Handbook of PHARMACEUTICAL EXCIPIENTS

Third Edition

Edited by

Arthur H. Kibbe, Ph.D.
Professor and Chair
Department of Pharmaceutical Sciences
Wilkes University School of Pharmacy
Wilkes-Barre, Pennsylvania

American Pharmaceutical Association
Washington, D.C.

London, United Kingdom

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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.

Arthur H. Kibbe
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Anthony Palmieri III
June 1999

Notice to Readers

The *Handbook of Pharmaceutical Excipients* is a reference work containing a compilation of information on the uses and properties of pharmaceutical excipients and the reader is assumed to possess the necessary knowledge to interpret the information the *Handbook* contains. The *Handbook* has no official status and there is no intent, implied or otherwise, that any of the information presented should constitute standards for the substances. The inclusion of an excipient in the *Handbook*, or a description of its use in a particular application, is not intended as an endorsement of that excipient or application. Similarly, reports of incompatibilities or adverse reactions to an excipient, in a particular application, may not necessarily prevent its use in other applications. Formulators should perform suitable experimental studies to satisfy themselves and regulatory bodies that a formulation is efficacious and safe to use.

While considerable efforts were made to ensure the accuracy of the information presented in the *Handbook* neither the publishers nor the compilers can accept liability for any errors or omissions. In particular, the inclusion of a supplier within the Suppliers' Directory is not intended as an endorsement of that supplier or its products and similarly the unintentional omission of a supplier or product from the directory is not intended to reflect adversely on that supplier or its product.

Although diligent effort was made to use as recent compendial information as possible, compendia are frequently revised and the reader is urged to consult current compendia, or supplements, for up-to-date information, particularly as efforts are currently in progress to harmonize standards for excipients.

The laboratory data presented for a particular excipient reflects only the results of testing a particular batch or sample and may not be representative of other batches or samples.

Relevant data and constructive criticism are welcome and may be used to assist in the preparation of any future editions of the *Handbook*. The reader is asked to send any comments to the Editor, Handbook of Pharmaceutical Excipients, Royal Pharmaceutical Society of Great Britain, 1 Lambeth High Street, London SE1 7JN, UK, or Editor, Handbook of Pharmaceutical Excipients, American Pharmaceutical Association, 2215 Constitution Avenue, N.W., Washington, DC 20037-2985.

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A selection of publications which contain information on pharmaceutical excipients is listed below:

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Abbreviations

Some units, terms, and symbols are not included in this list as they are defined in the text. Common abbreviations have been omitted. The titles of journals are abbreviated according to the general style of the *Index Medicus*.

≈ — approximately.
Ad — Addendum.
ADI — acceptable daily intake.
approx — approximately.
atm — atmosphere.
Aust — Austrian.
BAN — British Approved Name.
Belg — Belgian.
b.p. — boiling point.
BP — British Pharmacopoeia.
Br — British.
Braz — Brazilian.
BS — British Standard (specification).
BSI — British Standards Institution.
cal — calorie(s).
CAS — Chemical Abstract Service.
CFC — chlorofluorocarbon.
cm — centimeter(s).
cm^2 — square centimeter(s).
cm^3 — cubic centimeter(s).
cmc — critical micelle concentration.
CNS — central nervous system.
cP — centipoise(s).
cSt — centistoke(s).
CTFA — Cosmetic, Toiletry, and Fragrance Association.
D&C — designation applied in USA to dyes permitted for use in drugs and cosmetics.
DoH — Department of Health (UK).
DSC — differential scanning calorimetry.
EC — European Community.
e.g. — *exemplit gratia*, 'for example'.
et. al. — *et alii*, 'and others'.
EU — European Union.
Eur — European.
FAO — Food and Agriculture Organization of the United Nations.
FAO/WHO — Food and Agriculture Organization of the United Nations *and the* World Health Organization.
FCC — Food Chemicals Codex
FDA — Food and Drug Administration of the USA.
FD&C — designation applied in USA to dyes permitted for use in foods, drugs, and cosmetics.
FFBE — Flat face beveled edge.
Fr — French.
g — gram(s).
Ger — German.
GMP — Good Manufacturing Practice.
GRAS — generally recognized as safe by the Food and Drug Administration of the USA.
HC — hydrocarbon.
HCFC — hydrochlorofluorocarbon.
HFC — hydrofluorocarbon.
HIV — human immunodeficiency virus.
HLB — hydrophilic-lipophilic balance.
HSE — Health and Safety Executive (UK).
i.e. — *id est*, 'that is'.
IM — intramuscular.
Ind. — Indian.
INN — International Nonproprietary Name.
Int — International.
IP — intraperitoneal.
ISO — International Organization for Standardization.
It — Italian.
IV — intravenous.
J — joule(s).
JP — Japanese Pharmacopeia.
Jpn — Japanese.
kcal — kilocalorie(s).
kg — kilogram(s).
kJ — kilojoule(s).
kPa — kilopascal(s).
L — liter(s).
LAL — *Limulus* amoebocyte lysate.
LC_{50} — a concentration in air lethal to 50% of the specified animals on inhalation.
LD_{50} — a dose lethal to 50% of the specified animals or microorganisms.
Ld_{Lo} — lowest lethal dose for the specified animals or microorganisms.
m — meter(s).
m^2 — square meter(s).
m^3 — cubic meter(s).
M — molar.
max — maximum.
MCA — Medicines Control Agency (UK).
mg — milligram(s).
MIC — minimum inhibitory concentration.
min — minute(s) *or* minimum.
mL — milliliter(s).
mm — millimeter(s).
mM — millimolar.
mm^2 — square millimeter(s).
mm^3 — cubic millimeter(s).
mmHg — millimeter(s) of mercury.
mmol — millimole(s).
mN — millinewton(s).
mol — mole(s).
m.p. — melting point.
mPa — millipascal(s).
MPa — megapascal(s).
µg — microgram(s).
µm — micrometer(s).
N — newton(s) *or* normal (concentration).
Neth — Netherlands.
nm — nanometer(s).
Nord — Nordic.
o/w — oil-in-water.
o/w/o — oil-in-water-in-oil.
Pa — pascal(s).
pH — the negative logarithm of the hydrogen ion concentration.
PhEur — European Pharmacopeia.
pK_a — the negative logarithm of the dissociation constant.

