incluyendo los grupos funcionales que pueden formar sales, base de generación e hidrólisis y la característica principal: el cambio en las propiedades de solubilidad debido a la formación del enlace iónico. Esta parte también incluye referencias generales de trabajos y compilaciones anteriores. La siguiente parte involucra dos enfoques metodológicos para purificar ingredientes farmacéuticos. El primer enfoque se basa en extracciones de formación de sales seguidas de hidrólisis de sales. La segunda táctica se basa en la formación de sales y las propiedades de solubilidad. **Resultados:** Algunos ejemplos demostrarán las ventajas de estas herramientas. Un aporte interesante es la recopilación de varios métodos sintéticos para formar sales, incluyendo ejemplos y alternativas para casos sensibles (agua, forma sólida, intercambio iónico, etc.). Finalmente, se comentará la determinación de la estructura de la sal incluyendo las principales metodologías de caracterización.

Palabras Clave: Sales farmacéuticas, contenido de impurezas, formación de sales, hidrólisis de sales, purificación, extracciones, cambio de solubilidad, síntesis.

Resumo

Sais orgânicos como ferramenta para purificação de ingredientes farmacêuticos: revisão bibliográfica

Introdução: Os medicamentos visam melhorar a saúde da população; por esta razão, são necessários ingredientes farmacêuticos com alto nível de pureza. Neste

contexto, o teor de impurezas é uma das premissas na fabricação dos insumos farmacêuticos; para cumprir este parâmetro diversas operações unitárias podem ser implementadas. Nesse sentido, os sais farmacêuticos podem ser utilizados como alternativa no processo de purificação para gerar ingredientes farmacêuticos com alta pureza. **Objetivo:** Esta revisão discutirá, em primeira instância, a importância das impurezas no ambiente regulamentado (impurezas conhecidas, desconhecidas, genotóxicas, solventes residuais e impurezas elementares). Continuando com a base dos sais farmacêuticos incluindo grupos funcionais que podem formar sais, base de geração e hidrólise e a principal característica: a alteração nas propriedades de solubilidade devido à formação da ligação iônica. Esta parte também inclui referências gerais de trabalhos e compilações anteriores. A próxima parte envolve duas abordagens metodológicas para purificar ingredientes farmacêuticos. A primeira abordagem é baseada em extrações de formação de sal seguidas de hidrólise de sal. A segunda tática é baseada na formação de sal e nas propriedades de solubilidade. Alguns exemplos demonstrarão as vantagens destas ferramentas. **Resultados:** Uma contribuição interessante é a compilação de diversos métodos sintéticos para formação de sais, incluindo exemplos e alternativas para casos sensíveis (água, forma sólida, intercâmbio iônico, etc.). Por fim, será comentada a determinação da estrutura do sal incluindo as principais metodologias de caracterização.

Palavras-Chave: Sais farmacêuticos, teor de impurezas, formação de sal, hidrólise de sal, purificação, extrações, alteração de solubilidade, síntese.

Introduction

Medicine aims to improve the health of the population. Important data about the medicines is that most of 50 % of the active pharmaceutical ingredients (API) are sold as salts [1]. In this regard, the main objective of the use of a salt in an active substance is providing better absorption of the pharmaceutical ingredient contrasted with the parent drug. However, a less well-known application is the purification impact of pharmaceutical salts to improve the content of impurities in a pharmaceutical ingredient or intermediate. This alternative is not very known probably since this unit operation is poorly described in several reported procedures (mainly in patents). Nevertheless, it is a current synthetic step in the industrial manufacture of pharmaceutical ingredients to purify active substances. In this tessitura, the impurity content is one of the most important parameters evaluated in the pharmaceutical ingredients. Several byproducts are assessed as a routinely part of the analysis of the pharmaceutical ingredients. In this context the ICHQ3A defines an impurity as any component of the new drug subs-

tance that is not the chemical entity defined as a drug substance [2]. In the same guideline the impurity content in a pharmaceutical ingredient is limited to 0.10 % for the unknown impurities and 0.15 % for the known impurities. Concerning the genotoxic impurities, the limits are more restrictive (ICHM7) [3]. In addition to this, the residual solvents are *persé* considered as impurities and their content is limited by the ICHQ3C [4]. Finally, elemental impurities are assessed and limited by the ICHQ3D [5]. The reviewed approaches described in this compilation will be focused on the elimination of the organic impurities because the genotoxic, residual solvent and elemental impurities in general are eliminated and evaluated following other specific approaches.

To obtain active substances with a pharmaceutical degree (less than 0.10 % of unknown impurities and 0.15 % of known impurities) different unit operations have been developed. The first approach used is the improvement of the reaction conditions; this fact has as a consequence the control of the impurity generation *in situ* [6]. A second approach is establishing adequate quench conditions, maintaining ranges and avoiding excursions [7]. Other unit operations currently used as purification methods are: crystallizations, distillations, precipitations, solvent exchange, extractions, filtrations, seeding, charcoal treatment, pH control, use of scavengers and salt formation or hydrolysis. The last operation is a powerful tool to achieve pharmaceutical purity degrees in active substances. This review will be focused on the pharmaceutical salts, their use and application as a purification process. In addition, a perspective of their synthesis and structure determination will be mentioned.

Basic concepts

The solubility of a drug in aqueous systems is one of the characteristics required in the development of drug substances, because many of the new drugs are insoluble in water and this fact is not adequate for the absorption in the human body. Although there are several pharmaceutical advances to improve the solubility of a drug [8], the modifications using the salt formation approach is a rapid alternative to change the solubility properties without affecting the therapeutic effect. Historically, in 1950 Nelson demonstrated than several weak acids were absorbed better than the corresponding drug parents under a gastrointestinal pH [9], that fact attracted the attention of the industry and the academy and in consequence several reviews have been written about this topic [10-18]. But what it is an organic salt? In this context, a salt is defined as a multicomponent system where protons are transferred from an acid to a base in an ionic state [19]. This fact is possible because many of the approved drug substances have functional groups like weak acids or weak bases and this characteristic could be used for the preparation of pharmaceutical salts. Between the weak acid groups that

can be mentioned are carboxylic acids, sulfonic acids, sulfonamides, phenols, etc. On the other side, the weak bases can be aliphatic, cyclic, and aromatic amines, aminopyridines, etc. These types of molecules are shown in the Figure 1 (own creation).

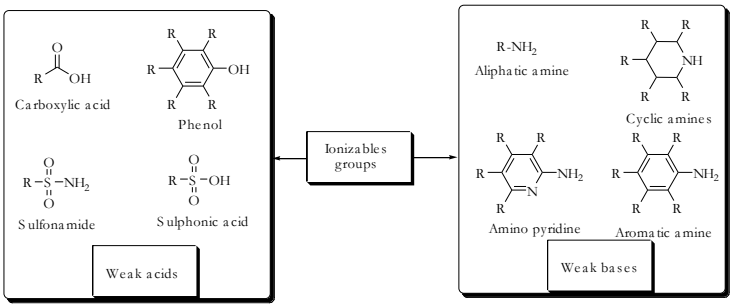


Figure 1. Functional groups that can form organic salts.

With the purpose of manufacturing an organic salt, it is necessary that the molecule comply with two requisites. First, the molecule needs to have ionizable groups and secondly, a compatible counterion it is necessary. Follow this idea, there are two possibilities for the salt formation: *i*) a pharmaceutical ingredient or intermediate with an acid (ionizable group) that reacts with a basic substance (counterion: organic or inorganic) (figure 2, figure a; own creation), and *ii*) a pharmaceutical ingredient or intermediate containing a basic ionizable group which can react with an acid substance (counterion: organic or inorganic) (figure 2, figure b; own creation).

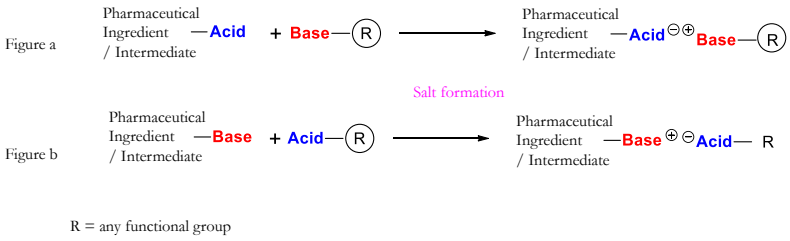


Figure 2. Typical reaction of salt formation.

In relation to stability, theoretically it is necessary a minimum difference of two or three units of pKa between the free base and the counterion to get a stable salt [20].

About the reactivity, the salt formation is a reversible reaction, so it is possible to prepare a salt and then purify the product (filtering, washing the cake, drying, etc.). After

these unit operations, the main compound could be recovered by salt hydrolysis. This fact is the main advantage of this methodology, and it is very useful to develop purification processes.

Regarding the solubility, in general for the neutral organic component (free acid or base) the solubility in organic solvents is preferred instead of the water [21]. In the opposite side, once the salt is formed the affinity for water is increased because an ionic bond is formed and in consequence the affinity for organic solvent is diminished (figure 3; own creation). This intrinsic behavior can be used to develop specific purifications to obtain pharmaceutical grades (high purity) in active substances or intermediates. It is necessary to point out that in some cases the solubility is affected by the ratio of hydrocarbon atoms presents in the parent molecule; this fact could affect the affinity for the organic solvent even if the molecule is an organic salt.

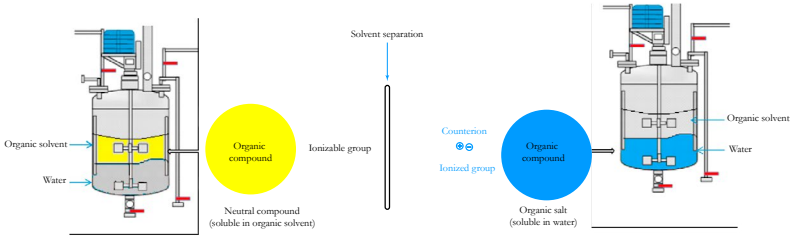


Figure 3. General solubility behavior of an organic salt.

After carrying out the purification methodology, the organic salt can be hydrolyzed using an organic or inorganic reagent with the opposite nature to the counterion and it is possible to recover the neutral compound. Both possibilities are represented in the figure 4 (own creation).

