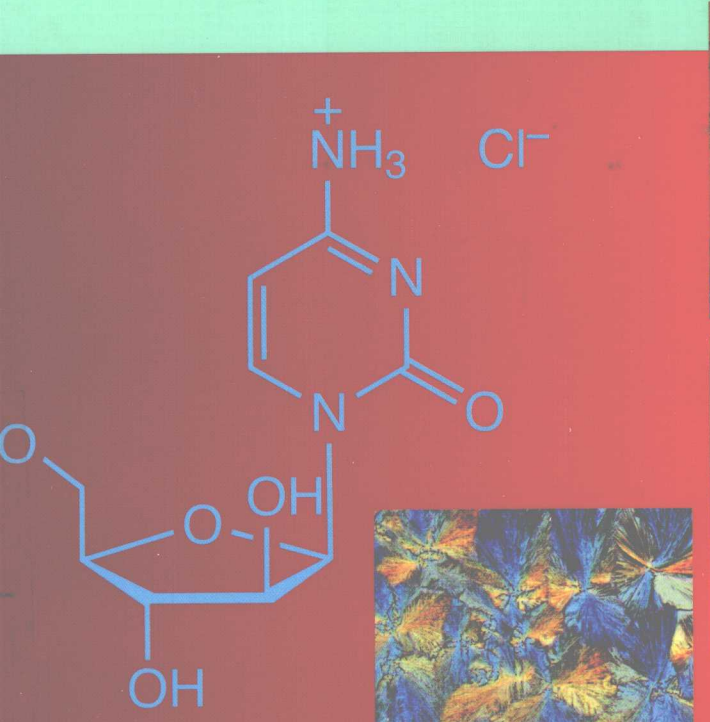
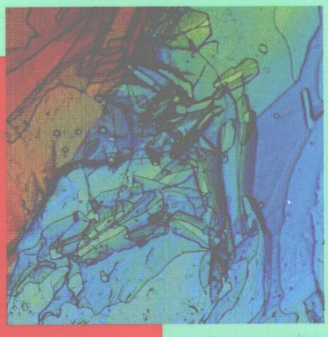
International Union
of Pure and Applied Chemistry (IUPAC)

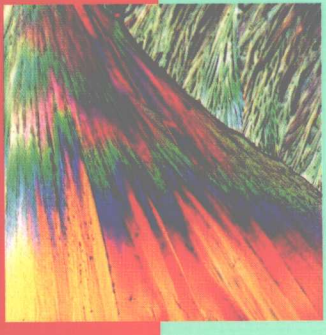
P. Heinrich Stahl, Camille G. Wermuth (Eds.)

Handbook of Pharmaceutical Salts

Properties, Selection, and Use







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Second, Revised Edition

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Properties, Selection, and Use

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

Second, Revised Edition

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Foreword

Salt formation is a widely used technique to modify and optimize the physicochemical properties of an ionizable compounds in research or development. Properties such as solubility, dissolution rate, hygroscopicity, stability, impurity profiles, and crystal habit can be influenced by using a variety of pharmaceutically acceptable counter-ions. Even polymorphism issues can be resolved in many cases by formation of salts. The crystal structure of a salt is usually completely different from the crystal structure of the conjugate base or acid, and also differs from one salt form to another. Modification of physicochemical properties such as solubility and dissolution rate through salt formation may also lead to changes in biological effects such as pharmacodynamics and pharmacokinetics, including bioavailability and toxicity profiles.

Owing to dramatic changes in the techniques applied in pharmaceutical discovery programs over the past 20 years, the physicochemical properties of development candidates have changed substantially. Drug design based on high throughput screening has in general led to more lipophilic compounds exhibiting low aqueous solubility. There are many well-known formulation techniques to increase aqueous solubility, *e.g.*, micronization, nano-sizing, or complexation with cyclodextrins. The use of solid solutions and solid dispersions is another way to improve bioavailability for development candidates with low solubility. Nevertheless, formation of salts is one of the few chemical techniques which can change aqueous solubility and dissolution rate without changing the structure of the API, and which can be invoked not only for oral but also parenteral administration. Additionally, the generation of a salt form may lead to additional advantages such as reduced hygroscopicity, better stability, improved crystallinity, and a reduction in the tendency to form polymorphs. As a result, salt screening and selection is an important step at the interface between pharmaceutical research and development. In recent years, the number of counter-ions being considered for formation of pharmaceutical salts has increased considerably, away from the standard '*sodium for acids, hydrochloride for bases*' to more exotic choices, as reflected by the newer entries in the *Orange Book* and other regulatory sources. The continuing enthusiasm for salts is underscored by the large number of articles covering physicochemical properties of pharmaceutical salts and

methods for salt screening that have been published in recent years. However, the fundamental resource for those working in the field of pharmaceutical salts remains the *Handbook of Pharmaceutical Salts*.

