Review

Salts of Therapeutic Agents: Chemical, Physicochemical and Biological Considerations

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Abstract: Choice of the salts of therapeutic agents or active pharmaceutical ingredients (API) is based on the physicochemical properties of API and the dosage form considerations. The appropriate salt can have positive effect on overall therapeutic and pharmaceutical effects of API. However, the incorrect salt form can negatively affect the overall pharmaceutical outcomes of the API. This review addresses various criteria for choosing appropriate salt form along with the effect of salt forms on API's pharmaceutical properties. In addition to comprehensive review of the criteria, this review also gives a brief historic perspective of the salt selection process.

Keywords: Chemistry, salt, water solubility, routes of administration, physicochemical, stability, degradation

1. Introduction

Salt of an Active Pharmaceutical Ingredient (API) often formed to achieve desirable formulation properties. Salt formation is a common strategy employed by pharmaceutical companies to address the issues of poor aqueous solubility, stability, toxicity, poor absorption and issues related to manufacturing processes. The importance of salts can be attested by the fact that approximately 50% of the US FDA approvals consist of APIs in the salt form(1). Moreover, half of the top 200 prescription drugs in the United States consists of pharmaceutical salts (2). Choice of the appropriate salt form is dictated by various factors. Formation of potentially marketable salt requires concerted efforts and thorough understanding of physical and chemical characteristics of the API as well as the counter ions used. A rational decision tree approach should be followed for the selection of the best salt in a most economical way. Furthermore, all necessary testing should be performed in the early phases of the drug development process to minimize failures. Salts can significantly alter physical/chemical properties of an API so much so that it can expedite the drug development process.

Suitability of a candidate for salt selection is determined by the physical and chemical properties of the API; different counterions can be utilized to address one or more shortcomings of the API.

Prediction of salt's qualitative and/or quantitative properties based on counter ion used, is an important research area. Several studies have described a link between salt properties and the counter ions used.(3-8) While some predictions can be made with some degree of accuracy, there is no reliable way of accurately envisaging salt properties based on counter ion used. Currently, there

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is a wide range of safe of counterions that can be used to prepare salts of API (Table 1)(9). This review will address various criteria for selection of salt forms and suitable examples for each category. Including all the examples for each criterion will be beyond the scope of this review; only few representative examples are included. It should be noted that although there are various textbooks published addressing salt forms of API, this review is aimed at offering a succinct report on the salt selection criteria and applications.

Salt selection can be studied based on following criteria:

2. Drug Chemistry Considerations

2.1. *API chemistry*

Presence of acidic or basic functional groups is an essential requirement for the formation of salts. Majority of the APIs discovered are suitable candidates for salt formation during drug Phdevelopment, as they are either weakly acidic or weakly basic in nature. Salt screening begins with characterization of acidic or basic functional groups. Depending upon the presence of these groups and pharmaceutical needs, possible counter ion can be selected. For example, Bozigian et. al. reported that compound NBI-75043, an investigational compound for the treatment of insomnia, was a crystalline, free base with low melting point (64 ^{o}C)(10) One of the important pharmaceutical requirements for this compound was to develop a salt possessing higher melting point. Since weakly basic drug requires acidic counter ions to form ionic bonds and, based on requirement of ionization energy of the bond required, 14 acids were selected as possible counter ions. Since low melting point was one of the concerns for this drug, initial approaches to characterize salt forms included differential scanning calorimetry (DSC); an important tool for determining the melting point as well as crystallinity, solvates, and presence or absence of the polymorphs. They were able to successfully find the salt form of NBI-75043. All these are important parameters to evaluate in early phases of drug development to reduce the possible number of salts to streamline drug development efforts.(10)

2. 2. *pka of the Drug*

The selection of a counter ion is based on degree of ionization of the acidic or basic functional groups present in the drug. Dissociation constant (pKa) of the drug is an important parameter for the selection of specific counter ions. Ideally, for basic drug, the pka should be at least 2 pH units higher than pka of the counter ion and for acidic drugs, pka of the drug should be at least 2 pH units lower than the pka of the counter ion chosen. This difference ensures strong binding energy between opposite ionic species, so that complexes formed will not readily breakdown into individual species, when not required. For example: Phenytoin is a well-known acidic drug with pKa value of 8.4; however, it has limited solubility. One important pharmaceutical property for this drug was to improve aqueous solubility. Due to acidic nature of the drug, basic counter ions with pKa value of >10.4 is likely to form pharmaceutically acceptable salts. Therefore, strong basic counter ions like NaOH is needed for a desirable salt of phenytoin. Salts with weakly basic counter ion like $Mg(OH)_2$, $Ca(OH)_2$ would not be able to form salt with phenytoin since these counter ions won't be able to raise the pH above pHmax value of 11 required for phenytoin.(11)

