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Handbook of
Pharmaceutical Salts
Properties, Selection, and Use

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Chapter 6

Salt-Selection Strategies

by Abu T. M. Serajuddin* and Madhu Pudipeddi

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1. Introduction

Because of the introduction of combinatorial chemistry and high-throughput screening (HTS) during the past ten years, the pharmaceutical in-

dustry is going through a revolutionary change in the way it has been discovering and developing drugs [1]. Larger, more lipophilic, and less water-soluble leads are being selected as a result of the quest for more potent and highly specific molecules. The widespread use of dimethyl sulfoxide (DMSO) in HTS also favors the selection of lipophilic, water-insoluble compounds, which are easily solubilized in this solvent. Since some of the attributes of newer drug molecules are unfavorable to their development as dosage forms, the 'developability' is becoming a critical consideration for the transition of a chemical entity from the discovery phase to the development phase [2] [3]. There is now a greater collaboration between discovery and development scientists in evaluating such developability criteria as solubility, dissolution rate, stability, permeability, and so forth, for the selection of optimal-development candidates. Since, as mentioned in *Chapt. 2*, salt formation can improve solubility and dissolution rate of basic and acidic drugs, thus increasing their absorption rate and bioavailability, we will present in this chapter various strategies for the selection of optimal salt forms for new drug candidates. The physicochemical principles to be described in this chapter will also be helpful in identifying acidic or basic drug candidates that can form more developable salts.

The salt selection should be viewed as a part of the overall objective of selecting the 'optimal form' of a drug candidate for development. When one refers to the optimal form, it involves both chemical and physical forms. A new chemical entity can be an acid, a base, or a neutral species. If it is a neutral species, there are no options for chemical manipulation to make it more developable other than possibly preparing prodrugs. On the other hand, if it is an acid or a base, one can select the free acid or base form, or, alternatively, one can select a salt form. In the selection of free vs. salt form, questions that need to be answered are: Is the acid or base form preferred because of biopharmaceutical considerations? Is the salt form more suitable? Is the preparation of stable salt forms feasible? Among various potential salt forms of a particular drug candidate, which has the most desirable physicochemical and biopharmaceutical properties?

Along with the evaluation of chemical form, the strategy for the selection of physical form must also be considered. One needs to determine whether the compound exists in crystalline or amorphous form, and, if crystalline, whether it exhibits polymorphism. One also needs to investigate: Does the compound exist in hydrate or solvate form? If so, how is such a form affected by temperature and moisture? How stable is a particular form in solid state and in solution? The ultimate selection of the 'optimal form' of a new drug candidate for development depends on a balance among the physicochemical properties of its various available chemical and physical forms.

been discovered. Water-soluble and high-boiling (DMSO) compounds, attributes of dosage forms, transition of phase [2] [3]. Development of dissolution rate, development of improve solubility their various strategies. The objective of

When one form is a new one, it is more difficult to handle, if it is an alternative question because of the preparation of a chemical and the selection of the form to determine if crystallization is such a particular form among the physical

Another critical element of a salt-selection process in any drug-development program is the timing. Here, the critical questions are: When does one start salt selection? Should a new drug candidate be selected after consideration of its feasibility for salt formation? Or should any such consideration be postponed, until the new candidate has been selected and forwarded to the development stage? How can the salt selection be integrated in the development process such that it does not become a rate-limiting step or does not extend development time?

The success of a salt-selection program also depends on how various disciplines within drug discovery and development interact and collaborate. The composition of a salt-selection team and the responsibilities of individual team members may have profound effects on time and resources spent on a salt-selection program.

Based on the above considerations, salt-selection strategies for new drug candidates may have the following components:

- i) selection of chemical forms of salts,
- ii) selection of physical forms of salts,
- iii) salt-selection timing,
- iv) composition of salt-selection team

In the present chapter, strategies for the selection of chemical forms of salts will be described in detail. Strategies for the selection of physical forms will be discussed in less detail, since *Chapt. 3* and *7* will also cover several aspects of these strategies. Salt-selection timing and composition of salt-selection teams will be discussed only briefly, since no clear picture of how these are practiced in various drug companies has emerged yet.

2. Selection of Chemical Forms of Salts

At the outset of any salt-selection program, it is important to determine whether a particular acid or base is amenable to salt formation. If the salt formation appears to be feasible, the question then arises is which one of the many available counter-ions would be most suitable for the purpose. Some of these issues will be addressed in this section.

2.1. Feasibility Assessment for Salt Formation

No predictive procedure to determine whether a particular acidic or basic drug would form a salt with a particular counter-ion has been reported in the literature. *Anderson* and *Flora* [4] reported that successful salt formation gen-

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