Pol — Polish.
Port — Portuguese.
pph — parts per hundred.
ppm — parts per million.
psia — pounds per square inch absolute.
RDA — recommended dietary allowance (USA).
rpm — revolutions per minute.
s — second(s).
SC — subcutaneous.
SEM — scanning electron microscopy *or* scanning electron microphotograph.
SI — Statutory Instrument *or* Système International d'Unites (International System of Units).
TPN — total parental nutrition.
TWA — time weighted average.
UK — United Kingdom.
US *or* USA — United States of America.
USAN — United States Adopted Name.
USP — The United States Pharmacopeia National Formulary.
UV — ultraviolet.
v/v — volume in volume.
v/w — volume in weight.
WHO — World Health Organization.
w/o — water-in-oil.
w/o/w — water-in-oil-in-water.
w/v — weight in volume.
w/w — weight in weight.

Units of Measurement

The information below shows Imperial to SI unit conversions for the units of measurement most commonly used in the *Handbook*. SI units are used throughout the *Handbook* with, where appropriate, Imperial units reported in parenthesis.

Area
1 square inch (in^2) = 6.4516×10^{-4} square meter (m^2)
1 square foot (ft^2) = 9.29030×10^{-2} square meter (m^2)
1 square yard (yd^2) = 8.36127×10^{-1} square meter (m^2)

Density
1 pound per cubic foot (lb/ft^3) = 16.0185 kilograms per cubic meter (kg/m^3)

Energy
1 kilocalorie (kcal) = 4.1840×10^3 joules (J)

Force
1 dyne (dynes) = 1×10^{-5} newton (N)

Length
1 angstrom (Å) = 10^{-10} meter (m)
1 inch (in) = 2.54×10^{-2} meter (m)
1 foot (ft) = 3.048×10^{-1} meter (m)
1 yard (yd) = 9.144×10^{-1} meter (m)

Pressure
1 atmosphere (atm) = 0.101325 megapascal (MPa)
1 millimetre of mercury (mmHg) = 133.322 pascals (Pa)
1 pound per square inch (psi) = 6894.76 pascals (Pa)

Surface tension
1 dyne per centimeter (dyne/cm) = 1 millinewton per meter (mN/m)

Temperature
1 degree Fahrenheit (°F) = 5/9 degree Celsius (°C)

Viscosity (dynamic)
1 centipoise (cP) = 1 millipascal second (mPa s)
1 poise (P) = 0.1 pascal second (Pa s)

Viscosity (kinematic)
1 centistoke (cSt) = 1 square millimeter per second (mm^2/s)

Volume
1 cubic inch (in^3) = 1.63871×10^{-5} cubic meter (m^3)
1 cubic foot (ft^3) = 2.83168×10^{-2} cubic meter (m^3)
1 cubic yard (yd^3) = 7.64555×10^{-1} cubic meter (m^3)
1 pint (UK) = 5.68261×10^{-4} cubic meter (m^3)
1 pint (US) = 4.73176×10^{-4} cubic meter (m^3)
1 gallon (UK) = 4.54609×10^{-3} cubic meter (m^3)
1 gallon (US) = 3.78541×10^{-3} cubic meter (m^3)

Glycerin

1. Nonproprietary Names

BP: Glycerol
JP: Concentrated Glycerin
PhEur: Glycerolum
USP: Glycerin

2. Synonyms

Croderol; E422; glycerine; *Glycon G-100*; *Kemstrene*; *Pricerine*; 1,2,3-propanetriol; trihydroxypropane glycerol.