2.3 *Lipophilicity*

Salt formation is well utilized technique to increase the aqueous solubility of a drug. However, sometimes, hydrophobic salt approaches are considered to increase the lipophilicity of a drug

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molecule.(12, 13) The decrease in aqueous solubility has been found to be a useful approach to provide greater chemical stability, particularly at high humidity and high temperature. One well known example is formation of sulfate as well as hydrophobic salts of xilobam. Sulfate salt of this drug was completely ionized It has been found that presence of aryl groups in the sulfate counterion for this drug protected an easily hydrolysable base due to high humidity and high temperature. By the formation of hydrophobic salt, the pharmaceutical company could make more lipophilic as well as much more stable drug without any adverse effect on the bioavailability. (14)

As shown in **Table 2**, Sarveiya et. al. correlated the effect of different counter ions of ibuprofen on log P value and membrane absorption.(15) This table clearly shows the effect of different counterions on log P values and effect of different salt forms on the flux across biological membranes.

2.4 Hygroscopicity

An anhydrous substance can take up moisture from humid environment, which, in turn, can alter mechanical and solubility properties affecting the performance of a drug. Readily hydrolyzable drugs are more easily degraded due to presence of water and pH alteration in the microenvironment of the salt. For example, salts of mineral acids tend to be very polar leading to increased hygroscopicity and low micro-environmental pH. These factors can affect stability of some drugs due to consequential increase in the rate of hydrolysis.

2.5 Water of Hydration

If a hydrate is exposed to dry environment, it can lose water of crystallization to attain lower state of hydration or an anhydrous form. Exchange of water between drug and excipients like starch or cellulose can also affect solubility and mechanical properties of a drug product.

2.6 Polymorphism

For a molecule to develop into a potential drug, existence of stable polymorph or a suitable pseudopolymorph needs to be established. Ritonavir (Norvir®) capsules represent a well-known example, where polymorphism problem led Abbott to temporarily withdraw this drug from the market, which was later introduced as tablet and oral suspension. RRR111423 was another anti-HIV candidate in the development phase. It was found to be a very weak base (pKa = 4.25). Mesylate and hydrochloride salts of this drug could be isolated as crystalline solids and were evaluated for further development.(16) While no polymorphic form for RPR111423 was detected, at least four polymorphs were detected for hydrochloride salt and six forms were detected for mesylate salt. Free base (RPR111423), therefore, appeared to be the better choice as it was free of polymorphism and investigated further. (16)

2.7 Chemical Stability

Acidic or basic counterions can alter the pH of the microenvironment in the liquid dosage forms. Changes in pH, in turn, can influence reactivity of an API with excipients and can lead to either

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improved stability or degradation of the API. Undesirable interactions can generate significant impurities in a drug product.

For example, amlodipine is a free base and was initially chosen for developing a maleate salt. The presence of maleic acid, however, changed the microenvironment of the drug product and this alteration lead to the formation of aspartic acid derivative (UK-57269) by Michael addition as shown in Figure 1. This degradation product was found to have different biological activity and therefore, amlodipine maleate was found to be unsuitable for further development. Although, such reactions could be minimized by careful selection of excipients and by avoiding alkaline conditions(17); besylate (benzenesulfonate) was chosen to be the suitable salt form with much less problems.(18)

2.8 Melting Point

Low molecular weight bases and acids have higher chances of being a liquid and have low melting point. Salt formation can be employed to augment their melting points and to convert and maintain them into solid state.