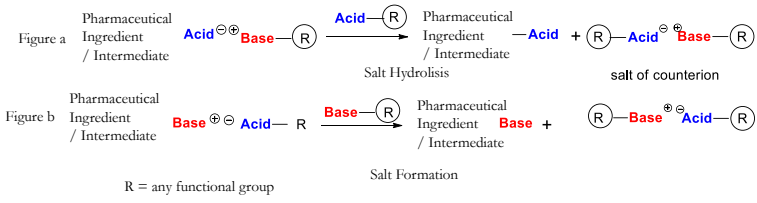


Figure 4. Typical scheme of salt hydrolysis.

Vis-à-vis of the counterions, it is possible to use different type of molecules to prepare pharmaceutical salts, in this context and from a biological point of view for pharmaceu-

tical ingredients Pfankuch *et al* had divided the counterions in three categories [22]: *i*) First class: the salt formers which are physiologically ubiquitous ions or that occurs as metabolites in biochemical pathways including the hydrochloride and sodium salts. Their use is considered unrestricted. *ii*) Second class of salt formers: those that are not naturally occurring but that have found common application and have not shown significant or tolerability issues, for example sulfonic acids. In this context Elder *et al.* [23] recently reported a review showing the advantages of sulfonic acids as counter ions. In the same line, Snodin reported an article about the regulation of alkyl sulfonates in sulfonic salts which is a very important concern in the use of this kind of counterions [24]. *iii*) Third class: These salt formers which are used in special circumstances to solve a particular problem. They are not naturally occurring in common use.

In the figure 5 (own creation), some examples of salt formers are shown. On the other hand, Paulekuhn *et al*. have reported the counterion trends for the manufacture of salts until 2007 [25]. Also usable as a counterion are the generally recognized as safe (GRAS) molecules [26]. In this context, in 2011 Tilborg *et al.* reported a review about the amino acids used as counterions. Amino acids are attractive counterions because; they are GRAS molecules that have interesting solubility properties. In this review several examples of amino acids used as counterions in active pharmaceutical ingredients are shown [27]. On the other hand in 2013, Saal and Becker reported a summary on doses of salt former from the Orange book [28]. One important information extracted from this report is that the first choice in the use of counterions are the hydrochlorides and sodium salts. However, in the synthesis of intermediates theoretically there are no restrictions and even lithium can be used as a counterion although there is not the case for a final active pharmaceutical ingredient (API) in which case a different counterion is previously established. Recently, Bharate reported a compilation about the FDA approved carboxylic acids used as counterions in Pharmaceutical salts from 1939 until 2020. In this review the technical advantages of using carboxylates over other counterions are discussed. The most useful carboxylic acids in salts are: acetate, maleate, tartrate, fumarate and succinate [29].

From a physicochemical and biological point of view, Gupta *et al* recently have published a review of pharmaceutical salts. This article describes succinctly the use of pharmaceutical salts in the preparation of pharmaceutical dosage forms [30]. Finally, Fujinuma *et al.* have described the triboelectric effect in a salt series and their respective counterions [31], this effect is very important in the commercial manufacture of actives substances in which hundreds of kilograms of final product are manufactured.

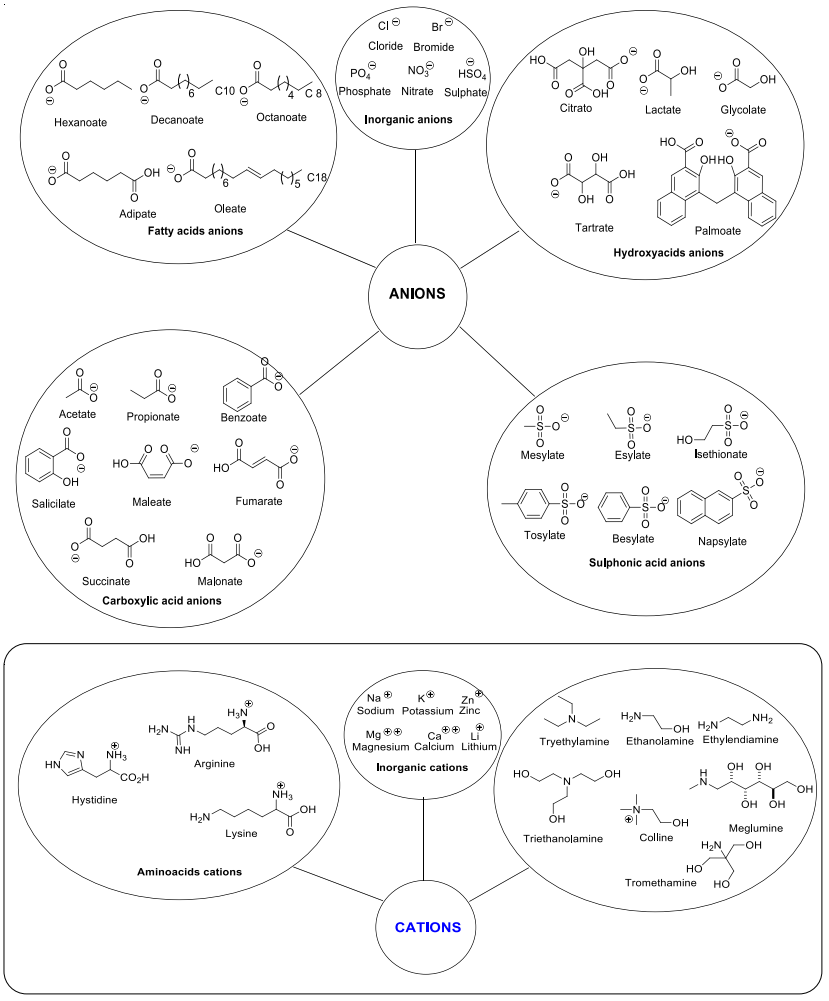


Figure 5. Some examples of counterions.

In general, the best choice for the purification of a molecule is applying the salt formation methodology using the simplest, accessible, and non-expensive reagent. For example, aqueous sodium hydroxide and hydrochloric acid are the first options. Two additional advantages are that the byproducts generated are easy to eliminate and the reagents have a low cost.

On the other hand, if the final product is salt, other criteria must be taken into account. For instance, solubility, crystallinity, toxicity, hygroscopicity, polymorphism and

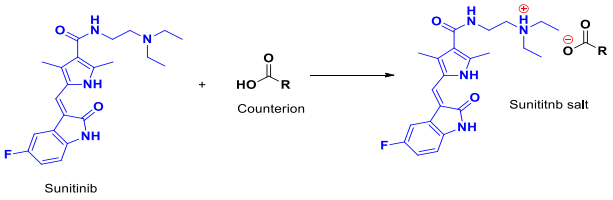
manufacturability, etc... It is important to remark that if the molecule does not have ionizable groups is not possible to form salts, for this kind of molecules is necessary other approaches (cocrystals or polymorphs, etc.).

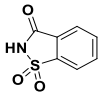
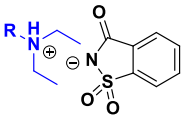
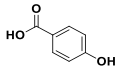
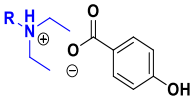
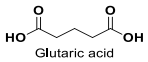
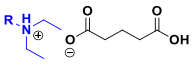
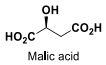
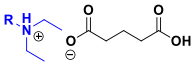
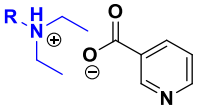
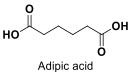
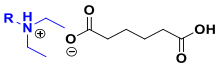
The main impact of the transformation of an organic compound by a salt is the solubility modification; this fact generates a sudden and radical change in the affinity for other solvent. An example that demonstrated the improvement of the solubility using salts in a pharmaceutical ingredient has been reported for the Sunitinib (antineoplasic). This drug substance is known to be a poorly soluble drug, such as the solubility of this API is 0.048 mg/mL in deionized water while the marketed Malate salt has a solubility of 25 mg/mL. In this study several examples of Sunitinib salts were prepared and their solubility was evaluated [32]. The data (Table 1) showed that the use of Adipic acid dramatically increased the solubility in deionized water and demonstrated the impact of the counterion in the solubility properties. The solubility in deionized water is improved until 272 mg/mL, this data is almost eleven times the solubility of the marketed salt and 5667 times *vis a vis* of the free base. This change in the solubility could suppose "like to work with other molecule with different physical properties". This modification in the solubility properties make it possible to develop purification strategies using this procedure because it can use a mixture of solvents to eliminate in a specific way the contaminants from the product (active ingredient or intermediate).

Salts as a purification method in the synthesis of pharmaceutical ingredients and intermediates

When a pharmaceutical ingredient is manufactured, it must comply with a specification including some parameters like titration, residual solvents, water content, and identity, among others. In this tessitura, the impurity profile is one of the most important parameters to get a safe pharmaceutical active substance because the impurities do not have therapeutic effect. Although sometimes the use of chromatographic purification methods is affordable, not always it is possible to apply this type of technology in a commercial way, mainly due to the complexity of the facilities and the high cost. Moreover, the solubility changes furnished by an organic salt represent one important alternative to achieve this task. One example of purification via salt formation / salt hydrolysis has been reported by Ley and Yates in 2008 [33]. In this work it was demonstrated that the purification methodology of the 2,4-dichloro-benzoic acid using α-methylbenzylamine to furnish the corresponding salt and then hydrolyzing them. The goal of this study was to purify the 2,4-dichloro-benzoic acid from some isomers with a higher content than 0.5 % and after the purification process the content was less than 0.05 %. The main advantages of this procedure were: *i*) to procure a product with a high quality, *ii*) be reproducible, *iii*) low cost of the starting materials, and *iv*) easiness of the process.

Table 1. Solubility of different salts of Sunitinib reported by Sangwan *et al.* [32]



Entry	Salt former	Structure:	Solubility (mg/mL in deionized water)	Solubility ratio versus the Drug Parent
a	None (Parent drug)		Approx. 0.048 (Parent drug reference data)	1
b	 Saccharin		2	42
c	 4-hidroxybenzoic acid		3.4	71
d	 Glutaric acid		6.2	129
e	 Malic acid		25 (Marketed salt)	520
f	 Nicotinic acid		162	3375
g	 Adipic acid		272	5667

The summary of the purification process from Ley *et al.* is depicted in the figure 6.