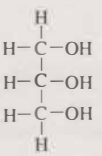
3. Chemical Name and CAS Registry Number

Propane-1,2,3-triol [56-81-5]

4. Empirical Formula Molecular Weight

$C_3H_8O_3$ 92.09

5. Structural Formula



6. Functional Category

Antimicrobial preservative; emollient; humectant; plasticizer; solvent; sweetening agent; tonicity agent.

7. Applications in Pharmaceutical Formulation or Technology

Glycerin is used in a wide variety of pharmaceutical formulations including oral, otic, ophthalmic, topical, and parenteral preparations. It is also used in cosmetics and as a food additive.

In topical pharmaceutical formulations and cosmetics, glycerin is used primarily for its humectant and emollient properties. In parenteral formulations glycerin is mainly used as a solvent.[1] In oral solutions glycerin is used as a solvent, sweetening agent, antimicrobial preservative, and viscosity-increasing agent. Glycerin is also used as a plasticizer of gelatin in the production of soft-gelatin capsules and gelatin suppositories. Glycerin is additionally employed as a therapeutic agent in a variety of clinical applications.

Use	Concentration (%)
Antimicrobial preservative	> 20
Emollient	Up to 30
Humectant	Up to 30
Ophthalmic formulations	0.5-3.0
Plasticizer in tablet film coating	Variable
Solvent for parenteral formulations	Up to 50
Sweetening agent in alcoholic elixirs	Up to 20

8. Description

Glycerin is a clear, colorless, odorless, viscous, hygroscopic liquid; it has a sweet taste, approximately 0.6 times as sweet as sucrose.

9. Pharmacopeial Specifications

Test	JP	PhEur	USP
Identification	+	+	+
Characters	+	—	+
Specific gravity	1.221-1.230	—	≥ 1.249
Color	+	—	+
Appearance of solution	—	+	—
Acidity or alkalinity	+	—	+
Refractive index	1.449-1.454	1.470-1.475	—
Residue on ignition	≤ 0.01%	—	≤ 0.01%
Sulfated ash	—	≤ 0.01%	—
Chloride	≤ 0.001%	≤ 10 ppm	≤ 0.001%
Ammonium	+	—	—
Calcium	+	—	—
Sulfate	≤ 0.002%	—	≤ 0.002%
Arsenic	≤ 2 ppm	—	≤ 1.5 ppm
Heavy metals	≤ 5 ppm	≤ 5 ppm	≤ 5 ppm
Chlorinated compounds (as Cl)	—	+	≤ 0.003%
Organic volatile impurities	—	—	+
Aldehydes	—	+	—
Acrolein, glucose and other reducing substances	+	+	—
Fatty acids and esters	+	+	+
Readily carbonizable substances	+	—	—
Sugars	—	+	—
Water	—	≤ 2.0%	≤ 5.0%
Assay	84%-87%	98-101%	99-101%

10. Typical Properties

Boiling point: 290°C (with decomposition)
Density:
1.2656 g/cm³ at 15°C;
1.2636 g/cm³ at 20°C;
1.2620 g/cm³ at 25°C.
Flash point: 176°C (open cup)
Freezing point:

Concentration of aqueous glycerin solution (% w/w)	Freezing point (°C)
10	-1.6
20	-4.8
30	-9.5
40	-15.4
50	-23
60	-34.7
66.7	-46.5
80	-20.3
90	-1.6

Hygroscopicity: hygroscopic.
Melting point: 17.8°C
Osmolarity: a 2.6% v/v aqueous solution is iso-osmotic with serum.