2.9 Solubility and Dissolution Rate

Salt approaches have widely been utilized to increase solubility and, therefore, dissolution rate of a drug. It is one of the most common methods to increase solubility of weakly acidic and basic drugs. Hydrochloride, mesylate, hydrobromide, acetate, and fumarate are the most common counterions used for basic chemical entities in the past 20 years. While sodium, calcium, potassium continue to be the most common counterions for weakly acidic drugs. One of the important properties, achieved by most of these counterions, was increase in aqueous solubility of the drugs. Slater et al studied the feasibility of salt formation for RPR2000765, having pKa of 5.3 and intrinsic free base solubility of 10 µg/ml.(16) The poor aqueous solubility yielded poor bioavailability in animals. While all salts forms (hydrochloride, hydrobromide, methanesulfonate, mesylate and camphorsulfonate) increased solubility of the parent drug; mesylate salt consistently produced a higher solubility of 39 mg/ml at 25 °C. Other factors like hygroscopicity, clean polymorphic profile, particle size, and flow properties were also considered and all these factors favored formation of mesylate salt for further development.

3 Pharmaceutical Considerations

3.1 Dosage form desired

3.1.1 Oral (Taste Masking/Suspensions)

Erythromycin (free base) is a freely water soluble macrolide and its bitter taste deters its use in pediatric formulations. Stearic acid salt of erythromycin was found to have decreased solubility; however, it allowed the formulation of suspension that effectively suppressed the bitter taste of the free base. This makes acidic salt form of erythromycin much more pharmaceutically acceptable, especially, in pediatric patients. Similar to erythromycin, to decrease solubility of an acidic or basic drug, salts can be synthesized to allow the development of suspension formulation. For acidic drugs, calcium salts or anion exchange resonates can be considered. For basic drugs, salts of long chain fatty acids (e.g. laurates and pamoates) and cation exchange resonates can be a good choice.(18)

Similarly, sweeteners like cyclamic acid or saccharin can be useful to make salts for basic drugs. In case of acidic drugs, basic salts like triethanolamines can be useful for improving the taste.

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3.1.2 Parenteral

Solubility of a drug in aqueous systems is an important factor in the development of parenteral formulations. Solubility experiment is an important tool for the selection appropriate counter ions. Most of the time, solubility can be increased by altering solution pH. One well known example is phenytoin sodium, where solubility of this acidic barbiturate is tremendously increased by addition of NaOH to phenytoin so as to allow parenteral administration at a desired concentration.(19) Chemical stability is another crucial factor as drugs in solution tend to be less stable than in solid dosage forms. For example, cephalosporin antibiotic is a neutral zwitterion and not very stable in solution. Mono counter ion salts did not offer much stability and though, di-counter ion salts yielded stable solution, these solutions were quite acidic with pH<2. This pH problem was resolved by preparing di-hydrochloride salt to be reconstituted with 2 moles of arginine at the time of the injection. This lead to a stable drug solution in a desired pH range.(18)

3.1.3 Topical

Highly polar transdermal drug candidates, generally, demonstrate ineffective percutaneous penetration. Counterions act as neutralizing agents by binding with the API via coulomb forces to permit passive absorption. For example, ion-pairing of salicylates with alkylamines and quaternary ammonium ions showed an increase percutaneous flux of the drug. Increased penetration was successfully attained with diethylamine salt of diclofenac as a topical gel while sodium salt is available for oral absorption.

3.1.4 Inhalational

Inhalation route is primarily targeted to bronchioles and lungs for local delivery of a drug. Various physiochemical and mechanical factors need to be considered for effective delivery. Salmeterol is a long acting beta adrenergic agonist useful for chronic obstructive pulmonary disease (COPD). Its solubility was reduced by making xinafoate salt, which dissolves slowly; thus potentiating long half-life of salmeterol. Thus, xinafoate salt of salmeterol was designed to tailor properties of API for desired outcomes.

3.2 Ease of Synthesis and Scale-up

3.2.1 Flowability

Flowability of the API affects blending, compression, filling, transportation and scale-up operations of solid dosage manufacturing. API with poor flow properties will result in final products with unacceptable uniformity content, weight variation and physical inconsistency. Salt formation improves solid state properties of API by promoting crystalline structure. The crystalline nature of API is amenable to techniques that improve flow properties.

