Principles of salt formation

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Abstract
It has been evaluated that approximately 50% of all drug molecules marketed as medicinal products are administered in a form of salts as they offer many benefits for the pharmaceutical drugs. Salt formation is a relatively simple and powerful pre-formation technique that can result in significant improvement of drug's physicochemical properties. Following the formation of candidate salt forms, the optimal form is chosen for further development. Salt selection is a rational and step-wise process, in which salts are analysed with regard to particular properties and the most suitable forms are examined further to ensure an optimal choice. Although the effects of salt formation may be highly beneficial to the drug’s performance, there are a number of properties that may deteriorate as a result of the drug being formulated as a salt.

1 Introduction
The physicochemical characteristics and economical state of a medicinal drug can be manipulated and improved by conversion to a salt form. Selecting the appropriate salt is considered to be a very important step since each salt shows distinctive properties to the parent drug. Usually the salt-forming agents are selected by testing and experience according to the cost of raw materials, simplicity of crystallization and the amount of yield produced.

It has been estimated that approximately 50% of all drug molecules marketed as medicinal products are administered in a form of salts. This simple statistic shows that salt formation of drug substances is a central pre-formulation process and it must be associated with significant advantages. Certainly, many drug molecules are characterised by undesirable physicochemical properties that can be effectively improved by converting a basic or acidic drug into a salt form.

Salts formation offer many advantages to the pharmaceutical products as it can improve the solubility, dissolution rate, permeability and efficacy of the drug. In addition, salts can help in the improvement of the hydrolytic and thermal stability. Also salts play an important role in targeted drug delivery of dosage form (e.g. in the cases of controlled release dosage forms). Furthermore, the organoleptic properties of the active pharmaceutical ingredients (e.g. taste acceptability can be modified by salt formation). It has been also stated that salts reduce the pain of injection (e.g. Morphine, diethylamine, N-methyl glucamine salts of cephalosporin).

2 Concept of Salt Formation
The process of salt formation is relatively simple and involves, in essence, pairing the parent drug molecule with an appropriate counterion. The essential prerequisite is the presence of ionisable functional groups in the drug's structure that allow sufficient ionic interaction between the drug and the salt former. The charged groups in the structure of the drug and the counterion are attracted by ionic intermolecular forces. At favourable thermodynamic conditions, the salt is precipitated in the crystallised form.

3 Salt former selection
The choice of the salt forming agent is dictated by a number of criteria that the salt is intended to meet. Formulation (dosage form) type may influence this choice – for solid dosage forms, oral solutions, and injectables, highly soluble hydrochlorides and mesylates can be chosen. Alternatively, for suspensions, relatively insoluble counterions such as embonate, estylate, and tosylate may be preferred.
Fig 1. Diagrammatic representation of salt formation process

Additionally, the molecular weight of the counterion may also play a role as for high-dose (low-potency) drugs ions of a low molecular weight are preferred, while for low-dose (potent) drugs the molecular weight of the counterion is not usually an issue. Moreover, the immediate drug release profile usually requires hydrochloride and sodium, while slow drug release is usually achieved with large and relatively insoluble counterions such as embonate, estylate, and tosylate.

Furthermore, the therapeutic indications of the drug is a limiting factor as the intake of some ions such as sodium is restricted in conditions such as hypertension and diabetes. Importantly, salt formers should also meet regulatory requirements. For example, counterions should not have adverse safety implications as well as they should not be characterised by known of potential toxicity (e.g. lithium).

The choice may also be influenced by intellectual property rights as commercial use of previously patented salt forms is restricted. Finally, marketing issues may an impact on the drug formulation choice or change, what may consequently influence the salt former used in order to achieve the desired dosage form presentation.

The degree of ionization is also considered to be a critical parameter for salt selection, where the difference in the pKa values of the drug and counterion are important for successful salt formation. For the synthesis of salt forms of basic drugs, the pKa of the counterion is required to be at least 2 pH units lower than the pKa of the drug. Conversely, for the synthesis of salt forms of acidic drugs, the pKa of the counterion should be at least 2 units higher than the pKa of the drug.

This rule of difference in pKa of the ionisable group of the drug molecule and of the salt former (acid or base) is to confirm that the proton transfer is energetically favourable. When that difference is significantly small, a complex may form but it may rapidly dissociate in an aqueous environment back into the drug and salt former components with no desirable influence on the drug properties.

4 Salt selection process

In the pre-formulation stages of drug development multiple salt forms can be prepared for a drug that is to be developed. Those salt forms need to be compared with regard to their physicochemical and biopharmaceutical properties. The main aim of the process is to choose an optimal salt form that will ensure the most desirable properties for processing, storage, and product performance.