Refractive index:
n_D^{15} = 1.4758;
n_D^{20} = 1.4746;
n_D^{25} = 1.4730.
Solubility:

Solvent	Solubility at 20°C
Acetone	Slightly soluble
Benzene	Practically insoluble
Chloroform	Practically insoluble
Ethanol (95%)	Soluble
Ether	1 in 500
Ethyl acetate	1 in 11
Methanol	Soluble
Oils	Practically insoluble
Water	Soluble

Specific gravity:

Concentration of aqueous glycerin solution (% w/w)	Specific gravity at 20°C
10	1.024
20	1.049
30	1.075
40	1.101
50	1.128
60	1.156

Surface tension:
63.4 mN/m (63.4 dynes/cm) at 20°C.
Vapor density (*relative*): 3.17 (air = 1)
Viscosity (*dynamic*):

Concentration of aqueous glycerin solution (% w/w)	Viscosity at 20°C (mPa s)
5	1.143
10	1.311
25	2.095
50	6.05
60	10.96
70	22.94
83	111

11. Stability and Storage Conditions

Glycerin is hygroscopic. Pure glycerin is not prone to oxidation by the atmosphere under ordinary storage conditions, but decomposes on heating, with the evolution of toxic acrolein. Mixtures of glycerin with water, ethanol, and propylene glycol are chemically stable.

Glycerin may crystallize if stored at low temperatures; the crystals do not melt until raised to 20°C.

Glycerin should be stored in an airtight container, in a cool, dry, place.

12. Incompatibilities

Glycerin may explode if mixed with strong oxidizing agents such as chromium trioxide, potassium chlorate, or potassium permanganate. In dilute solution, the reaction proceeds at a slower rate with several oxidation products being formed. Black discoloration of glycerin occurs in the presence of light, on contact with zinc oxide or basic bismuth nitrate.

An iron contaminant in glycerin is responsible for the darkening in color of mixtures containing phenols, salicylates, and tannin.

Glycerin forms a boric acid complex, glyceroboric acid, which is a stronger acid than boric acid.

13. Method of Manufacture

Glycerin is mainly obtained from oils and fats as a by-product in the manufacture of soaps and fatty acids. It may also be obtained from natural sources by fermentation of, for example, sugar beet molasses in the presence of large quantities of sodium sulfite. Synthetically, glycerin may be prepared by the chlorination and saponification of propylene.

14. Safety

Glycerin occurs naturally in animal and vegetable fats and oils that are consumed as part of a normal diet. Glycerin is readily absorbed from the intestine and is either metabolized to carbon dioxide and glycogen or is used in the synthesis of body fats.

Glycerin is used in a wide variety of pharmaceutical formulations including oral, ophthalmic, parenteral, and topical preparations. Adverse effects are mainly due to the dehydrating properties of glycerin.

Oral doses are demulcent and mildly laxative in action. Large doses may produce headache, thirst, nausea, and hyperglycemia. The therapeutic parenteral administration of very large glycerin doses, 70-80 g over 30-60 minutes in adults to reduce cranial pressure, may induce hemolysis, hemoglobinuria, and renal failure.[2] Slower administration has no deleterious effects.[3]

Glycerin may also be used orally in doses of 1.0-1.5 g/kg body-weight to reduce intraocular pressure.

When used as an excipient or food additive, glycerin is not usually associated with any adverse effects and is generally regarded as a nontoxic and nonirritant material.

LD_{50} (guinea pig, oral): 7.75 g/kg[4]
LD_{50} (mouse, IP): 8.98 g/kg
LD_{50} (mouse, IV): 6.2 g/kg
LD_{50} (mouse, oral): 4.1 g/kg
LD_{50} (mouse, SC): 0.09 g/kg
LD_{50} (rat, IP): 8.3 g/kg
LD_{50} (rat, IV): 5.6 g/kg
LD_{50} (rat, oral): 12.6 g/kg
LD_{50} (rat, SC): 0.1 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. In the UK, the recommended long-term (8-hour TWA) exposure limit for glycerin mist is 10 mg/m^3.[5] Glycerin is combustible and may react explosively with strong oxidizing agents, *see* Section 12.

16. Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (inhalations, injections, nasal, ophthalmic, oral capsules, solutions, suspensions and

tablets, otic, rectal, topical, transdermal, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK.

17. Pharmacopeias

China, Eur, Int, Jpn, and US.

Eur and Int also include glycerin (85%); Pol includes glycerin (86%).

18. Related Substances

–

19. Comments

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20. Specific References

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22. Authors

JC Price.

Mannitol

1. Nonproprietary Names

BP: Mannitol
JP: D-Mannite
PhEur: Mannitolum
USP: Mannitol

2. Synonyms

Cordycepic acid; E421; D-mannitol; manna sugar; mannite; *Pearlitol.*

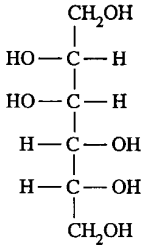
3. Chemical Name and CAS Registry Number

D-Mannitol [69-65-8]

4. Empirical Formula Molecular Weight

$C_6H_{14}O_6$ 182.17

5. Structural Formula



6. Functional Category

Sweetening agent; tablet and capsule diluent; tonicity agent; vehicle (bulking agent) for lyophilized preparations.