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3.2.2 Corrosiveness of Counterions

Weakly basic drugs with low dissociation constant (pKa) values; generally, require salts of much stronger counterion acids to be physically stable. This may lead to acidic aqueous solution of the salt. Highly acidic aqueous solutions can corrode metal containers, manufacturing tools, and other equipment. Therefore, part used in tableting like punches, dies and die tables are more vulnerable to the damage caused by corrosive solids as they are in continuous contact with tablet mixtures and that too under high pressure and friction. Capsule filling machines and mechanical forces involved in filling can also corrode metal surface. Corrosive salts can make tableting technically impossible and, if used, can lead to metal trace in the tablets during compression. Consequently, the types of corrosive counterions should not be used to form salt forms or sufficiently diluted with excipients so that low dose substances will not cause serious problems. Salts of a drug product with pH values of 2.5 or lower for saturated aqueous solutions are generally found to be corrosive. Corrosiveness test should be conducted if the pH value of a saturated aqueous solution is less than or equal to 4. For example, weakly basic drug (pKa = 4.7), mentioned by Stahl et al, was considered to be developed as either free based or hydrochloride/methanesulfonate salts. However, hydrochloride salt was later dropped out due to extreme corrosiveness. Methanesulfonate was not corrosive on stainless steel and only slightly corrosive on grey cast iron and tool steel alloys. Therefore, methanesulfonate was chosen as preferred counter ion followed by further development.

3.2.3 Compatibility with Excipients

Selection of the counter ion should be based on understanding of the types of chemical interactions with the excipients.

For example, compound CGP6085, designed as an antidepressant, is a free base and its interaction with tablet excipient lactose leads to significant degradation of the API (Figure 2). However, hydrochloride salt form of CGP6085 improved stability of API and eventually suppressed interaction with lactose (18). This suggests salt forms can have significant influence on the drug stability and counterions should be able to increase the stability of a drug in the chosen dosage form.

3.3 Route of Administration

Different salt forms or free acid/base can be used based on the route of administration selected. For some drugs, it is even more important to have a salt form than a nonsalt form. For example, formation of salt is much more important for injectable dosage forms than oral or transdermal dosage forms. Historically, more injectable salt forms were approved than any other salt forms. A review article by Paulekuhn et. al. described more than 2/3rd injectable dosage forms contained salts as compared to only 50-60% of oral dosage forms.(20) A greater need for a highly soluble salt for injectable dosage forms is one of the important driving forces behind salts forms. Injectable dosage forms are generally concentrated since only a few millimeters can be used for each injection. Thus, salt formation is one of the important ways to achieve the desired characteristics in a drug like increased solubility for parenteral route of administration. While, most commonly used anions for oral dosage forms are chloride, sulfate and maleate, for injectable dosage forms chloride, sulfate and acetate were three top anions used. For oral formulations on the other hand sodium, potassium and calcium were three tops cations used, however, sodium, calcium were top cations used for injectable dosage forms. Recently, lysine counterion has become a popular choice for injectable amongst approximately 15% injectable salts approved between 2002-2006.(20)

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Different salt forms of the same drug can be suitable for different routes of administration as well. For example, sodium, potassium and free acid form of diclofenac are approved as oral medications. Diclofenac sodium 1% gel (Voltaren Gel®) and diclofenac sodium topical solution 1.5% w/w (Pennsaid®) are also available as topical products, however its epolamine salt (Flector®) is approved as transdermal patch due to its better skin permeation than sodium or potassium salts.(21)

3.4 Controlled Release Dosage Forms

APIs can demonstrate different dissolution properties when attached with different counterions. Therefore, clinically one salt form may be preferred over another for desired release characteristics. A highly soluble drug can be designed into controlled release formulation by using sparingly soluble salts. This decrease in drug solubility may retard the drug release desired. Therefore, selecting appropriate counterion to slow down drug release can be helpful in sustained release formulations. For example, imipramine, a tricyclic antidepressant, was initially designed as hydrochloride salt as an immediate release (IR) formulation (Figure 3). However, a controlled release formulation was more desirable in this case and therefore; imipramine pamoate was designed with reduced solubility. This retard in drug release rate was suitable for desired SR formulation.

Another important example that illustrates importance of dissolution is demonstrated by different salt forms of diclofenac. Fini et. al. examined the dissolution of 30 different salt forms of diclofenac.(22) While both potassium and free acid form is now used as immediate release form in the USA, only sodium salt form is used as either extended or delayed release dosage form. Thus, different counterions attached to the same drug can influence dissolution rates and therefore, can influence dosage forms desired in clinical practice.