Morris et al developed a multi-staged approach by allowing effective and efficient salt screening. Every tier of the process is designed to test different physicochemical properties and the analysed salts can be rejected or progressed to the subsequent stages based on their performance.

The first stage of salt selection is the crystallinity assessment. Crystalline structure is associated with a higher stability and therefore the properties of a crystalline salt may be expected not to vary extensively during transportation, handling, storage, and use. However, the amorphous salt form may have advantages (e.g. improved solubility profile).

After that, the hygroscopicity profile of the salt form is evaluated to define the degree of variability of the properties in the varying humidity conditions. The salt forms with appropriate hygroscopicity profiles are subsequently evaluated for their solubility. The acceptable salts are tested for their physicochemical stability that includes polymorphic stability and excipient compatibility.

Subsequently, polymorphism of the salt forms is investigated and its influence on the variability of salt’s properties is assessed. After the stage of polymorphism assessment, the acceptable salt forms are tested for process control, economic feasibility, and processability. At this stage the parameters of corrosiveness, taste, wettability, and flowability are assessed.

Finally, the selected salt form is tested in regard to its pharmacological properties (onset and the duration of activity) and drug release profile. These stages may be followed by safety studies. Upon satisfying completion of the tests, the optimal salt form will enter pre-clinical and clinical testing phases.

5 Effects of salt formation

Salt forms of drugs have significant effects on physicochemical properties of the drug influencing its quality, safety, and performance. Importantly, different salt forms rarely change drug’s pharmacological properties.
One of the main effects is the drug’s increased solubility and dissolution rate. If the drug is a weak base and formulated as a salt, its solubility and dissolution rate will increase in the intestine (pH ca. 7.0) due to the buffering action of the salt. Namely, upon dissolution the salt form will release protons to the medium decreasing the pH of the drug’s microenvironment (drug’s microclimate or diffusion layer) and increasing the dissolution rate of the basic drug. Conversely, if the drug is a weak acid, upon dissolution in the stomach (pH ca. 1.5), its salt will increase the pH of the drug’s microenvironment resulting in a higher dissolution rate of the acidic drug.\(^4\)

For example, the sodium salt form of an oral hypoglycaemic agent tolbutamide is known to dissolve 5,000 times faster in acidic media if compared to the free acid. Similarly, the sodium salt of a non-steroidal anti-inflammatory drug naproxen has a better solubility profile if compared with the free acid form and as a result of that the salt form is absorbed faster. Analogically, strongly acidic salt forms of weakly basic drugs such as chlorpromazine and ranitidine\(^10\) (as hydrochlorides) have enhanced dissolution profiles in gastric and intestinal media if compared to the free base forms.

Other desirable physicochemical effects of salt formation include improved thermal, hydrolytic, and photo-stability, enhanced organoleptic properties, and improved compactibility. Furthermore, salt formation may be used to achieve a controlled release of a drug through the control of the drug microenvironment’s pH that is independent of the varying bulk pH (as demonstrated with salicylic acid, benzoic acid, and sulfathiazole). Moreover, targeted drug delivery to the colon can be achieved by forming salts and thus availing the reduced absorption of the ionised drug\(^5\).

Despite the vast application of salts, salt formation may have a number of undesirable effects on the drug’s properties and ultimately affect its performance in vivo. Firstly, as counterions are therapeutically inactive, the proportion of the drug in the formulation is decreased resulting in higher powder volumes for capsule loading and tablet compaction. These in turn can result in larger dosage units and consequently pose problems at administration\(^14\).

Moreover, introducing counterions to the drug structure may result in the increased formation of hydrates and polymorphs what ultimately leads to increase in variability of the drug’s pharmaceutical properties. Furthermore, salts prepared from strong acids and bases are usually highly hygroscopic posing problems with storage and reducing product’s shelf life\(^14\).

In addition, salts may cause problems with corrosiveness resulting in impaired manufacturing process (e.g. hydrochloride salts may cause deterioration of the punch tooling). What is more, hydrochloride salts may experience reduced dissolution rate and solubility in the stomach due to precipitated free acid or base at the surface of the solid dosage form\(^4\).

Finally, as salt forms are ionised species their partitioning into lipophilic phases may be reduced. This may in turn reduce their permeability through biological membranes (such as gastro-intestinal membranes) and consequently reduce absorption and drug’s bioavailability. However, drug’s bioavailability may be improved through salt formation, what was achieved with piroxicam (formulated as an ethanolamine salt)\(^15\).

6 Conclusion

Selecting an ideal salt form is a very essential step to guarantee a successful development of a highly safe and efficient drug product. A well designed screening plan is required to meet the essential and desirable criteria that set the standard for salt screening. Furthermore, the selection processes of the salt must also measure the regulatory and marketing considerations to balance the drug's physicochemical and biopharmaceutical properties against commercial considerations.

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8 References