7. Applications in Pharmaceutical Formulation or Technology

Mannitol is widely used in pharmaceutical formulations and food products. In pharmaceutical preparations it is primarily used as a diluent (10-90% w/w) in tablet formulations, where it is of particular value since it is not hygroscopic and may thus be used with moisture-sensitive active ingredients.

Mannitol may be used in direct-compression tablet applications,[1-5] for which the granular and spray-dried forms are available, or in wet granulations.[6] Granulations containing mannitol have the advantage of being dried easily. Specific tablet applications include antacid preparations, glyceryl trinitrate tablets, and vitamin preparations. Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and 'mouth feel'.[7,8]

In lyophilized preparations, mannitol (20-90% w/w) has been included as a carrier to produce a stiff, homogeneous cake that improves the appearance of the lyophilized plug in a vial.[9-12] A pyrogen-free form is available specifically for this use.

Mannitol has also been used to prevent thickening in aqueous antacid suspensions of aluminum hydroxide (< 7% w/v). It has been suggested as a plasticizer in soft-gelatin capsules, as a component of sustained-release tablet formulations,[13] and is used in food applications as a bulking agent.

Therapeutically, mannitol administered parenterally is used as an osmotic diuretic, as a diagnostic agent for kidney function, as an adjunct in the treatment of acute renal failure and as an agent to reduce intracranial pressure, treat cerebral edema, and reduce intraocular pressure. Given orally, mannitol is not absorbed significantly from the GI tract, but in large doses it can cause osmotic diarrhea, *see* Section 14.

8. Description

Mannitol is D-mannitol. It is a hexahydric alcohol related to mannose and is isomeric with sorbitol.

Mannitol occurs as a white, odorless, crystalline powder, or free-flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol.

9. Pharmacopeial Specifications

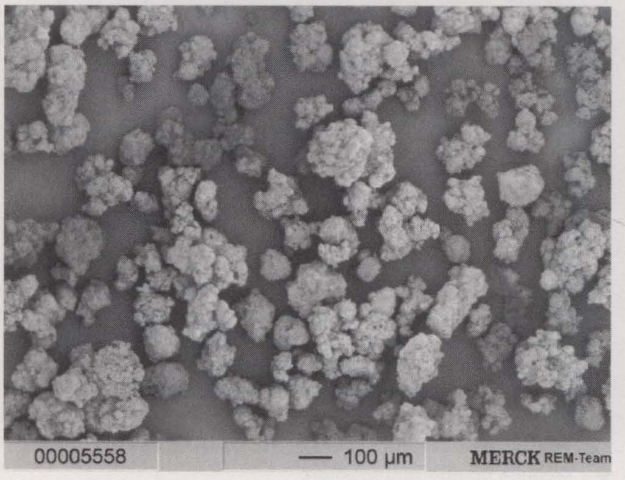
Test	JP	PhEur	USP
Identification	+	+	+
Characters	+	+	—
Solution appearance	+	+	—
Melting range	166-169°C	165-170°C	164-169°C
Specific rotation	+137° to +145°	+23° to +25°	+137° to +145°
Acidity	+	+	+
Loss on drying	≤ 0.30%	≤ 0.5%	≤ 0.3%
Chloride	≤ 0.007%	≤ 50 ppm	≤ 0.007%
Sulfate	≤ 0.01%	≤ 100 ppm	≤ 0.01%
Arsenic	≤ 1.3 ppm	–	≤ 1 ppm
Lead	–	≤ 0.5 ppm	—
Nickel	+	≤ 1 ppm	—
Heavy metals	≤ 5 ppm	–	—
Reducing sugars	+	+	+
Sulfated ash	≤ 0.10%	≤ 0.1%	—
Sorbitol	–	≤ 2.0%	—
Bacterial endotoxins	–	+[a]	—
Assay	≤ 98.0%	98-101.5%	96-101.5%

[a] Test applied only if the mannitol is to be used in the manufacture of parenternal dosage forms.