4 Pharmacokinetics (PK), Pharmacodynamics (PD) and Safety Considerations

4.1 Toxicological Consideration

Sometimes salt approaches have been utilized to reduce gastrointestinal (GI) toxicity of the parent drug. Various examples (23-25) demonstrate this use of counterions that were readily metabolized and excreted and, thus, were helpful in reducing GI toxicity. Salicylates are well-known to cause GI bleeding and related disturbances like ulcers. Choline is an important counterion which is almost non-toxic and it has been reported that choline salicylate demonstrated lower incidences of GI toxicity and better tolerated at higher doses.(23)

4.2 Distribution and Clearance

Salt formation has also been shown to affect distribution and clearance of a drug molecule. Malek et al(26) demonstrated that distribution properties of some antibiotics can be significantly altered by using macromolecular counterions. Macromolecules such as polysaccharides, polyacrylic acids, sulfonic and polyuronic acids were combined with popular antibiotics like streptomycin and neomycin. As compared to streptomycin sulfate salt, these high molecular weight counterion salts with streptomycin showed higher distribution of the drug to the lymph nodes and less drug present in the plasma. Selective distribution then resulted in the delayed clearance of the streptomycin.

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4.3 Onset and Termination of Therapeutic Effects

Based on therapeutic indication, some drug formulations require slower onset and termination of therapeutic effect. Single salt amphetamine of dextroamphetamine preparations may not be a good choice for psychostimulant effect. Adderall XR® was designed as a combination of aspartate and sulfate salts of amphetamine plus saccharate and sulfate salts of dextroamphetamine. These different salts in a single drug product allowed different metabolism rates and possessed different onsets of action. This resulted in faster induction of therapeutic effect while maintaining that effect for sufficiently long time.

4.4 Safety of Counterions Used

One important criterion in selection of counter ions is to employ agents that are generally regarded as safe (GRAS) by FDA of those that have previously been used in FDA approved drugs.(7)

4.5 Counteracting Side Effects

Sometimes counterions are used in such manner that the side effects of the parent drug can be decreased by the counterion used. Since penicillin has potential to cause allergic response in patients; antihistaimes salts of peniciliin have been reported in the literature. Main idea was to mitigate allergic response of penicillin by using well documented anti-allergic drugs.(27)

One well known example is Dramamine® (diphenhydramine+8-chloro theophylline) where 8-chloro theophylline acts as a stimulant to counteract drowsiness caused by diphenhydramine.(28, 29)

4.6 Drug interactions

Presence of free acid/base form or a particular counterion can have some clinically relevant drug interactions particularly when it is co-manufactured or co-administered with other drugs. Prasugrel represents an important example of drug interaction with proton pump inhibitors (PPIs), when co-administered.(30) Even during manufacturing of prasugrel, salt form can convert to free base form and can affect pharmacokinetics and thus, the biological response. Prasugrel is available as hydrochloride salt and it was found that salt form offers better absorption at higher gastric pH, when compared to free base form. However, during manufacturing of the drug, it has been found that the acid-base reaction can convert salt form to the free base form, thus affecting pharmacokinetics. This is further complicated by common use of PPIs along with prasugrel and co-administration can alter gastric pH as well as salt to base ratio. So, bioequivalence studies with or without PPIs became clinically relevant. It was found that when prasugrel in different salt/base ratios was co-administered with lansoprazole, all forms exhibited similar extent of absorption, however, rate of absorption was found to be different. This was a very important clinical outcome as high salt to base conversion significantly delayed maximal platelet aggregation achieved by prasugrel; an important therapeutic goal following myocardial infarction. Thus, different salt forms as well as drug interaction can have important clinical implications.

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5 Economic Considerations

5.1 Intellectual Property (IP) Considerations

Over the years, various generic pharmaceutical manufacturers have tried to bring different salt forms of an approved API to gain entry into the market even before original patent had expired. A newer salt form may offer important advantages and allow original company to extend proprietary rights or give market exclusivity to a generic manufacturer. Some of the benefits offered by innovative salt forms that may deserve patent protection are simplified manufacturing procedures, more stable analogues, newer routes of administration or a completely different therapeutic use.

One of the well-known examples is the request by Dr. Reddy's Laboratories to gain market approval of amlodipine maleate even before patent expiration of amlodipine besylate. This plea was rejected in favor of original patent. However, some manufactures are successful by modifying certain dosage characteristics. One well known example is diclofenac epolamine (Flector®) approved and patented as transdermal patch while its sodium and potassium salts were already available as generic tablets, capsules, topical gels and solutions. Inst Biochem has patent on Flector®. Original patent was issued on March 4, 1997. Drug was approved by FDA on January 31, 2007. However, it holds a patent on this this product till April 13, 2019 (31). Thus, sometimes patenting new salt forms of the same API gives market exclusivity to some of the products.