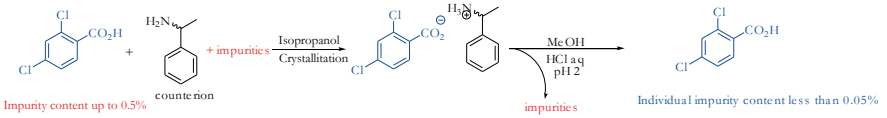


Figure 6. Purification of 2,4-dichloro-benzoic acid via salt formation-hydrolysis reported by Ley and Yates [33].

In the same way, in 2011 Anson and coworkers reported the use of this methodology for the purification of the first synthetic step in the synthesis of the one S1P1 agonist [34].

For a neophyte it could be a trivial procedure, but the perspective could change if it is necessary to purify several tons of an organic compound in a productive Plant. Furthermore, the salt preparation or hydrolysis is a unit operation largely used in the manufacture of pharmaceutical ingredients and intermediates.

As it was pointed out previously, in our context the main property of salts is the different solubility versus the free base, this property is applied in two approaches which are used in the synthesis of pharmaceutical ingredients to obtain good impurity profiles. The first approach is: salt formation, followed by extractions and salt hydrolysis. In a second instance with the aim to recover the product other unit operations can be applied. For example: salt hydrolysis, crystallization or precipitation, filtration and drying of the product. Normally in this case the free base is obtained as a final product. The second approach is: salt formation followed by crystallization. In this case the solid is isolated by crystallization or precipitation. In this case usually a salt is obtained.

Both approaches are shown in Fig. 7 (own creation).

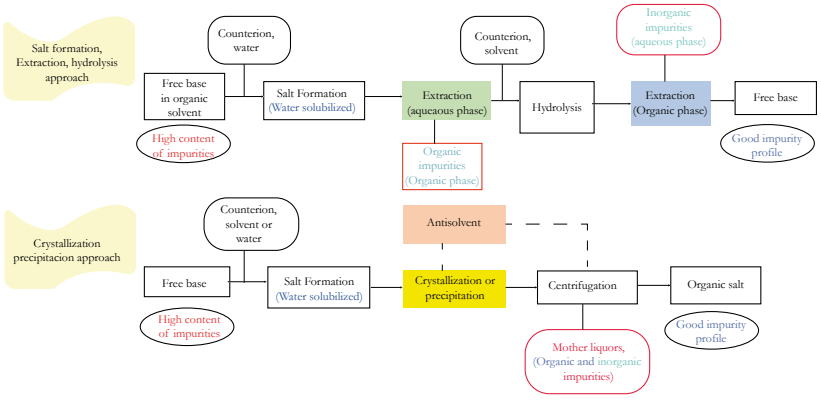


Figure 7. Purification approaches with salts.

Salts formation, extractions, salt hydrolysis

During the synthesis of an intermediate or pharmaceutical ingredient, in only a few cases the starting material is transformed to a product in a quantitative yield. In general, in the process a percentage of byproducts are generated and mixed with the product. For this reason, it is necessary to purify the procured intermediate. In many cases a chromatographic purification is not affordable at an industrial level. The alternative tool to eliminate impurities is the salt formation or salt hydrolysis. This approach is based on the solubility differences between a salt versus the neutral compound. This methodology works as follows: A reaction is started and monitored and after reaching the desired transformation (in process-control, etc.), the reaction mixture must be quenched. At that point, the compounds in the reactor are: *i*) product (with ionizable group), *ii*) inorganic impurities, and *iii*) organic impurities (Fig. 8A)

With the aim to purify the mixture it is necessary to prepare an organic salt. As a general methodology a counterion is added to the reactor mixture followed by water, the result is the formation of an organic salt in a biphasic system (Fig. 8B). The organic salt and the inorganic impurities have affinity for the aqueous phase, while the organic impurities have affinity for the organic phase. A separation of the organic layer eliminates the organic impurities from the reaction mixture. The product and the inorganic impurities stay in the aqueous layer (Fig. 8C). The next step is to add a new counterion with the opposite nature to the first counterion added. A second requirement is the use of a clean organic solvent that must be immiscible with water. In this step the free base is recovered by hydrolysis of the organic salt (Fig. 8D). The desired compound is soluble in the organic phase 2 and the inorganic impurities stay in the aqueous phase 2. A second layer separation furnished the free base with a high purity in the organic phase 2 (Fig. 8E). Finally, this compound is recovered from the organic phase 2 by crystallization or precipitation (Fig. 8F). This methodology is depicted in Fig. 8.

The formation and hydrolysis of a salt is a very suitable tool in the development of a process in the pharmaceutical industry to obtain acceptable impurity content, specifically for the purification of intermediates and pharmaceutical ingredients. Some examples reported in the literature will demonstrate the advantages of this methodology.

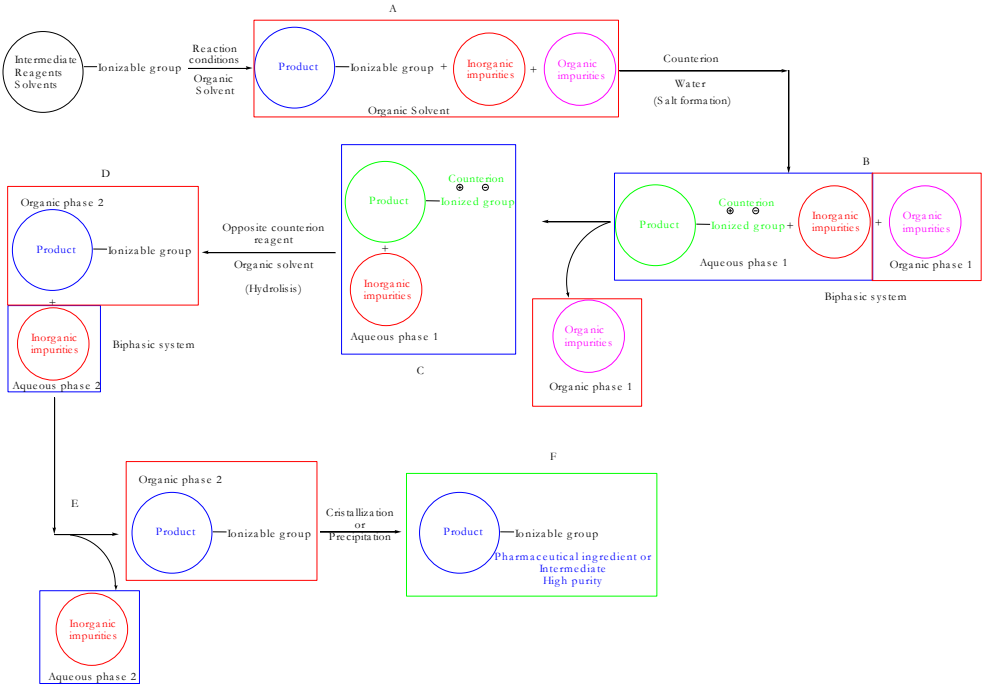


Figure 8. Typical scheme using salt formation/hydrolysis in the pharmaceutical industry (own creation).

Through the synthesis of the Omeprazole magnesium (inhibitor of the proton pump) a sodium salt was prepared by the reaction between Omeprazole and sodium hydroxide at a laboratory scale (0.1 g). After the salt formation reaction, the Omeprazole is insoluble and become soluble when it is transformed to the corresponding sodium salt. The residual starting material (Omeprazole) is insoluble in water. So, for the elimination of this residual compound methylene chloride was added to the reaction mixture. In this binary system, the Omeprazole was solubilized in the organic phase and the Omeprazole sodium salt was solved in the aqueous phase. A separation phase eliminates the organic impurities and starting material unreacted (Omeprazole) in the organic phase. To the generated Omeprazole sodium salt (aqueous phase) magnesium chloride is added; this reagent furnishes the Omeprazole magnesium by cation interchange. The magnesium salt precipitates in the aqueous medium because the product is an Omeprazole dimer (high organic ratio vs the ionic bond). The residual inorganic impurities were eliminated in the mother liquors (water). After centrifugation and drying, the optical purity for the isolated Magnesium salt was 98 % (Entry 1, Table 2) [35].

In the scale-up development of a new process for the manufacture of Quetiapine hemifumarate (antipsychotic), a problem regarding the impurity profile was found. To solve this inconvenience one hydrochloride salt was prepared. The salt procedure started by toluene dissolution of the intermediate which was treated with hydrochloric acid and the corresponding salt was generated. This intermediate was isolated in the aqueous phase and the organic impurities were eliminated in the organic phase (toluene). Then the pH of the aqueous phase was adjusted to 9 / 10 units with sodium carbonate. This change hydrolyzed the salt and furnished the free base which has been isolated in methylene chloride. The aqueous phase was eliminated with the inorganic impurities. After this separation the solvent of the second organic phase was distilled and the free base was solved in ethanol. In the next step the free base was reacted with fumaric acid generating the pharmaceutical ingredient with a good impurity profile (99.9 % of purity) (Entry 2, Table 2) [36]. In this example two approaches are combined, first the purification by extraction / salt formation and in a second place the salt formation and crystallization.

A synthetic step using a salt was included during the optimization of a new process for the synthesis of Raloxifene hydrochloride (estrogen receptor modulator). The deprotection of the two phenols groups was carried out with potassium hydroxide and the bis-potassium salt was provided as an intermediate. Once the reaction was finished, the pH of the reactions was changed until 11 units and the product was isolated by filtration. The inorganic impurities were eliminated in the aqueous phase. After the solid was solved in methanol water was added, after the decoloration with activated charcoal the product was filtered. Then the pH of the filtrate was modified until to 2 units with hydrochloric acid and heated to a temperature of 65 °C. The Piperidinium salt was isolated as intermediate. To precipitate the entire product additional water was added and then the reaction mixture was cooled. The product was isolated by filtration and after drying the isolated compound furnished a purity of 99.9 %. Although the product is a salt, probably it was precipitated in water because the organic ratio of the molecule is clearly bigger *vis a vis* of the ionic bond. In addition, it is necessary to point out that this molecule has two acid groups (phenols) and a basic one (Piperidine) that make it possible to use both sides of pH scale to prepare salts. (Entry 3, Table 2) [37].