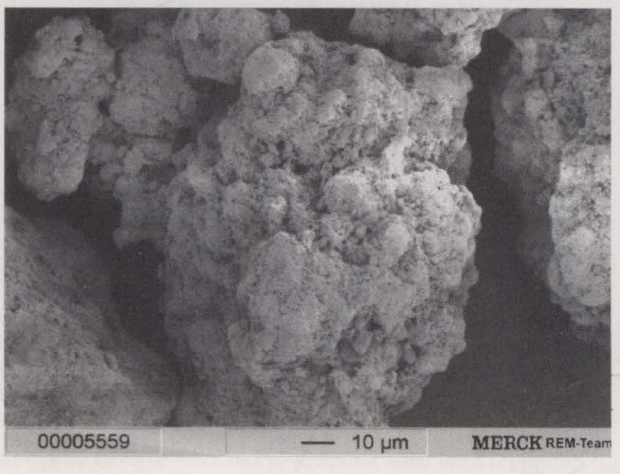
10. Typical Properties

Compressibility: *see* Figs. 1 and 2.[a]
Density (bulk): 0.430 g/cm^3[b] for powder; 0.7 g/cm^3[b] for granules.
Density (tapped): 0.734 g/cm^3[b] for powder; 0.8 g/cm^3[b] for granules
Density (true): 1.514 g/cm^3[b]
Dissociation constant: pK_a = 13.5 at 18°C
Flash point: > 150°C
Flowability: powder is cohesive, granules are free flowing.
Heat of combustion: 16.57 kJ/g (3960 cal/g)
Heat of solution: -120.9 J/g (-28.9 cal/g) at 25°C
Melting point: 166-168°C
Moisture content: *see* Fig. 3.[b]

SEM: 1
Excipient: Mannitol
Manufacturer: Merck
Magnification: 50×
Voltage: 3.5 kV



SEM: 2
Excipient: Mannitol
Manufacturer: Merck
Magnification: 500×
Voltage: 3.5 kV



Osmolarity: a 5.07% w/v aqueous solution is iso-osmotic with serum.

Particle size distribution: maximum of 0.1% greater than 500 µm and minimum of 90% greater than 200 µm in size for *Pearlitol 300 DC*; maximum of 20% greater than 500 µm and minimum of 85% greater than 100 µm in size for *Pearlitol 400 DC*; maximum of 0.5% greater than 841 µm and minimum of 90% greater than 150 µm in size for *Pearlitol 500 DC*. Average particle diameter is 250 µm for *Pearlitol 300 DC*, 360 µm for *Pearlitol 400 DC* and 520 µm for *Pearlitol 500 DC*.[14] *See* Fig. 4.[a]

Refractive index: n_D^{20} = 1.333

SEM: 3
Excipient: Mannitol powder
Manufacturer: SPI Polyols, Inc
Lot No: 3140G8
Magnification: 100×

SEM: 4
Excipient: Mannitol granular
Manufacturer: SPI Polyols, Inc
Lot No: 2034F8
Magnification: 100×

Solubility: *see* table below.

Solvent	Solubility at 20°C
Alkalis	Soluble
Ethanol (95%)	1 in 83
Ether	Practically insoluble
Glycerin	1 in 18
Propan-2-ol	1 in 100
Water	1 in 5.5

Specific surface area: 0.37-0.39 m^2/g[b]

[a] *Handbook of Pharmaceutical Excipients*, First Edition.

[b] Results of laboratory project for third edition.

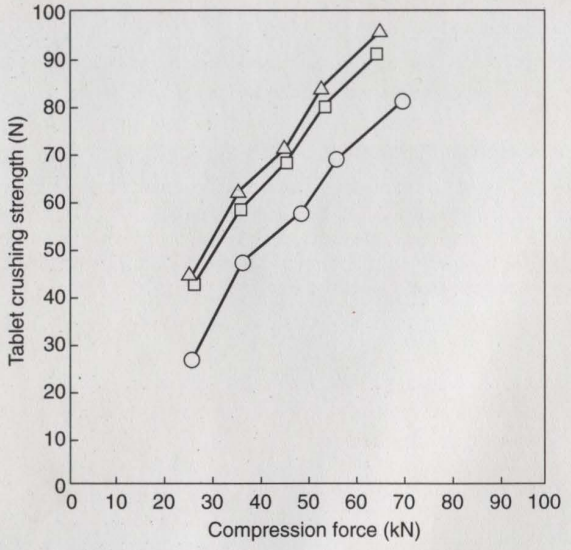


Fig. 1: Compression characteristics of granular mannitol (*Pearlitol*, Roquette Freres).
○ : *Pearlitol FG*
□ : *Pearlitol MG*
△ : *Pearlitol GG2*
Tablet diameter: 20 mm
Lubricant: magnesium stearate 0.7% w/w for *Pearlitol MG* and *Pearlitol GG2*, magnesium stearate 1% w/w for *Pearlitol FG*

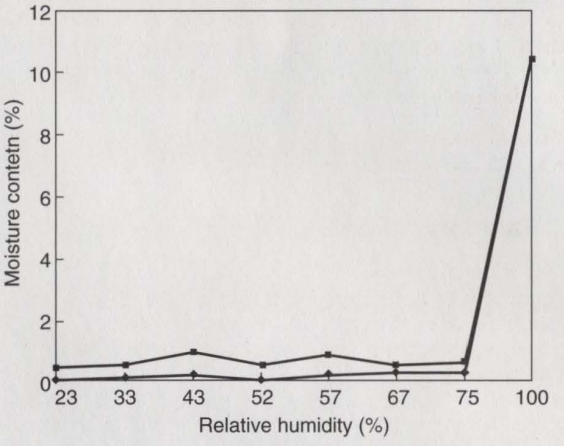


Fig. 3: Sorption-desorption isotherm for mannitol.
◆ : sorption equilibrium moisture
■ : desorption equilibrium moisture