Conclusions

Salt formation of API is an integral part of formulation development process. The choice of right salt form can improve solid state properties of the API and can ease the burden of time consuming and expensive formulation development. Counterions of the salts used can positively affect the applicability of drug in various dosage forms by improving the formulation properties. The appropriate salt of form of the API is important to achieve the desired outcome and can also have immense economic impact.

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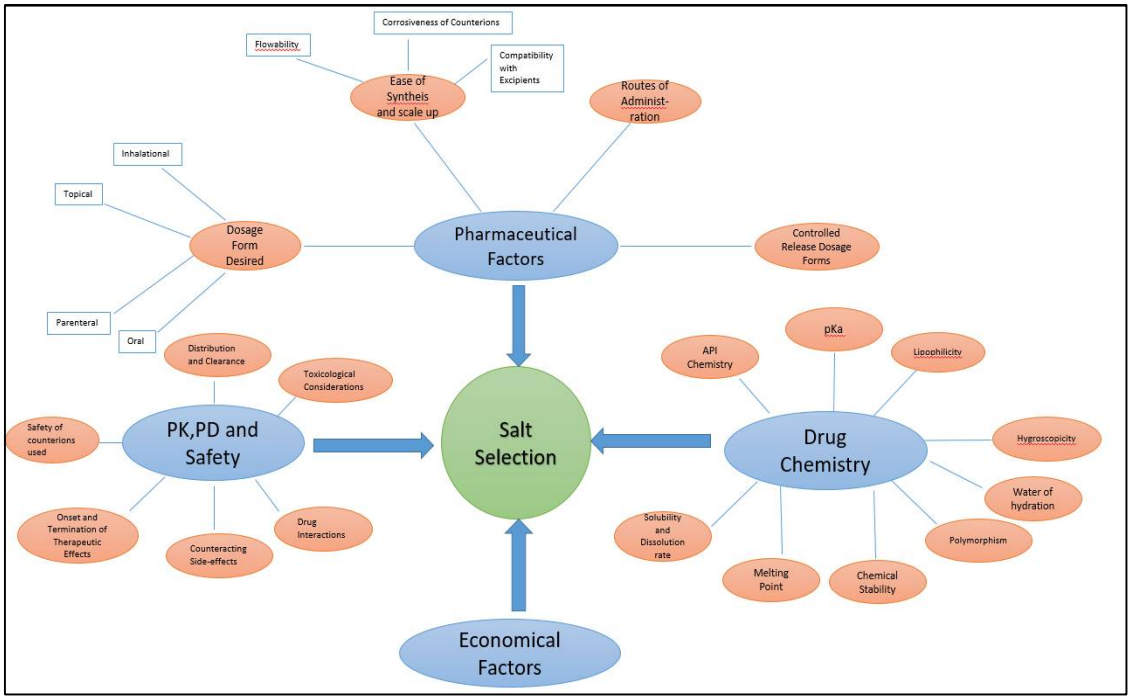

Figure 1. Various factors affecting the salt selection process.

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386 **Table 1. List of currently available counterions for salt formation(9)**

Chemistry	Examples	
Cations	Aluminum	Lysine
	Arginine	Magnessium
	Benzathine	Histidine
	Calcium	Lithium
	Chloroprocaine	Meglumine
	Choline	Potassium
	Diethanolamine	Procaine
	Ethanolamine	Sodium
	Ethylenediamine	Triethylamine
		Zinc
Anions	Acetate	Lactobionate
	Aspartate	Malate
	Benzenesulfonate	Maleate
	Benzoate	Mandelate
	Besylate	Mesylate
	Bicarbonate	Methylbromide
	Bitartrate	Methylnitrate
	Bromide	Methylsulfate
	Camsylate	Mucate
	Carbonate	Napsylate
	Chloride	Nitrate
	Citrate	Octanoate
	Decanoate	Oleate
	Edetate	Pamoate
	Esylate	Pantothenate
	Fumarate	Phosphate
	Gluceptate	Polygalacturonate
	Gluconate	Propionate
	Glutamate	Salicylate
	Glycolate	Stearate
	Glycollylarsanilate	Subacetate
	Hexanoate	Succinate
	Hydrabamine	Sulfate
	Hydroxynaphthoate	Tartrate
	Iodide	Teoclate

