International Union
of Pure and Applied Chemistry (IUPAC)

Handbook of

Pharmaceutical Salts

Properties, Selection, and Use

P. Heinrich Stahl, Camille G. Wermuth (Eds.)

Verlag Helvetica Chimica Acta · Zürich

WILEY-VCH

Weinheim · New York · Chichester
Brisbane · Singapore · Toronto

Dr. P. Heinrich Stahl
Lerchenstrasse 28
D-79104 Freiburg im Breisgau

Prof. Camille G. Wermuth
Louis Pasteur University, Strasbourg
Faculty of Pharmacy
74, route du Rhin
F-67400 Illkirch

Published jointly by
VHCA, Verlag Helvetica Chimica Acta, Zürich (Switzerland)
WILEY-VCH, Weinheim (Federal Republic of Germany)

Editorial Directors: Thomas Kolitzus, Dr. M. Volkan Kisakürek
Production Manager: Norbert Wolz

Cover Design: Bettina Bank

Library of Congress Card No. applied for.

A CIP catalogue record for this book is available from the British Library.

Die Deutsche Bibliothek – CIP-Cataloguing-in-Publication-Data

A catalogue record for this publication is available from Die Deutsche Bibliothek

ISBN 3-906390-26-8

Printing: Konrad Triltsch, Print und Digitale Medien, D-97199 Ochsenfurt-Hohestadt
Printed in Germany

TICAL SALTS:

a, D. Hensch-
dag, Heidelberg,

Klaassen, 5th

senschaftsver-

1962, *51*, 509.

based on EU
of revision: EU
ion (EU).

Chapter 6

Salt-Selection Strategies

by **Abu T. M. Serajuddin*** and **Madhu Pudipeddi**

Contents

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.

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-

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.