In the revised edition, Dr. *Stahl* and his co-authors have made a major effort to address the needs of industrial scientists, introducing chapters on automated screening techniques and large-scale salt manufacture. Moreover, the chapters concerning pharmaceutical and biological aspects of salt selection, patenting salts, and getting them through regulatory hurdles have been updated to reflect current thinking and regulations in these areas. The monographs on acids and bases have also been extended. All in all, this book represents a timely update of a genuine classic in the pharmaceutical literature, which will dovetail with the recent upswing in interest in pharmaceutical salts.

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Preface

The origin of this book goes back to a proposition made by one of us (*C. G. W.*) at a meeting of the *Medicinal Section of Division VII* of *IUPAC* to write useful handbooks for medicinal chemists. Among the topics suggested, the preparation of pharmaceutically acceptable salts was rapidly considered as important and timely. As a matter of fact, an estimated half of all drug molecules used in medicine are administered as salts. The salt formation of drug candidates has been recognized as an essential preformulation task, as the selection of a suitable salt prior to the initiation of dosage form development has become a decision point in the netplans of the Preclinical Phase of modern drug development. Surprisingly, however, a chemist in search of a book dealing with the preparation, significance, and selection of pharmaceutically active salts will fail to find one, and also the scientific literature on this topic is rather limited and scattered across many journals and patents. On the other hand, the majority of medicinal chemists working in the pharmaceutical industry are organic chemists whose main concern is to design and to synthesize novel compounds as future drug entities. While they focus on this challenging primary goal, salt formation is often restricted to a marginal activity with the short term aim of obtaining nicely crystalline material. Moreover, chemists are not explicitly trained in the various aspects of pharmaceutical salts and their inherent opportunities. By bringing together the necessary theoretical foundations and a lot of practical experience, the objective of the present book is to fill this long felt gap in the pharmaceutical bibliography.

A concise introduction reviewing the various objectives pursued in forming salts is followed by contributions presenting the theoretical background of salt formation: dissociation and ionic equilibria, solubility and dissolution (*Chapt. 1* and *2*), basics and the evaluation of solid-state properties (*Chapt. 3*), safety and biopharmaceutical as well as pharmaceutical-technological aspects (*Chapt. 4* and *5*). *Chapt. 6–9* reflect the practice of salt formation in an industrial research and development environment. They describe salt selection strategies, industrial large scale aspects of salt production, and the significance of salt formation in industrial processing. The involvement of authorities is dealt with in *Chapt. 10* and *11*, which are devoted to patent and regulatory issues, respectively. Addressing the practitioners at the lab bench, the last chapters of the book feature practical examples of preparation of salts

presented in the style of model procedures (*Chapt. 12*) and a comprehensive annotated compilation of the individual salt-forming acids and bases with their relevant properties (*Chapt. 13*), followed by an *Appendix* containing tables with the acids and bases sorted alphabetically, and by pK_a values and supplemented with other useful facts and data.

Altogether, these chapters reflect the multidisciplinary character of formation and selection of suitable salt forms of drug substances. An attempt is made to establish an up-to-date guide and source of information not only serving medicinal chemists, but also all the other scientists who are involved in the research and development of drugs and their pharmaceutical dosage forms.

A book dealing with such a truly interdisciplinary subject relies on contributions of a well-coordinated team of authors from industry and academia representing the various disciplines involved in the process of drug-salt formation and selection for pharmaceutical products in an industrial environment. The editors wish to thank all the authors for their engaged cooperation and their patience during the revision procedures that were necessary to arrive at this comprehensive and well-balanced handbook. Thanks are also due to *F. O. Ajayi*, *H. Asche*, and *C. Hoff*, who accepted to contribute to the book in the very last moment. The editors wish to acknowledge the smooth and excellent cooperation with *Verlag Helvetica Chimica Acta* in the preparation of the volume: *Thomas Kolitzus*, Assistant Editor, for his patient and attentive handling of all the practical details of the editorial process, and Dr. *M. Volkan Kisakürek*, Managing Director and Editor-in-Chief, for his inspiration and for his untiring scrutiny in bringing his considerable comprehensive knowledge into this project. Thanks are also expressed to *Larry Lesko* of the U. S. Food and Drug Administration for establishing helpful contacts. One of the editors (*P. H. S.*) gratefully acknowledges the support granted by *Novartis AG*, Basel, and the permission to use their Scientific Library facilities.