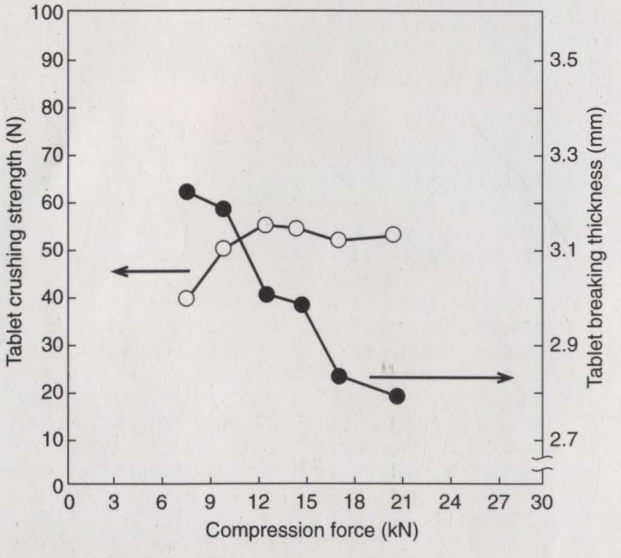


Fig. 2: Compression characteristics of granular mannitol.
Mean tablet weight: 500 mg
Minimum compressional force for compaction: 7.35 kN
Compressional force resulting in capping: 24.5 kN

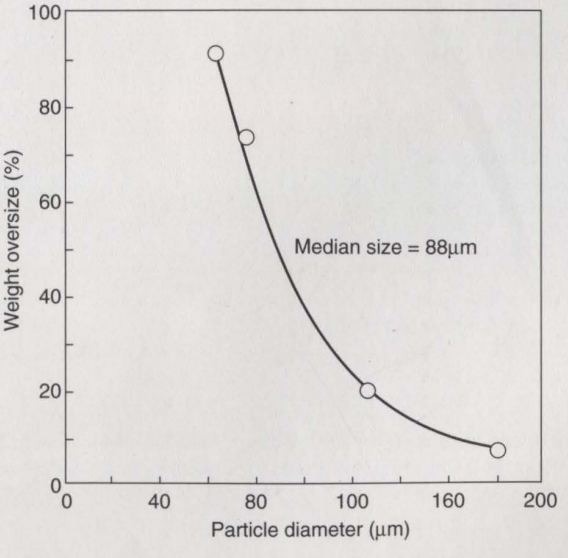


Fig. 4: Particle size distribution of mannitol powder.

11. Stability and Storage Conditions

Mannitol is stable in the dry state and in aqueous solutions. Solutions may be sterilized by filtration or by autoclaving and if necessary may be autoclaved repeatedly with no adverse physical or chemical effects.[15] In solution, mannitol is not attacked by cold, dilute acids or alkalis, nor by atmospheric oxygen in the absence of catalysts. Mannitol does not undergo Maillard reactions.

The bulk material should be stored in a well-closed container in a cool, dry, place.

12. Incompatibilities

None reported in the dry state. Mannitol solutions, 20% w/v or stronger, may be salted out by potassium or sodium chloride.[16] Precipitation has been reported to occur when a 25% w/v mannitol solution was allowed to contact plastic.[17] Sodium cephapirin at 2 mg/mL and 30 mg/mL is incompatible with 20% w/v aqueous mannitol solution. Mannitol is incompatible with xylitol infusion and may form complexes with some metals (Fe, Al, Cu). Reducing sugar impurities in mannitol have been implicated in the oxidative degradation of a peptide in a lyophilized formation.[18] Mannitol was found to reduce the oral biovailability of cimetidine compared to sucrose.[19]

13. Method of Manufacture

Mannitol may be extracted from the dried sap of manna and other natural sources by means of hot alcohol or other selective solvents. It is commercially produced by the catalytic or electrolytic reduction of monosaccharides such as mannose and glucose.