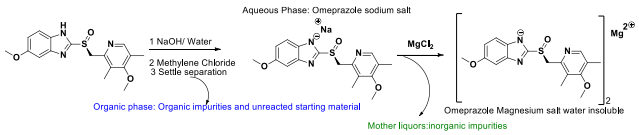
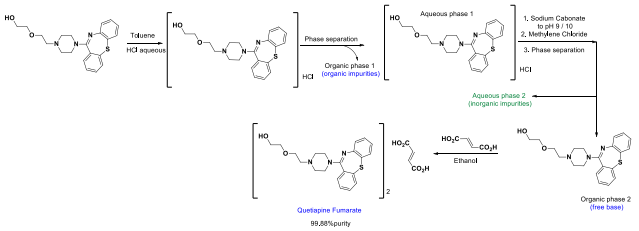
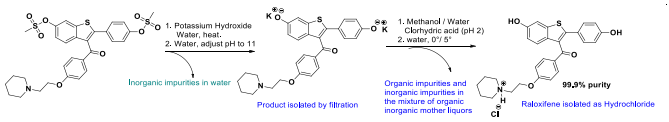
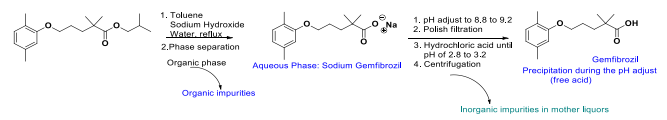
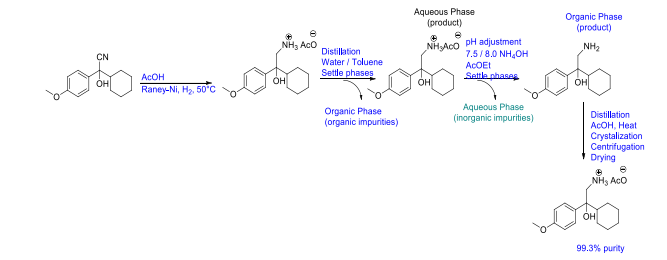
For improving the manufacturing process of Gemfibrozil (antihyperlipidemic agent) a sodium salt was prepared starting by the isobutyl ester intermediate. The hydrolysis of the ester moiety generated the sodium salt. This compound was prepared in a mixture of water and toluene using sodium hydroxide as a counterion. After reaction completion, the Gemfibrozil sodium salt was isolated in the aqueous phase (140 g scale). The organic impurities were removed from the organic phase (toluene). Then the pH of the aqueous phase was adjusted to 8.8 to 9.2 pH units and the aqueous solution was

filtered to eliminate foreign particles. Finally, the free base was obtained by pH adjustment to 2.8 to 3.2 pH units with hydrochloric acid. The product precipitated in the reaction mixture and then filtered; the inorganic impurities were eliminated in the mother liquors. After drying, the product was obtained with a purity of 100 % (Entry 4, Table 2) [38].

Another example was reported for the procurement of Venlafaxine Hydrochloride (antidepressant) free of impurities at large scale. During the reduction step with Raney Nickel of an intermediate at a 60 kg scale, the acetate salt was generated. The solvent of this reaction (acetic acid) was distilled, and the residue was solubilized in water. Toluene was added and the phases were settled, the aqueous phase (containing the product) was kept and the organic phase which contains the organic impurities was eliminated. Then the pH of the solution was adjusted to 7.5/8.0 with aqueous ammonia and then ethyl acetate was added. A settlement of the phases was executed, and the aqueous phase was eliminated. The solvent of the organic phase was distilled, and the residue was solved in acetic acid. After heating and cooling, the product was isolated by centrifugation and the product was dried generating the acetate salt. This compound showed a purity of 99.3 % by HPLC (Entry 5, Table 2) [39].

The methodologies discussed in this section were chosen because they reflected the approach of the salt preparation, extraction, and salt hydrolysis. This purification system is very common in the commercial manufacture of pharmaceutical ingredients but sometimes is not adequately detailed in the reports because it is part of the industry expertise. However, after to understanding the easiness of the methodology it is possible to use this purification in many organic compounds having the adequate functional groups. In addition, there are no restrictions to prepare salts of intermediates because after the purification process, the counterion could be eliminated.

Table 2. Examples of Purification with pharmaceutical salts in intermediates and active substances

Entry	Scheme	Reference
1		[39]
2		[40]
3		[41]
4		[42]
5		[43]

Salt formation/hydrolysis followed by crystallization to generate the product with a high purity

The intermediates or final product solubility changes under the influence of an ionic bond (salt formation) and could have an important impact in the crystallization, specifically in the impurity profile. So, the creation of an ionic bond generates new solubility properties in the product and is virtually like to work with another compound with totally different solubility properties. This solubility behavior can be used to crystalize the product and eliminate byproducts. As it was mentioned, the most important

advantage of this methodology is the reversibility of the reaction because the original molecule can be recovered with a hydrolysis reaction without affecting the impurity profile. It is also important to point out the use of seed to induce the desired characteristic in the final product. This type of purification process is currently applied at industrial level in the manufacture of intermediates and pharmaceutical ingredients. Several examples will demonstrate the impact of this methodology in the purification of intermediates.

During the improvement process for the manufacture of Solifenacin succinate (antagonist of the muscarinic receptors) a salt was used in the last step of the synthesis. The Solifenacin crude (diastereomeric mixture) was purified using racemic succinic acid. The diastereomeric crystallization was optimized, taking in account several parameters (temperature, solvents, counterion ratio, etc.). The final report described the reaction of the Solifenacin isomer mixture and succinic acid in ethyl acetate, the mixture was seeded with the Solifenacin Succinate and stirred to 25/30 °C for 8 hours. The purity at this point was 98.75 % and the chiral purity 93.69 %. Two additional crystallizations generated the Solifenacin succinate with a chemical and chiral purity of 99.9 %. As a result of this procedure, the salt solubility was different between the diastereomers, this fact made possible the resolution to obtain the Solifenacin succinate with a content of the non-desired diastereomer of 0.06 % (Entry 1, Table 3) [40].

In the last step of the manufacture of Saxagliptin hydrochloride (antidiabetic) a salt was used. The salt was formed simultaneously after the hydrolysis of a carbamate function. Then the carbamate intermediate was solved in ethyl acetate and aqueous hydrochloric acid was added. The salt was precipitated in situ, isolated by filtration, and washed with additional ethyl acetate. The purity for the Saxagliptin hydrochloride was 99.9 % by HPLC. As a note, the previous intermediate had a 94.36 % purity, so the inorganic and organic impurities were eliminated in the mother liquors (Entry 2, Table 3) [41].

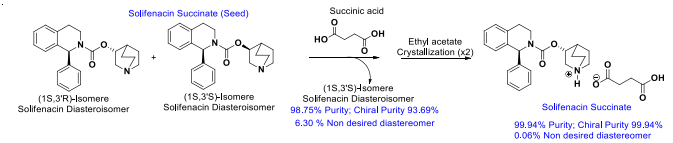
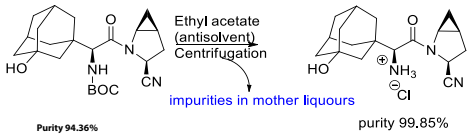
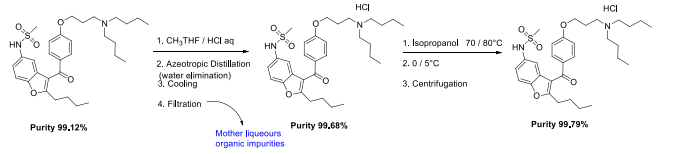
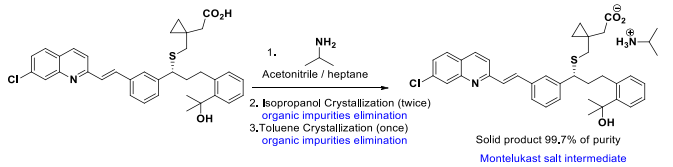
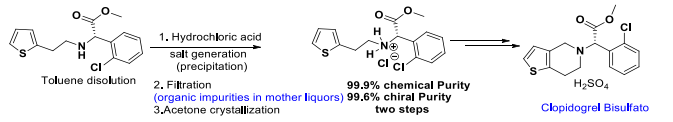
A salt was used during the improvement of the process for manufacture of Dronedarone hydrochloride (antiarrhythmic drug). Hydrochloric acid was used after a sequence of reaction (reduction of nitro group and protecting the generated amine with a methanesulfonyl group) at a scale of 4.5 kg. The process was reported as follows. The advanced intermediate was washed with diluted aqueous hydrochloric acid at 10%. The organic phase was kept, and the residual water was distilled until 1 % to avoid loss of product. The Dronedarone hydrochloride was isolated from the reaction by cooling the mixture to 0°C. The purity of the API at this stage was 99.7 %. An additional crystallization in isopropanol furnished the API with a purity of 99.8 % (Entry 3, Table 3) [42].

Due to the difficulty to obtain pharmaceutical grades of Montelukast sodium in a scale-up plant an organic salt using isopropylamine as a counterion was developed. In this context, to a toluenic Montelukast dissolution (free base) was added isopropylamine and acetonitrile. The scale for this reaction was 0.95 kg executed in a scale up plant. Then to start the precipitation of the product a small quantity of heptane was added. After 1 hour of the reaction, the addition of more heptane completes the precipitation of the amorphous solid. After 1 hour of ageing, the product was isolated by centrifugation and the cake was washed with toluene / acetonitrile. The product was crystallized twice in isopropanol and once in toluene. After analysis the final purity by HPLC was 99.7 %. Furthermore, it is important to mention that in the preliminary screening several Montelukast salts were evaluated, basic counterions furnished amorphous solids. Between the studied amines it can be mentioned n-propylamine, tert-butylamine, benzylamine, α-methylamine, dicyclohexylamine, diisopropylethylamine, etc. This fact emphasizes the relative easiness in the preparation of pharmaceutical salts (Entry 4, Table 3) [43].

