Handbook of PHARMACEUTICAL EXCIPIENTS

Third Edition

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Preface

Pharmaceutical dosage forms contain both active ingredients and inactive materials called excipients. The behavior of the dosage form is dependent on process variables and the interrelationship between the various excipients and their impact on the active ingredient. Suppliers of excipients have developed novel excipient mixtures and new physical forms of excipients, which give them improved characteristics. In addition, the international nature of the pharmaceutical industry and its suppliers demands that formulators throughout the world have as much information as possible about the chemical and physical nature of excipients and combinations of excipients. Formulators are also concerned about the effect of the finished product on the patient it is intended to treat. Therefore, they are concerned about general and specific toxic effects of the excipients, allergic reactions to excipients, disease-specific intolerance to excipients and interactions between the excipient and the active ingredient. In addition, formulators need to be aware of the potential environmental impact of the use of excipients. Lastly, the effect of regulatory change associated with harmonization is also a concern of the professional formulator.

The *Handbook of Pharmaceutical Excipients* is a joint publication of the American Pharmaceutical Association and the Royal Pharmaceutical Society of Great Britain. The *Handbook of Pharmaceutical Excipients,* originally published in 1986, was the first English-language publication to comprehensively and systematically describe the chemical and physical properties of pharmaceutical excipients. The first edition contained 145 monographs, and the second contained 203. The present edition contains 210 monographs authored by experts in pharmaceutical formulation or excipient manufacture from around the world. This edition also contains the results of extensive laboratory testing carried out over the last two years in laboratories in Great Britain and the United States. Some data developed by the first edition's laboratory project are retained. It is clearly noted as such in the monographs. The new data generated for this edition should help the formulator in the selection of appropriate excipients for various dosage forms. A major development since the publication of the last edition of the *Handbook* has been the trend towards global pharmaceutical harmonization. To reflect this, where appropriate, more detailed information on excipients used in Japan has been included in this edition. Additionally the index has been revised and expanded and the suppliers' directory has been completely updated.

The *Handbook of Pharmaceutical Excipients* collects in a systematic and uniform manner essential data on the physical properties of excipients such as: boiling point, bulk and tap density, compression characteristics, hygroscopicity, flowability, melting point, moisture content, moisture-absorption isotherms, particle size distribution, rheology, specific surface area, and solubility. Scanning electron microphotographs (SEMs) are also included for many of the excipients. The *Handbook* contains information from various international sources, but also includes laboratory data determined specifically for the *Handbook* and personal observation and comments from the monograph author, steering committee members, and the editor. It also contains information on the safe use and potential toxicity of the materials.

All of the monographs in the *Handbook* are thoroughly cross-referenced and indexed so that excipients may be identified by either a chemical, nonproprietary, or trade name. Most monographs list related substance(s) to help the formulator develop a list of possible materials for use in a new dosage form or product. Related substances are not directly substitutable for each other but are excipients that have been used for similar purposes in various dosage forms.

The *Handbook of Pharmaceutical Excipients* is a comprehensive, uniform guide to the uses, properties, and safety of pharmaceutical excipients and is an essential reference source for those involved in the development, production, control or regulation of pharmaceutical preparations. Since many pharmaceutical excipients are also used in other applications, the *Handbook of Pharmaceutical Excipients* will also be of value to persons with an interest in the formulation or production of confectionery, cosmetic, and food products.

Arrangement

The *Handbook* consists of monographs that are divided into 22 sections to make it easy for the reader to go directly to the information of interest. Although it was originally intended that each monograph contain only information about a single excipient, it rapidly became clear that some substances or groups of substances must be discussed together. This gave rise to such monographs as 'Coloring Agents' and 'Hydrocarbons.' In addition, some materials have more than one monograph depending on the physical characteristics of the material due mainly to its preparation. A good example of this is the various starch monographs, particularly Starch vs. Pregelatinized Starch. Regardless of the complexity of the monograph they are all divided in 22 sections as follows:

1. Nonproprietary Names
2. Synonyms
3. Chemical Name and CAS Registry Number
4. Empirical Formula and Molecular Weight
5. Structural Formula
6. Functional Category
7. Applications in Pharmaceutical Formulation or Technology
8. Description
9. Pharmacopeial Specifications
10. Typical Properties
11. Stability and Storage Conditions
12. Incompatibilities
13. Method of Manufacture
14. Safety
15. Handling Precautions
16. Regulatory Status
17. Pharmacopeias
18. Related Substances
19. Comments
20. Specific References
21. General References
22. Authors

To make it easy for the first time user, descriptions of the sections appear below with information from an example monograph if needed.

Section 1, **Nonproprietary Names,** lists the excipient names used in the current British Pharmacopoeia, European Pharmacopeia, Japanese Pharmacopeia, and the United States Pharmacopeia. For nonpharmacopeial excipients the appropriate approved name, e.g., USAN or INN is indicated.

Section 2, **Synonyms,** lists other names for the excipient, including trade names used by suppliers; trade names are listed in italics. The inclusion of one supplier's trade name and the absence of others should in no way be interpreted as an

endorsement of one supplier's product over the other. The large number of suppliers internationally makes it impossible to include all the trade names.

Section 3, **Chemical Name and CAS Registry Number,** indicates the unique Chemical Abstract Services number for an excipient along with the chemical name, e.g., Acacia [9000-01-5].

Sections 4 and 5, **Empirical Formula and Molecular Weight** and **Structural Formula,** are self-explanatory. Many excipients are not pure chemical substances, in which case their composition is described either here or in Section 8.

Section 6, **Functional Category,** lists the function(s) that an excipient is generally thought to perform, e.g., diluent, emulsifying agent, etc.