Camille G. Wermuth and *P. Heinrich Stahl*
Strasbourg and Freiburg, January 2002

Preface to the 2nd Edition

Admittedly, salt formation and selection is but a narrow step, an almost point-like spot, when compared to the curriculum of an NCE, a '*new chemical entity*', on its way to become an API, an '*active pharmaceutical ingredient*', counting years from the research chemist's laboratory bench to the final product ready to be used in therapy. Yet, it constitutes an important decision point with far-reaching consequences in further product development. This handbook germinated in the Preformulation Laboratory at *Ciba* in the early 1970s and grew its first leaves in 1992 as a *Guide to Salt Formation of Drug Substances* for the Research Chemists within *Ciba-Geigy*, Basel. Thanks to *Camille Wermuth*, then Professor of Pharmaceutical Chemistry at the University of Strasbourg, those early efforts could be merged to a full-size Handbook project, which he carried forward under the auspices of *IUPAC*, as the head of the Section of Medicinal Chemistry. The first edition of this book has been well accepted by the scientists active in the various disciplines of the pharmaceutical industry as a guide and support for such decisions, and likewise useful in academic teaching and for authorities as well.

The present 2nd edition accounts for advances achieved in the field. While the basic theoretical chapters of salt formation, solubility, and dissolution remain unchanged, and those reporting on past experience have been retained, a new chapter describing the advanced laboratory techniques enabling HTE (high-throughput evaluation) of API solid-state search has been included, reflecting current industrial practice that combines salt *and* polymorphism screening. The chapter on large-scale production of API salts, addressing the salt-specific particulars, was written by a new author who addresses real salt-specific issues encountered in industrial processing. Also, new authors could be gained to present the current status of the regulatory aspects in the USA and the EU. More examples for preparing salts were added to the *Selected Procedures for Salt Formation*, and, wherever possible, the former contributions were updated, and errors, admittedly present, were eliminated. Also, a few additional items and numerous detail data have amended the salt-former monographs, particularly appreciated by the users.

The Editor of this edition is particularly grateful to the authors who contributed new chapters or updated existing ones. In view of the increasing workload of all scientists in the present-day industrial environment, their

willingness to accept and shoulder such an extra task of sharing their knowledge and experience, in written form, with the community of fellow scientists and practitioners deserves high acknowledgement. At this point, we wish to express our deep regret that Professor *David J. W. Grant* passed away in December 2005. He had contributed to three chapters in the first edition which remain unchanged. We will miss him as an outstanding scientist and friendly advisor.

The Editor wishes to thank *Larry Lesko* of the *U.S. Food and Drug Administration* for establishing contacts, for a second time, to first-hand specialists in Regulatory Affairs within the authority.

During the preparation of this 2nd edition, the Editor could again fully rely on the friendly, helpful, and encouraging cooperation with *M. Volkan Kisakürek* and *Thomas Kolitzus* of *Verlag Helvetica Chimica Acta*. Their competence, patience, thorough and careful handling of the manuscripts, as well as their readiness to solve problems are highly appreciated and deserve particular thanks.

P. Heinrich Stahl
Freiburg im Breisgau, January 2011

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Introduction

by **Camille G. Wermuth** and **P. Heinrich Stahl**

When the first 'vegetable alkalis', those nitrogen-containing bases later termed alkaloids, were extracted from plant materials, they were isolated and purified as well-crystallizing salts. In contrast to the free bases, the salts were found to be water-soluble and also more stable. Such properties qualified the salts of these biologically highly active compounds as the preferred forms for use as therapeutic agents (morphine hydrochloride, atropine sulfate, quinine sulfate, pilocarpine nitrate, codeine phosphate, to name only a few of them). If we turn to endogenous biological agents, we see that almost all neurotransmitters, which are biogenetically derived from amino acids, are also nitrogenous bases able to form salts. Nitrogenous functional groups are present in many synthetic drugs that mime the neurotransmitters and account for the old adage 'no medicaments without nitrogen'. This assertion is certainly exaggerated as it excludes therapeutic agents such as the steroids, the prostaglandins and their derivatives, also the fibrates and acidic anti-inflammatory drugs like aspirin, diclofenac, and ibuprofen. Many of these classes of drugs contain a carboxylic function, and, therefore, salt formation can evidently also be considered.

An estimated half of all the drug molecules used in medicinal therapy are administered as salts, and salification of a drug substance has become an essential step in drug development. The solid-state properties of a drug, as well as its properties in solution, can be modified by salt formation. Therefore, the search for a suitable salt form is important, and salt selection may have far-reaching consequences and can open new opportunities. In modern pharmaceutical research and development, a variety of objectives are pursued in the formation of salts. The most important of these objectives and points to be considered, as they become significant along the pathway of the development of a new drug, are reviewed here.

Improving Solubility

Before undergoing pharmacological evaluation and other preclinical studies, synthetic or natural active principles must usually be dissolved. In the majority of cases, the objective is to render the compound water-soluble.