During the development of a scalable synthetic route to manufacture Clopidogrel bisulfate (antiplaquetary agent) and hydrochloride salt was prepared. Several parameters like addition time, reaction time, base, hydrochloric acid, and solvent ratio, etc., were studied to improve the impurity profile. The author reported and industrial procedure with 100 kg of starting material. In an advanced intermediate in toluene solution was added aqueous hydrochloric acid and the resultant salt was precipitated spontaneously in the reaction mixture. The salt was isolated by filtration and then the solid was further purified in acetone / hydrochloric acid. The product was isolated and washed with acetone and dried. Finally, the hydrochloride intermediate furnished a chemical purity of 99.9 % and a chiral purity of 99.6 %. This is a remarkable result because it was evaluated for the two synthetic steps (Entry 5, Table 3) [44].

As it was demonstrated with these examples, the pharmaceutical impurity level can be reached using the salt formation procedure in an adequate solvent. This methodology is very simple and furnishes very good results. This reaction can be used from a laboratory scale working with a few grams until several tons in a commercial scale in a Good Manufacturing Practice (GMP) environment. It is necessary to point out, that some requirements, using this methodology are necessary. For example, the purity of the counterion to avoid related impurities, the hydration level, or the polymorphism because these kinds of parameters could impact the desired characteristic of the product and could have a relevant importance if the final product is the active pharmaceutical ingredient.

Table 3. Examples of purification with pharmaceutical salts in intermediates and active substances.

Entry	Scheme	Reference
1		[45]
2		[46]
3		[47]
4		[48]
5		[49]

Synthesis

To synthesize pharmaceutical salts several approaches are available; the main difference depends on the final use of the compound to be generated. For example, for the manufacturing of an active pharmaceutical ingredient (API) the conditions must be strictly controlled following the GMP´s. This fact following batch records with well-established unit operations in a regulated environment (ICHQ7). The generated product must comply with the current specifications for the final active ingredient or intermediate including parameters such as polymorphism, particle size, impurity profile, foreign particles, water content, etc. [45]. It is important to remark that the use of a counterion in this step requires a high quality of the reagents (low impurity content).

On the other hand, if it is not necessary to comply with a GMP environment, the salt could be prepared easily. Basically, by mixing the free base and the counterion in an

adequate solvent. The generation of the ionic bond changes the solubility properties of the molecule, for instance if the free base is soluble, in general the corresponding salt is insoluble doing the isolation feasible by crystallization or precipitation in the reaction media. In both cases, the generation of the pharmaceutical salt is the objective, and the difference is the unit operations, scale or the GMP environment. Several examples will demonstrate the easiness of this methodology.

If the main objective is to modify the salt physical properties for example; the solubility, dissolution rate, permeability, stability, mechanical properties, polymorphism, flow properties, compaction properties, etc., some modifications in the counterion can be applied [46]. In this context, Gross *et al.* was reported a decision-tree format in order to choose the better counter ion in drug candidates [47]. By his side Fernandez-Casares studied the in-situ salt screening, with two methods: the saturated solution and the high-throughput method over two active substances (Aripiprazole, antipsychotic and Desvenlafaxine, antidepressant). In this study the first approach furnished better results [48]. Sometimes, the salt formation is an easy procedure, this fact is exemplified by a series of 28 different salts derivatives of Olanzapine (antipsychotic) reported by Keltjens in a study to improve the properties of the pharmaceutical ingredient [49]. Or the 3600 trials reported by Remenar *et al.* that it will discuss furtherly [50].

Concerning the synthesis, usually is easy to prepare a salt, basically mixing the compound with the adequate functional group and a counterion in a solvent, nevertheless, when other parameters are important to meet it is possible to use alternative methodologies in order to control specific characteristics in pharmaceuticals salts modifying once of the following parameters: solvent hydration level, availability of the reagents, counterion type, solvent, temperature, reagent ratios, etc.

For example, when the solvent hydration level can affect the final product by hygroscopicity or solubility (impact in the yield) it is possible to use an anhydrous solvent and the appropriate counterion avoiding the use of water. Hydrogen chloride in several solvents for instance isopropanol [51], dioxane [52], or trimethylsilane chloride in methanol [53], acetyl chloride in methanol [54] or ethanol [55]. Also, in the case of Zabofloxacin D-aspartate (antibiotic) was used D-aspartic acid in anhydrous ethanol to prepare the corresponding salt [56]. All these procedures are alternatives reported in the literature for the procurement of anhydrous salts.

As a counterpart if no anhydrous conditions are required, the use of aqueous dissolutions of hydrochloric acid or sodium hydroxide are available for the preparation of salts, this method is extended used in the synthesis of pharmaceutical ingredients because these reagents are readily available and not expensive. As an illustration, it was reported their use in the synthesis of a sodium salt of Tenatoprazole (inhibitor of the

proton pump) using aqueous sodium hydroxide [57]. The lithium hydroxide also was used in the hydrolysis of an ester moiety and subsequently salt formation in the synthesis of antiviral compounds. In this case the free base is solved in methanol and the counterion is solved in water and then added over the API methanol solution. The hydrolysis generated the lithium salt which is purified by extractions. In this case, the free acid is recovered by salt hydrolysis with hydrochloric acid [54]. The use of aqueous hydrochloric acid also was reported in formation of Raloxifene hydrochloride after the procurement of the Raloxifene through a Diels Alder reaction, in this case methanol was used as a cosolvent [58]. In a study to improve the synthesis of a potential antidepressant pharmaceutical ingredient it was used the 2N hydrochloric acid in order to form the corresponding salt, the mixture was refluxed and the hydrochloride salt was isolated by filtration. This salt was re-disolved and the salt was hydrolyzed with sodium hydroxide then concentrated hydrochloric acid was added and the product purified by filtration in order to get the pharmaceutical purity [59]. In another example, the free base was solved in isopropanol and then the hydrochloric acid was added. The hydrochloride salt was isolated by cooling the suspension [60].

Different counterions can be used to prepare a salt. In this context, magnesium hydroxide was used for the generation of Omeprazole magnesium directly in a Pilot Plant scale. The free base was solved in tetrahydrofuran and the magnesium hydroxide was solved in water. The magnesium salt was formed and then isolated by precipitation in cyclohexane. The product was purified in methanol and then in ethyl acetate [61]. In another example metallic magnesium also was used to obtain the same salt. The metal was dissolved in methanol and dichloromethane then this solution was added to a solution of Esomeprazole in methanol [62].

Polymorphism plays crucial role in the manufacture of an active pharmaceutical ingredient because polymorphism can impact the solubility of the API in the human body or because the solid forms can be intellectual restrictions. In this context, there are several methods to obtain different solid forms. In this regard, Remenar *et al.* reported high-throughput experiments with the Sertraline (antidepressant) in this report 3600 crystallizations were executed to identify and characterize 18 crystalline salt forms of the pharmaceutical ingredient [50]. The counterions used in this study were mono ionic acids (acetic, hydrobromide, benzoic, benzenesulfonic, ethanesulfonic, lactic, methanesulfonic) and also di and tri acidic salt formers (citric, fumaric, maleic, malonic, sulfuric and succinic acids). The authors demonstrated that even minor differences in the salt formers can deeply impact the effect of the number of polymorphs and solvates of a salt [50].

In a laboratory approach, Elati *et al.* describe several methodologies to obtain polymorphs exemplified with the salt formation of Donoprezil (a drug for treating Alzheimer and senile dementia) [63]. These approaches are: *i*) reacting the drug parent with the counterion in an aqueous media, *ii*) crystallizing the pharmaceutical salt in several solvents, *iii*) crystallizing the pharmaceutical salts in different mixtures of solvent systems, *iv*) precipitating the pharmaceutical salt in different mixture of solvent anti solvent combination systems, *v*) suspending the pharmaceutical salt in several solvents or mixture of solvents, and *vi*) dissolving pharmaceutical salts in different solvents followed by evaporation.

Moreover, to these approaches, it is possible to evaluate the impact of a seed. The seed, which is a sample of the final product that contains all the suitable characteristics in a pharmaceutical ingredient to induce a well-controlled crystallization (saturation, cooling, etc.) in a solution of the pharmaceutical salt and obtain a specific solid form. A pair of examples has been reported for the manufacture of Prasugrel hydrochloride (platelet aggregation inhibitor) [64] and Palbocyclib (anticarcinogenic) [65].

Although a crystalline form is the first choice in the pharmaceutical salts, sometimes it is necessary to manufacture amorphous compounds in this case the salt is prepared in a solution and then an antisolvent is added. The inverse procedure also can be used. One example of this method has been reported for Montelukast sodium (antiasthmatic) [66].

The procurement of a salt by ion substitution also has been used; the Omeprazole magnesium has been prepared with this procedure [35]. A similar case was reported for the Montelukast (antiasthmatic) using isopropylamine salt [67] has been interchanged by a sodium atom using sodium methylate. During the development of a purification method for Palladium from the Ceftolozane (antibiotic) a cation interchange of triflluoroacetic acid by ammonium hydrogen sulfate in a 30 kg scale was reported [68]. Choline also was used as a counter ion for some anti-inflammatory carboxylic acids. In a recent synthesis of the Avibactam (antibiotic) a couple of salts were prepared. The first salt was prepared using as a counterion an aqueous solution of tetrabutylammonium acetate in n-butyl acetate. This ammonium salts were reacted with sodium 2-ethyl hexanoate in ethanol and by an ion interchange the Avibactam sodium was reached [69].

Another methodology to prepare salts is the grindstone method [70]. A case was described for the preparation of salt synthesis of several carboxylic acids without solvent only using the mixture of the carboxylic acid and the counterion. During this procedure it was observed an increase of the temperature during the salt formation. The counterions used in this approach were salicylic, oxalic, tartaric and citric acid. Evidently, this approach cannot be used from a commercial point of view but is a good example of green chemistry (non-solvent used).

Concerning the salt hydrolysis normally an adequate solvent and counterion is used to obtain the free base which is insoluble in the media. The product is isolated by filtration and then dried furnishing the free base. An example for the antidepressant Trazodone and Sertraline hydrochloride (antidepressant) hydrolyses was reported. The hydrochloride salt was dissolved in water and then aqueous sodium hydroxide was added. The free base was insoluble in water and isolated easily [71]. In addition all the examples cited in the section of salt formation / salt hydrolysis can be consulted.

Furthermore, the salt formation can be executed in a telescopic way, the following three examples will demonstrate this fact.