Section 7, **Applications in Pharmaceutical Formulation or Technology,** describes the various applications of the excipient.

Section 8, **Description,** includes details of the physical appearance of the excipient, e.g., white or yellow flakes, etc.

Section 9, **Pharmacopeial Specifications,** briefly presents the compendial standards for the excipient. Information included is obtained from the British Pharmacopoeia (BP), European Pharmacopeia (PhEur), Japanese Pharmacopeia (JP), and the United States Pharmacopeia/National Formulary (USP). Information from the JP and USP are included if the substance is in those compendia. Information from the PhEur is also included. If the excipient is not in the PhEur but is included in the BP, information is included from the BP. The pharmacopeias are continually updated and revisions or supplements are published. It was necessary to select a point in time and use that as our reference when selecting the information to be included in this section. Therefore the information is from the following volumes:

BP – 1998 Edition
JP – Thirteenth Edition 1996
PhEur – Third Edition plus supplements to 1999
USP – USP 24 NF 19 2000 Edition

Since the USP and NF were combined into a single reference many years ago it was felt that a single abbreviation would be sufficient. Therefore throughout the *Handbook* whenever the USP abbreviation is used it refers to this combined text.

Section 10, **Typical Properties,** describes the physical properties of the excipient which are not shown in Section 9. All data are for measurements made at 20°C unless otherwise indicated. Where the solubility of the excipient is described in words, the following terms describe the solubility ranges:

Very soluble	1 part in less than 1
Freely soluble	1 part in 1-10
Soluble	1 part in 10-30
Sparingly soluble	1 part in 30-100
Slightly soluble	1 part in 100-1000
Very slightly soluble	1 part in 1000-10 000
Practically insoluble or insoluble	1 part in more than 10 000

Experimental data were determined specifically for the *Handbook* and are included in this section. Data from the HPE Laboratory Project in support of the third edition are clearly marked as such. The methods that were used to collect that data are included in **Appendix II: HPE Laboratory Methods**. Data from the HPE Laboratory Project performed for the first edition are either replaced by the new data or referenced as such in each monograph. The reader is referred to the earlier editions of this book for the methods used.

Section 11, **Stability and Storage Conditions,** describes the conditions under which the bulk material as received from the supplier should be stored. In addition some monographs report on storage and stability of the dosage forms that contain the excipient.

Section 12, **Incompatibilities,** describes the reported incompatibilities for the excipient either with other excipients or with active ingredients. If an incompatibility is not listed it does not mean it does not occur but simply that it has not been reported or is not well known. Every formulation should be tested for incompatibilities prior to use in a commercial product.

Section 13, **Method of Manufacture,** describes the common methods of manufacture and additional processes that are used to give the excipient its physical characteristics. In some cases the possibility of impurities will be indicated in the method of manufacture.

Section 14, **Safety,** describes briefly the types of formulations in which the excipient has been used and presents relevant data concerning possible hazards and adverse reactions that have been reported. Relevant animal toxicity data are also shown.

Section 15, **Handling Precautions,** indicates possible hazards associated with handling the excipient and makes recommendations for suitable containment and protective methods. A familiarity with current good laboratory practice (GLP) and current good manufacturing practice (GMP) and standard chemical handling procedures is assumed.

Section 16, **Regulatory Status,** describes the accepted uses in foods and licensed pharmaceuticals where known. The status of excipients varies from one nation to another, even in this time of harmonization. Dependence on this reference in place of checking with the regulatory body in the nation in which the product is to be sold is unwise.

Section 17, **Pharmacopeias,** lists the pharmacopeias in which the excipient is listed. If the excipient is listed in the European Pharmacopeia (PhEur), countries that are party to the PhEur are not listed; only "Eur" is. The following countries are party to the PhEur: Austria, Belgium, Bosnia-Herzegovina, Croatia, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, the Netherlands, Norway, Portugal, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, the United Kingdom of Great Britain and Northern Ireland, and the former Yugoslav Republic of Macedonia. The information from the four major pharmacopeias is listed in Section 9.

Section 18, **Related Substances,** lists the excipients similar to the excipient discussed in the monograph. The reader should look at the monographs for the related substance for comparative information.

Section 19, **Comments,** includes additional information and observations relevant to the excipient. Where appropriate, the different grades of the excipient available are discussed. Comments are the opinion of the listed author(s) unless referenced or indicated otherwise.

Section 20, **Specific References,** is a list of references cited within the monograph.

Section 21, **General References,** lists references which have general information about this type of excipient or the types of dosage forms made with these excipients.

Section 22, **Authors,** lists in alphabetical order the current authors of the monograph. Authors of previous editions can be found in the earlier editions.

Acknowledgments

This edition of the *Handbook of Pharmaceutical Excipients* is the result of the efforts of many individuals and corporations. The publication of the *Handbook* continues to depend on the support of hundreds of scientists throughout the world who act as authors or members of the HPE Laboratory Project and the members of the two steering committees. The members of the US and UK steering committees reviewed all the monographs and contributed to their overall quality. Without the energetic and enthusiastic effort by these two steering committees this book would be impossible to produce. Specifically I would like to thank the chair of the UK steering committee Paul Weller from the Royal Pharmaceutical Society of Great Britain staff who was the co-editor of the second edition. His work on that edition and his advice on every aspect of this edition made my job much easier. In addition, this edition had extensive laboratory work done by the HPE Laboratory Project headed by Anthony Palmieri III. It is rare in life to find an individual such as Tony who is both a good and dear friend and an accomplished colleague. Many others have contributed to the project and their assistance is appreciated, especially Linda Svok of my staff and Julian Graubart from the American Pharmaceutical Association.

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