Isthionate	Tosylate
Lactate	Triethiiodide

Table 2: Counter ions of ibuprofen and their respective log P values and membrane absorption values

Ibuprofen counter ion	Log P	Intestinal flux (μg.cm-1.h-1)
Sodium	0.92	3.09
Ethylamine	0.97	5.42
Ethylenediamine	1.11	15.31
Diethylamine	1.12	7.91
Triethylamine	1.18	48.4

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Abbreviations

API	Active Pharmaceutical Ingredient
FDA	Food and Drug Administration
IR	Immediate Release
PPI	Proton Pump Inhibitors
GRAS	Generally Regarded as Safe

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References

1. Paulekuhn GS, Dressman JB, Saal C. Trends in Active Pharmaceutical Ingredient Salt Selection based on Analysis of the Orange Book Database. Journal of Medicinal Chemistry. 2007;50(26):6665-72. doi: 10.1021/jm701032y.

2. Prohotsky DL, Zhao F. A survey of Top 200 Drugs—Inconsistent Practice of Drug Strength Expression for Drugs Containing Salt Forms. Journal of Pharmaceutical Sciences. 2012;101(1):1-6. doi: https://doi.org/10.1002/jps.22735.

3. Rubino JT. Solubilities and solid state properties of the sodium salts of drugs. J Pharm Sci. 1989;78(6):485-9. Epub 1989/06/01. PubMed PMID: 2760824.

4. Thomas E, Rubino J. Solubility, melting point and salting-out relationships in a group of secondary amine hydrochloride salts. International Journal of Pharmaceutics. 1996;130(2):179-85. doi: http://dx.doi.org/10.1016/0378-5173(95)04269-5.

5. Chowhan ZT. pH-solubility profiles or organic carboxylic acids and their salts. J Pharm Sci. 1978;67(9):1257-60. Epub 1978/09/01. PubMed PMID: 29115.

6. Forbes RT, York P, Davidson JR. Dissolution kinetics and solubilities of p-aminosalicylic acid and its salts. International Journal of Pharmaceutics. 1995;126(1â€“2):199-208. doi: http://dx.doi.org/10.1016/0378-5173(95)04126-5.

7. Gould PL. Salt Selection for Basic Drugs. Int J Pharm. 1986;33(1-3):201-17.

8. Pandit NK, M. Strykowski J, Shtohryn L. The effect of salts on the distribution and solubility of an acidic drug. International Journal of Pharmaceutics. 1989;50(1):7-13. doi: http://dx.doi.org/10.1016/0378-5173(89)90174-9.

9. Wiedmann TS, Naqwi A. Pharmaceutical salts: Theory, use in solid dosage forms and in situ preparation in an aerosol. Asian Journal of Pharmaceutical Sciences. 2016;11(6):722-34. doi: https://doi.org/10.1016/j.ajps.2016.07.002.

10. Gross TD, Schaab K, Ouellette M, Zook S, Reddy JP, Shurtleff A, et al. An Approach to Early-Phase Salt Selection:â€‰ Application to NBI-75043. Organic Process Research & Development. 2007;11(3):365-77. doi: 10.1021/op060221a.

11. Serajuddin AT, Jarowski CI. Influence of pH on release of phenytoin sodium from slow-release dosage forms. J Pharm Sci. 1993;82(3):306-10. Epub 1993/03/01. PubMed PMID: 8450427.

12. Miller JM, Dahan A, Gupta D, Varghese S, Amidon GL. Quasi-equilibrium analysis of the ion-pair mediated membrane transport of low-permeability drugs. J Control Release. 2009;137(1):31-7. Epub 2009/03/07. doi: S0168-3659(09)00129-1 [pii]

10.1016/j.jconrel.2009.02.018 [doi]. PubMed PMID: 19264104.

13. Miller JM, Dahan A, Gupta D, Varghese S, Amidon GL. Enabling the intestinal absorption of highly polar antiviral agents: ion-pair facilitated membrane permeation of zanamivir heptyl ester and guanidino oseltamivir. Mol Pharm. 2010;7(4):1223-34. Epub 2010/06/12. doi: 10.1021/mp100050d [doi]. PubMed PMID: 20536260.