During the development of a ERK inhibitor, a one pot synthesis of a besylate salt was developed. In this case the benzensulfonic acid served by one side as a catalyst for the desililation reaction and in a second place as a counterion for the salt formation. One interesting data is the use of tetrahydrofuran/water addition in order to control the generation of the methyl benzenesulfonate impurity [72].

The methane sulfonic acid was used for the preparation of a chloropurine salt which is a potent HSP90 inhibitor (anticarcinogenic) [73]. The salt formation was carried out after a benzylation process in a telescopic way. Basically, the substrates were reacted with potassium carbonate in dimethylacetamide after reaction completion the product (soluble) was cooled and filtered. The filtrate was reacted with the methanesulfonic acid and then methyltertbutyl ether was used as an antisolvent. The purity by HPLC of the corresponding salt was 99.3 % to 99.6 %. This product was scaled up until the obtention of 220 kg. Malic acid was used to make a resolution of the building block *R*-3,5-bis(trifluoromethyl)-*α*-methyl-*N*-methylbenzylamine. This salt was formed after the deactivation of an imine reduction reaction. The solvent used was ethyl acetate, after adding the counterion heating and then cooling and seeding the product was isolated by filtration [74].

Another example of the use of hydrochloric acid in isopropanol was reported recently. The salt formation was executed after a debenzylation reaction, the corresponding salt was isolated directly by filtration [75].

Finally, Mithu *et al* reported a review with advanced methodologies to salt synthesis (antisolvent crystallization, spray dryer, freezed drying, supercritical fluid, mechanochemical grinding) [76], these approaches are under development.

In summary, all these procedures demonstrate the easiness of this transformation and open the alternatives to procure high purity in the synthesis of intermediates and final pharmaceutical ingredients. In figure 9 (own creation) it is shown the main procurement methods for the manufacture of pharmaceutical salts.

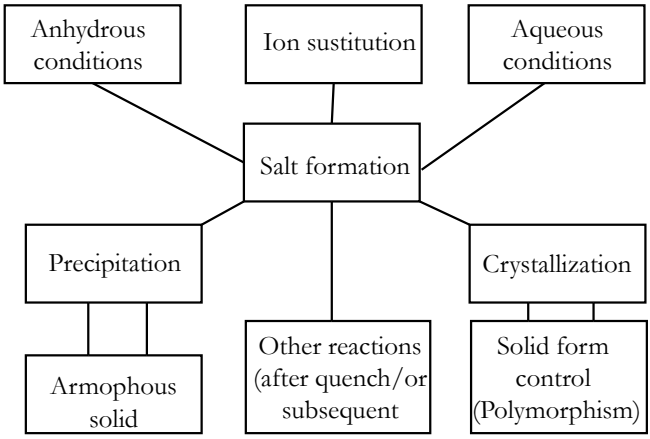


Figure 9. Methods of salt formation

Determination of salt structure

The choice of the adequate solid form has an imperative importance for therapeutic efficacy, toxicity, bioavailability, pharmaceutical process, stability and intellectual properties. In the pharmaceutical industry there are several alternatives for the final solid form of an active pharmaceutical ingredient. Some of these are: polymorphs, solvates, hydrates, cocrystals, amorphous, salts and mixtures of them [77]. The pharmaceutical salts also shown polymorphism or can exist as solvate or hydrates, so different solid forms must be characterized. There are several methodologies in order to determine the structure and solid state. The main analytical tools used for determination of salt structure are: differential scanning calorimetry, X-ray diffraction, microcalorimetry, thermal gravimetry mass spectroscopy (TG-MS) and infrared spectroscopy. Some examples can be consulted in the review of Giron. Although the structures are not shown the characterization of these salt is very illustrative [78]. Moreover, some interesting examples of synthesis and salt characterization has been reported for the Perphenazine Fumarate (antipsychotic). In this example two salts were prepared and characterized by several techniques (differential scanning calorimetry, powder X-ray diffraction, Fourier infrared spectroscopy and scanning electron microscopy coupled with energy dispersive X-ray diffraction). In addition the improvement in solubility versus the parent drug was demonstrated [79].

Conclusions

The impurity content is one of the main parameters to control during the synthesis of the intermediates and active pharmaceutical ingredients. The use of salt formation / hydrolysis methodology is a powerful tool to achieve this goal. The synthesis of salts from pharmaceutical ingredients or intermediates is an easy operation and the reversibility of the reaction is the main advantage of this methodology. Once the salt is formed, the ionic bond confers new solubility properties to the molecule, these modifications could be used for the development of purification strategies as well specific crystallizations. These advantages permit to afford pharmaceutical ingredients with excellent impurity content. An important characteristic is that the change does not affect the main structure and the reaction is reversible. However, these kinds of processes are underestimated because sometimes it is no easy to recognize their use and these procedures are not well described in the publications because they are part of the know-how of the manufacturing companies. In addition, the synthesis of organic salts is easy to achieve and depends on the final objective of the project (GMP´s or laboratory). For these reasons the organic salt represents a very useful tool to furnish pharmaceutical impurities profiles in pharmaceutical active ingredients.

Acknowledgment

I would like to thank José Moctezuma Arellano for reviewing the manuscript.

Conflicts of interest

The author declares no conflict of interest.

References

1. C.G. Wermuth, P.H. Stahl, Introduction, in: P.H. Stahl, C.G. Wermuth (editors), *Handbook of Pharmaceutical Salts: Properties, Selection and Use*, Wiley-VCH, Zurich, 2002, pp. 1–7.

2. The International Council for Harmonisation of Technical Requirements for Pharmaceutical for Human Use, *ICH Harmonised Tripartite Guideline: Impurities in New Drug Substances Q3A(R2)*, 2006. URL: https://database.ich.org/sites/default/files/Q3A_R2__Guideline.pdf, accessed September 5, 2023.

3. The International Council for Harmonisation of Technical Requirements for Pharmaceutical for Human Use, *ICH Harmonised Guideline: Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk M7(R1)*, 2017. URL: https://database.ich.org/sites/default/files/M7_R1_Guideline.pdf, accessed September 5, 2023.

4. The International Council for Harmonisation of Technical Requirements for Pharmaceutical for Human Use, *ICH Harmonised Guideline: Impurities: Guideline for residual solvents Q3C(R6)*, 2016. URL: https://database.ich.org/sites/default/files/Q3C-R6_Guideline_ErrorCorrection_2019_0410_0.pdf, accessed September 5, 2023.

5. The International Council for Harmonisation of Technical Requirements for Pharmaceutical for Human Use, *ICH Harmonised Guideline: Guideline for elemental impurities Q3D*, 2019. URL: https://database.ich.org/sites/default/files/Q3D-R1EWG_Document_Step4_Guideline_2019_0322.pdf, accessed September 5, 2023.

6. G.N. Anderson, Optimization process by minimizing impurities, in: G.N. Anderson (editor), *Practical Process Research and Development: A Guide for Organic Chemists*, 2nd ed., Elsevier, Inc., 2012, pp. 237–260. URL: https://www.sciencedirect.com/book/9780123865373/practical-process-research-and-development

7. G.N. Anderson, Work up, in: G.N. Anderson (editor), *Practical Process Research and Development: A Guide for Organic Chemists*, 2nd ed., Elsevier, Inc., 2012, pp. 289–327. URL: https://www.sciencedirect.com/book/9780123865373/practical-process-research-and-development

8. D.V. Bhalani, B. Nutan, A. Kumar, A.K.S. Chandel, Bioavailability enhancement techniques for poorly aqueous soluble drugs and therapeutics, *Biomedicines*, **10**(9), 2055 (2022). Doi: https://doi.org/10.3390/biomedicines10092055

9. E. Nelson, Comparative dissolution rates of weak acid and their sodium salts, *Journal of the American Pharmaceutical Association: Scientific Edition*, **47**(4), 297–299 (1958). Doi: https://doi.org/10.1002/jps.3030470422

10. K. Lokesh, A. Amin, A.K. Bansal, Salt selection in drug development, *PharmTech*, **32**(3), 128–145 (2008). URL: https://www.pharmtech.com/view/salt-selection-drug-development

11. P. Makary, Principles of salt formation, *Pharmaceutical and Biosciences Journal*, **2**(4), 1-4 (2014). Doi: https://doi.org/10.20510/ukjpb/2/i4/91101

12. B. Sarma, J. Chen, H.-Y. Hsi, A.S. Myerson, Solid forms of pharmaceuticals: Polymorphs, salts and cocrystals, *Korean Journal of Chemical Engineering*, **28**(2), 315–322 (2011). Doi: https://doi.org/10.1007/s11814-010-0520-0

13. A. Becker, Pharmaceutical salts of small molecule drugs: Opportunities and challenges, *European Pharmaceutical Review*, **19**(5), 70–74 (2014). URL: https://www.europeanpharmaceuticalreview.com/article/27753/pharmaceutical-salts--small-molecule-drugs/

14. A.T.M. Serajuddin, Salt formation to improve drug solubility, *Advanced Drug Delivery Reviews*, **59**(7), 603–616 (2007). Doi: https://doi.org/10.1016/j.addr.2007.05.010

15. J.C. Ortiz-Lara, A. Balderrábano-López, Importancia de las sales orgánicas en la industria farmacéutica, *Revista Mexicana de Ciencias Farmacéuticas*, **48**(1), 18–42 (2017). URL: https://www.redalyc.org/pdf/579/57956614003.pdf

16. B. Kratochvíl, Solid forms of pharmaceutical molecules, in: J. Šesták, J.J. Mareš, P. Hubík (editors), *Glassy, Amorphous and Nano-Crystalline Materials. Thermal Physics, Analysis, Structure and Properties*, Springer, Dordrecht, 2011, pp. 129–140. Doi: https://doi.org/10.1007/978-90-481-2882-2

17. S. Gaisford, M. Saunders, Salt selection, in: *Essentials of Pharmaceutical Preformulation*, Wiley Blackwell, 2012, p. 99. Doi: https://doi.org/10.1002/9781118423226.ch6

18. W.-Q. Tong, Salt screening and Selection: New challenges and considerations in the modern pharmaceutical research and development paradigm, in: Y. Qiu, Y. Chen, G.G.Z. Zhang (editors), *Developing Solid Oral Dosage Forms. Pharmaceutical Theory and Practice*, Academic Press, 2009, pp. 75–86. Doi: https://doi.org/10.1016/B978-0-444-53242-8.00004-7

19. R. Banerjee, P.M. Bhatt, N.V. Ravindra, G.R. Desiraju, Saccharin salts of active pharmaceutical ingredients, their crystal structures, and increased water solubility, *Crystal Growth & Design*, **5**(6), 2299–2309 (2005). Doi: https://doi.org/10.1021/cg050125l

20. W.-Q.T. Tong, G. Whitesell, *In situ* salt screening - A useful technique for discovery support preformulation studies, *Pharmaceutical Development and Technology*, **3**(2), 215–223 (1998). Doi: https://doi.org/10.3109/10837459809028498

21. A.M. Hyde, S.L. Zultanski, J.H. Waldman, Y.-L. Zhong, M. Shevlin, F. Peng, General principles for salting-out informed by the Hofmeister series, *Organic Process Research & Development*, **21**(9), 1355–1370 (2017). Doi: https://doi.org/10.1021/acs.oprd.7b00197

22. F. Pfankuch, H. Rettig, P.H. Stahl, Biological effect of the drug salt form, in: P.H. Stahl, C. Wermuth (editors), *Handbook of Pharmaceutical Salts. Properties, Selection and Use*, Wiley VCH, Zurich, 2011, p. 126.

23. P.D. Elder, D.J. Snodin, Drug substances presented as sulfonic acid salts: Overview of utility, safety and regulation, *Journal of Pharmacy and Pharmacology*, **61**(3), 269–278 (2009). Doi: https://doi.org/10.1211/jpp.61.03.0001

24. D.J. Snodin, Elusive impurities-evidence versus hypothesis. Technical and regulatory update on alkyl sulfonates acid salts, *Organic Process Research & Development*, **23**(5), 695–710 (2019). Doi: https://doi.org/10.1021/acs.oprd.8b00397

25. G.S. Paulekuhn, J.F. Dressman, C. Saal, Trends in active pharmaceutical ingredient salt selection based on analysis of the Orange book database, *Journal of Medicinal Chemistry*, **50**(26), 6665–6672 (2007). Doi: https://doi.org/10.1021/jm701032y

26. The United Stated Food Drug Administration, *Generally recognized as safe (GRAS)*, 2019. URL: https://www.fda.gov/food/ingredientspackaginglabeling/gras/, accessed September 5, 2023.

27. A. Tilborg, B. Norberg, J. Wouters, Pharmaceutical salts and cocrystals involving amino acids: A brief structural overview of the state-of-art, *European Journal of Medicinal Chemistry*, **74**, 411–426 (2014). Doi: https://doi.org/10.1016/j.ejmech.2013.11.045

28. C. Saal, A. Becker, Pharmaceutical salts: A summary on doses of salts formers from the Orange Book, *European Journal of Pharmaceutical Sciences*, **49**(4), 614–623 (2013). Doi: https://doi.org/10.1016/j.ejps.2013.05.026

29. S.S. Bharate, Carboxylic acid counterions in FDA-approved pharmaceutical salts, *Pharmaceutical Research*, **38**(8), 1307–1326 (2021). Doi: https://doi.org/10.1007/s11095-021-03080-2

30. D. Gupta, D. Bhatia, V. Dave, V. Sutariya, S.V. Gupta, Salts of therapeutic agents: Chemical, physicochemical and biological considerations, *Molecules*, **23**(7), 1719 (2018). Doi: https://doi.org/10.3390/molecules23071719

31. K. Fujinuma, Y. Ishii, Y. Yashihashi, E. Yonemochi, K. Sugano, Triboelectrification of active pharmaceutical ingredients: weak acids and their salts, *International Journal of Pharmaceutics*, **493**(1-2), 434–438 (2015). Doi: https://doi.org/10.1016/j.ijpharm.2015.08.008

32. S. Sangwan, T. Panda, R. Thiamattan, S.K. Dewan, R.K. Tapper, Novel salts of sunitinib an anticancer drug with improved solubility, *International Research Journal of Pure and Applied Chemistry*, **5**(4), 352–365 (2015). Doi: https://doi.org/10.9734/irjpac/2015/13578

33. C.P. Ley, M.H. Yates, Purification of 2,4-dichlorobenzoic acid, *Organic Process Research & Development*, **12**(1), 120–124 (2008). Doi: https://doi.org/10.1021/op7001547

34. M.S. Anson, J.P. Graham, A.J. Roberts, Development of a fully telescoped synthesis of the S1P1 agonist, *Organic Process Research & Development*, **15**(3), 649–659 (2011). Doi: https://doi.org/10.1021/op2000095

35. P.L. Lindberg, M.S. Von Unge, Compositions, US Patent 5,714,504, Example 3, 1998. URL: https://patentimages.storage.googleapis.com/30/ce/93/1c3210d22368a1/US5714504.pdf

36. N.C. Niphade, A.C. Mali, B.S. Pandit, K.M. Jagtap, S.A. Jadhav, M.N. Jachak, V.T Mathad, An improved and single pot process for the production of quetiapine hemifumarate substantially free from potential impurities, *Organic Process Research & Development*, **13**(4), 792–797 (2009). Doi: https://doi.org/10.1021/op900097q

37. P.K. Bathini, V.R. Kandula, P.R. Gaddameedhi, An improved synthesis of raloxifene hydrochloride: A selective estrogen receptor modulator, *Heteroletters*, **4**(4), 515–518 (2014). URL: https://www.heteroletters.org/issue44/Paper-5.pdf

38. S.R. Madasu, N.A. Vekariya, H. Velladurai, A. Islam, P.D. Sanasi, R. B. Korupolu, Improved process for preparation of gemfibrozil, an antihypolipidemic, *Organic Process Research & Development*, **17**(7), 963–966 (2013). Doi: https://doi.org/10.1021/op400034f

39. M. Saravanan, B. Satyanarayana, P.P. Reddy, An improved and impurity-free large-scale synthesis of venlafaxine hydrochloride, *Organic Process Research & Development*, **15**(6), 1392–1395 (2011). Doi: https://doi.org/10.1021/op200221y

40. G.N. Trinadhachari, A.G. Kamat, B.V. Balaji, K.J. Probahar, K.M. Naidu, K.R. Babu, P. D. Sanasi, An improved process for the preparation of highly pure solifenacin succinate via resolution through diastereomeric crystallization, *Organic Process Research & Development*, **18**(8), 934–940 (2014). Doi: https://doi.org/10.1021/op500083y

41. P. Macharla, K.C. Akula, G. Varanasi, R. Bandichhor, M.R. Ghanta, An efficient and telescopic process for synthesis of saxagliptin hydrochloride, *Oriental Journal of Chemistry*, **30**(1), 291–297 (2014). Doi: http://doi.org/10.13005/ojc/300137

42. A.C. Mali, S.S. Ippar, M.B. Bodke, N.S. Patil, V.T. Mathad, An improved and efficient process for the production of Dronedarone hydrochloride, an antiarrhytmia drug, *Organic Process Research & Development*, **17**(5), 863–868 (2013). Doi: https://doi.org/10.1021/op400008e

43. A. Halama, J. Jirman, O. Bouškova, P. Gibala, K. Jarrah, Improved process for the preparation of Montelukast: development of an efficient synthesis, identification of critical impurities and degradants, *Organic Process Research & Development*, **14**(2), 425–431 (2010). Doi: https://doi.org/10.1021/op900311z

44. L.R. Madivada, R.R. Anumala, G. Gilla, M. Kagga, R. Bandichhor, An efficient and large scale synthesis of Clopidogrel: Antiplatelet drug, *Der Pharma Chemica*, **4**(1), 479–488 (2012). URL: https://www.derpharmachemica.com/pharma-chemica/an-efficient-and-large-scale-synthesis-of-clopidogrel-antiplatelet-drug.pdf

45. S. Lee, C. Hoff, Large scale aspects of salt formation: Processing of intermediate and final products, in: P.H. Stahl, C. Wermuth (editors), *Handbook of Pharmaceutical Salts. Properties, Selection and Use*, Wiley VCH, Germany, 2011, p. 191–219.

46. D. Zhou, Y. Qiu, Understanding drug properties in formulation and process design of solid oral products, *Journal of Validation Technology*, 74–84 (2010).

47. T.D. Gross, K. Schaab, M. Ouellete, S. Zook, J.P. Reddy, A. Shurtleff, A.I. Sacaan, T. Alebic-Kolbah, H. Bozigian, An approach to early-phase salt selection: Application to NBI-75043, *Organic Process Research & Development*, **11**(3), 365–377 (2007). Doi: https://doi.org/10.1021/op060221a

48. A. Fernández-Casares, W.M. Nap, G.T. Figás, P. Huizenga, R. Groot, M. Hoffman, An evaluation of salt screening methodologies, *Journal of Pharmacy and Pharmacology*, **67**(6), 812–822 (2015). Doi: https://doi.org/10.1111/jphp.12377

49. R. Keltjens, Stable salts of olanzapine, US Patent 7,459,449 B2, 2008. URL: https://patentimages.storage.googleapis.com/ea/d1/b1/46e034280e3add/US7459449.pdf

50. J.F. Remenar, J.M. MacPhee, B.K. Larson, V.A. Tyagi, J.H. Ho, D.A. Mellroy, M.B. Hickey, P.B. Shaw, O. Almarsson, Salt selection and simultaneous polymorphism assessment via high-throughput crystallization: The sertraline case, *Organic Process Research & Development*, **7**(6), 990–996 (2003). Doi: https://doi.org/10.1021/op034115+

51. J.R. Vyas, V.S.V. Nidadavolu, D.H. Shah, Ropivacaine hydrochloride anhydrate and the preparation thereof, US Patent Application Publication US 2009/0187024A1, 2009. URL: https://patentimages.storage.googleapis.com/18/f8/17/b32f14c7ec35ef/US20090187024A1.pdf

52. S. Ninkovic, J.F. Braganza, M.R. Collins, J.C. Kath, H. Li, D.T. Ritchter, 6 Substituted 2-heterocyclyamino pyrazine compounds as CHK-1 inhibitors, WO 2010/016005 A1, 2010. URL: https://patentimages.storage.googleapis.com/3b/34/71/be6e7ef8fe076e/WO2010016005A1.pdf