14. Walkling WD, Reynolds BE, Fegely BJ, Janicki CA. Xilobam: Effect of salt form on pharmaceutical properties. Drug Development and Industrial Pharmacy. 1983;9(5):809-19. doi: doi:10.3109/03639048309039889.

15. Sarveiya V, Templeton JF, Benson HA. Ion-pairs of ibuprofen: increased membrane diffusion. J Pharm Pharmacol. 2004;56(6):717-24. Epub 2004/07/03. doi: 10.1211/0022357023448 [doi]. PubMed PMID: 15231036.

16. Bastin RJ, Bowker MJ, Slater BJ. Salt Selection and Optimisation Procedures for Pharmaceutical New Chemical Entities. Organic Process Research & Development. 2000;4(5):427-35. doi: 10.1021/op000018u.

17. Dinesh Dayaramji Chakole DRsLL, inventor; Stabilized pharmaceutical formulations containing amlodipine maleate. UNited States2003.

18. Stahl PH, Skinner, F. S. Pharmaceutical Aspects of the API Salt Form. In: Stahl PH, Wermuth, C.G., editor. Pharmaceutical Salts: Properties, Selection, and Use, 2nd Revised Edition. 2nd ed: WILEY-VCH; 2011. p. 85-124.

19. Carmichael RR, Mahoney CD, Jeffrey LP. Solubility and stability of phenytoin sodium when mixed with intravenous solutions. Am J Hosp Pharm. 1980;37(1):95-8. Epub 1980/01/01. PubMed PMID: 7361779.

20. Paulekuhn GS, Dressman JB, Saal C. Trends in active pharmaceutical ingredient salt selection based on analysis of the Orange Book database. J Med Chem. 2007;50(26):6665-72. Epub 2007/12/07. doi: 10.1021/jm701032y. PubMed PMID: 18052022.

21. McPherson ML, Cimino NM. Topical NSAID formulations. Pain Med. 2013;14 Suppl 1:S35-9. Epub 2014/01/01. doi: 10.1111/pme.12288. PubMed PMID: 24373109.

22. Fini A, Fazio G, HervÃ¡s M-JFn, Holgado MA, Rabasco AM. Factors governing the dissolution of diclofenac salts. European Journal of Pharmaceutical Sciences. 1996;4(4):231-8. doi: http://dx.doi.org/10.1016/0928-0987(95)00051-8.

23. Broh-Kahn RH. Choline salicylate: a new, effective, and well-tolerated analgesic, anti-inflammatory, and antipyretic agent. Int Rec Med. 1960;173:217-33. Epub 1960/04/01. PubMed PMID: 13804696.

24. Duesel BF, Berman H, Schachter RJ. Substituted xanthines. I. Preparation and properties of some choline theophyllinates. J Am Pharm Assoc Am Pharm Assoc (Baltim). 1954;43(10):619-22. Epub 1954/10/01. PubMed PMID: 13211404.

25. Duesel BF, Fand TI. Choline theophyllinate, a new stable theophylline derivative of enhanced solubility. Int Rec Med Gen Pract Clin. 1954;167(5):245-7. Epub 1954/05/01. PubMed PMID: 13162620.

26. Malek P, Kolc J, Herold M, Hoffman J. Lymphotrophic antibiotics; antibiolymphins. Antibiot Annu. 1957;5:546-51. Epub 1957/01/01. PubMed PMID: 13521854.

27. Boger WP, Strickland SC, Gylfe JM. The penicillinate of benzhydrylamine; its oral administration. Antibiotic Med Clin Ther. 1955;1(7):372-6. Epub 1955/07/01. PubMed PMID: 13239090.

28. Cusic JW. 8-haloxanthine salts of dialkylaminoalkyl type antihistamine bases. Google Patents; 1950.

29. Cusic JW. B-haloxantfflne salts of diarylalkyl. Google Patents; 1950.

30. Seiler D, Doser K, Salem I. Relative bioavailability of prasugrel free base in comparison to prasugrel hydrochloride in the presence and in the absence of a proton pump inhibitor. Arzneimittelforschung. 2011;61(4):247-51. Epub 2011/06/10. doi: 10.1055/s-0031-1296195 [doi]. PubMed PMID: 21650084.

31. Akazawa M. Diclofenac, hydroxyethyl-pyrroldine or piperidine. Google Patents; 1997.

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