53. N. Hashimoto, H. Yasuda, M. Hayashi, Y. Tanabe, Aza Diels Alder reaction of methyl 2- [(R)-1-phenylethyl] iminoethanoate with cyclopentadiene using practical and environmentally friendly biphasic solvent system, *Organic Process Research & Development*, **9**(1), 105–109 (2005). Doi: https://doi.org/10.1021/op049828m

54. K.M. Allan, S. Fujimori, L.V. Heumann, G.M. Huynh, K.A. Keaton, C.M. Levins, G.R. Pamulapati, B.J. Roberts, K. Sarma, M.G. Teresk, X. Wang, S.A. Wolckenhauer, Process for preparing antiviral compounds, WO 2015/191437 A1, 2015. URL: https://patentimages.storage.googleapis.com/32/cc/bf/8e4392ba15f1e8/WO2015191437A1.pdf

55. A. Nudelman, Y. Bechor, E. Falb, B. Fischer, A.W. Barry, A. Nudelman, Acetyl chloride-methanol as a convenient reagent for: a) quantitative formation of amine hydrochlorides b) carboxylate ester formation c) mild removal of N-t-Boc-protective group, *Synthetic Communications*, **28**(3), 471–474 (1998). Doi: https://doi.org/10.1080/00397919808005101

56. D.R. Choi, J.K. Lim, J.U. Choi, D.H. Shin, S.H. Kim, D.Y. Won, J.H. Kim, J.C. Roh, An improved manufacturing method of zabofloxacin. WO 2015/178663, 2015. URL: https://patentimages.storage.googleapis.com/79/30/fb/06e158c-14f0f8f/WO2015178663A1.pdf

57. S. Sripathi, R.R. Bojja, V.R. Karnati, V.V.N.K.V.P. Raju, M.D. Khunt, An improved synthesis of antiulcerative drug Tenatoprazole, *Organic Process Research & Development*, **13**(4), 804–806 (2009). Doi: https://doi.org/10.1021/op800173u

58. R. Chavakula, C.J.S. Saladi, N.R. Mutyala, V.R. Maddala, R.K. Babu, Industrially viable demethylation reaction in the synthesis of raloxifene hydrochloride, *Organic Chemistry: An Indian Journal*, **14**(13), 128 (2018). URL: https://www.tsijournals.com/articles/industrially-viable-demethylation-reaction-in-synthesis-of-raloxifene-hydrochloride.pdf

59. Y. Tao, D.W. Widlicka, P.D. Hill, M. Couturier, G.R. Young, A scalable synthesis of CE-157119 HCl salt, and SRI/5HT2A antagonist, *Organic Process Research & Development*, **16**(11), 1805–1810 (2012). Doi: https://doi.org/10.1021/op3002273

60. D.R. Mowrey, J.J. Reif, K.L. Milkiewicz, S.P. Allwein, Development of a novel process for the kilogram-scale synthesis of spiro[2,3-d][1,3]oxazine-4,4′-piperidine]-2-one, *Organic Process Research & Development*, **22**(9), 1236–1240 (2018). Doi: https://doi.org/10.1021/acs.oprd.8b00202

61. B. Toker, S. Merey, Process for the preparation of magnesium salt of omeprazole, WO 2005/082888 A1, 2005. URL: https://patentimages.storage.googleapis.com/5d/24/cb/09068c1cda450b/WO2005082888A1.pdf

62. S.V.N. Raju, K. Purandhar, P.P. Reddy, G.M. Reddy, L.A. Reddy, K.S. Reddy, K. Sreenath, K. Mukkanti, G.S. Reddy, Preparation of optically pure Esomeprazole and its related salt, *Organic Process Research & Development*, **10**(1), 33–35 (2006). Doi: https://doi.org/10.1021/op049779d

63. C.R. Elati, P.J. Wankawala, S.R. Chalamala, N.G. Kolla, S. Gangula, H. Vurimidi, S. Venkataraman, V.T. Mathad, Polymorphic study of Donopezil hydrobromide, *Indian Journal of Chemistry -Section B*, **44**(6), 1231–1235 (2005). URL: https://nopr.niscair.res.in/bitstream/123456789/9114/1/IJCB%2044B%286%29%201231-1235.pdf

64. W. Du, Q. Yin, J. Gong, Y. Bao, X. Zhang, X. Sun, S. Ding, C. Xie, M. Zhang, H. Hao, Effects of solvent on polymorph formation and nucleation of Prasugrel Hydrochloride, *Crystal Growth & Design*, **14**(9), 4519-4525 (2014). Doi: https://doi.org/10.1021/cg5006067

65. B.P. Chekal, J. Ewers, S.M. Guinness, N.D. Ide, K.R. Leeman, R.J. Post, A.M. Rane, K. Sutherland, K. Wang, M. Webster, M.G.J. Withbroe, J. Draper, D. Lynch, M. McAuliffe, J. Keane, Palbociclib commercial manufacturing process development. Part III. Deprotection followed by crystallization for API particle control, *Organic Process Research & Development*, **20**(7), 1217–1226 (2016). Doi: https://doi.org/10.1021/acs.oprd.6b00071

66. H.S.P. Chawla, A.M. Patel, A.S. Chowdhary, V.P. Joshi, M.P. Patel, Process for the manufacture of montelukast sodium, US Patent Application Publication US 2009/0182148 A1, 2009. URL: https://patentimages.storage.googleapis.com/18/c9/d1/cff81ef1807d09/US20090281323A1.pdf

67. A. Halama, J. Jirman, O. Bouskova, P. Gibala, K. Jarrah, Improved process for the preparation of Montelukast: development of an efficient synthesis, identification of critical impurities and degradants, *Organic Process Research & Development*, **14**(2), 425–431 (2010). Doi: https://doi.org/10.1021/op900311z

68. H. Ren, C.A. Strulson, G. Humprey, R. Xiang, G. Li, D.R. Gauthier, K. Maloney, Potassium isopropyl xanthate (IX): an ultra–efficient palladium scavenger, *Green Chemistry*, **19**, 4002–4006 (2017). Doi: https://doi.org/10.1039/C7GC01765K

69. T. Wang, L.-D. Du, D.-j. Wan, X. Li, X.-Z. Chen, G.-F. Wu, Use of lipase catalytic resolution in the preparation of ethyl (2S,5R)-5-((Benzyloxy)amino)piperidine-2-carboxylate, a key intermediate of the B-lactamase inhibitor Avibactam, *Organic Process Research & Development*, **22**(12), 1738–1744 (2018). Doi: https://doi.org/10.1021/acs.oprd.8b00173

70. M.M.A. El Azziz, A.G. Melad, A.S. Ashour, Grindstone neutralization reaction for the preparation of various salts of carboxylic acids, *Bioorganic & Organic Chemistry*, **3**(2), 31–36 (2019). URL: https://medcraveonline.com/MOJBOC/MOJBOC-03-00095.pdf

71. B.M. Collman, J.M. Miller, C. Seadeek, J.A. Stambek, A.C. Blackburn, Comparison of a rational vs high throughput approach for rapid salt screening and selection, *Drug Development and Industrial Pharmacy*, **39**(1), 29–38 (2013). Doi: https://doi.org/10.3109/03639045.2012.656272

72. X. Linghu, N. Wong, H. Iding, V. Jost, H. Zhang, S.G. Koenig, C.G. Sowell, F. Gosselin, Development of a practical synthesis of ERK inhibitor GDC-0994, *Organic Process Research & Development*, **21**(3), 387–398 (2017). Doi: https://doi.org/10.1021/acs.oprd.7b00006

73. X. Shi, H. Chang, M. Grohmann, W.F. Kiesman, D.-l.A. Kwok, Process development of an N-benzylated chloropurine at the kilogram scale, *Organic Process Research & Development*, **19**(3), 437–443 (2015). Doi: https://doi.org/10.1021/op5003903

74. C.M. Brandel, J.W.B. Cooke, R.A.J. Horan, F.P. Mallet, D.R. Stevens, Optimization of the preparation of (*R*)-3,5-bis(trifluoromethyl)-*α*-methyl-*N*-methylbenzylamine L-(-)-malic acid salt through classical resolution, *Organic Process Research & Development*, **19**(12), 1954–1965 (2015). Doi: https://doi.org/10.1021/acs.oprd.5b00283

75. T.A. Martinot, B.C. Austad, A. Coté, K.M. Depew, D. Genov, L. Grenier, J. Helble, A. Lescarbeiu, S. Nair, M. Trudeau, P. White, L.-N. Yu, A design of experiments approach to a robust final deprotection and reactive crystallization of IPI-926, a novel hedgehog pathway inhibitor, *Organic Process Research & Development*, **19**(11), 1693–1702 (2015). Doi: https://doi.org/10.1021/acs.oprd.5b00214

76. M.S.H. Mithou, S. Economidou, V. Trivedi. S. Bhatt, D. Douroumis, Advanced methodologies for pharmaceutical salt synthesis, *Crystal Growth & Design*, **21**(2), 1358–1374 (2021). Doi: https://doi.org/10.1021/acs.cgd.0c01427

77. R. Hilfiker, Relevance of solid–state properties for pharmaceutical products, in: R. Hilfiker (editor), *Polymorphism in the Pharmaceutical Industry*, Wiley-VCH, Germany, 2006. Ch. 1, p 2.

78. D. Giron, Characterization of salts of drug substances, *Journal of Thermal Analysis and Calorimetry*, **73**(2), 441–457 (2003). Doi: https://doi.org/10.1023/A:1025461625782

79. G. Bruni, M. Maietta, L. Maggi, M. Bini, D. Capsoni, S. Ferrari, M. Boiocchi, V. Berbenni, C. Milanese, A. Marini, Pherphenazine-fumaric acid salts with improved solubility: preparation physico-chemical characterization and *in vitro* dissolution, *CrystEngComm*, **14**, 6035–6044 (2012). Doi: https://doi.org/10.1039/C2CE25846C

How to cite this article

J.C. Ortiz-Lara, Organic salts as a tool for pharmaceutical ingredient purification: Bibliographic review, *Rev. Colomb. Cienc. Quim. Farm.*, **53**(1), 184-218 (2024). https://doi.org/10.15446/rcciquifa.v53n1.112981