14. Safety

Mannitol is a naturally occurring sugar alcohol found in animals and plants; it is present in small quantities in almost all vegetables. When consumed orally in large quantities, laxative effects may occur.[20] If used in foods as a bodying agent and daily ingestion of over 20 g is foreseeable, the product label should bear the statement 'excessive consumption may have a laxative effect'. After intravenous injection, mannitol is not metabolized to any appreciable extent and is minimally reabsorbed by the renal tubule, about 80% of a dose being excreted in the urine in 3 hours.[21]

A number of adverse reactions to mannitol have been reported primarily following the therapeutic use of 20% w/v aqueous intravenous infusions.[22] The quantity of mannitol used as an excipient is considerably less than that used therapeutically and is consequently associated with a lower incidence of adverse reactions. However, allergic, hypersensitive-type reactions may occur when mannitol is used as an excipient.

An acceptable daily intake of mannitol has not been specified by the WHO since the amount consumed as a sweetening agent was not considered to represent a hazard to health.[23]

LD_{50} (mouse, IP): 14 g/kg[24]

LD_{50} (mouse, IV): 7.47 g/kg

LD_{50} (mouse, oral): 22 g/kg

LD_{50} (rat, IV): 9.69 g/kg

LD_{50} (rat, oral): 13.5 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Mannitol may be irritant to the eyes; eye protection is recommended.

16. Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (IP, IM, IV, and SC injections, infusions, buccal, oral and sublingual tablets and capsules). Included in nonparenteral and parenteral medicines licensed in the UK.

17. Pharmacopeias

China, Eur, Int, Jpn, Pol, and US.

18. Related Substances

Sorbitol.

19. Comments

Mannitol is an isomer of sorbitol, the difference between the two polyols occurring in the planar orientation of the OH group on the second carbon atom. Each isomer is characterized by its own individual set of properties, the most important difference being the response to moisture. Sorbitol is hygroscopic while mannitol resists moisture sorption, even at high relative humidities.

Granular mannitol flows well and imparts improved flow properties to other materials. However, it usually cannot be used with concentrations of other materials exceeding 25% by weight. Recommended levels of lubricant are 1% w/w calcium stearate or 1-2% w/w magnesium stearate. Suitable binders for preparing granulations of powdered mannitol are gelatin, methylcellulose 400, starch paste, povidone, and sorbitol. Usually, 3-6 times as much magnesium stearate or 1.5-3 times as much calcium stearate is needed for lubrication of mannitol granulations than is needed for other excipients.

Mannitol has been reported to sublime at 130°C.[25]

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22. Authors

NA Armstrong, GE Reier.

Propylene Glycol

1. Nonproprietary Names

BP: Propylene glycol
JP: Propylene glycol
PhEur: Propylenglycolum
USP: Propylene glycol

2. Synonyms

1,2-Dihydroxypropane; 2-hydroxypropanol; methyl ethylene glycol; methyl glycol; propane-1,2-diol.

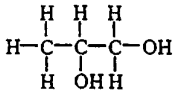
3. Chemical Name and CAS Registry Number

1,2-Propanediol [57-55-6]

4. Empirical Formula Molecular Weight

$C_3H_8O_2$ 76.1

5. Structural Formula



6. Functional Category

Antimicrobial preservative; disinfectant; humectant; plasticizer; solvent; stabilizer for vitamins; water-miscible cosolvent.

7. Applications in Pharmaceutical Formulation or Technology

Propylene glycol has become widely used as a solvent, extractant, and preservative in a variety of parenteral and nonparenteral pharmaceutical formulations. It is a better general solvent than glycerin and dissolves a wide variety of materials, such as corticosteroids, phenols, sulfa drugs, barbiturates, vitamins (A and D), most alkaloids, and many local anesthetics.

As an antiseptic it is similar to ethanol, and against molds it is similar to glycerin and only slightly less effective than ethanol.

Propylene glycol is commonly used as a plastizer in aqueous film-coating formulations.

Propylene glycol is also used in cosmetics and in the food industry as a carrier for emulsifiers and as a vehicle for flavors in preference to ethanol, since its lack of volatility provides a more uniform flavor.

Use	Dosage form	Concentration (%)
Humectant	Topicals	≈ 15
Preservative	Solutions, semisolids	15-30
Solvent or cosolvent	Aerosol solutions	10-30
	Oral solutions	10-25
	Parenterals	10-60
	Topicals	5-80

8. Description

Propylene glycol is a clear, colorless, viscous, practically odorless liquid with a sweet, slightly acrid taste resembling glycerin.

9. Pharmacopeial Specifications

Test	JP	PhEur	USP
Identification	+	+	+
Appearance	—	+	—
Specific gravity	1.038-1.037	1.035-1.040	1.035-1.037
Acidity	+	+	+
Water	≤ 0.0.5%	≤ 0.2%	≤ 0.2%
Residue on ignition	≤ 0.005%	—	≤ 0.007%
Sulfated ash	—	≤ 0.01%	—
Chloride	≤ 0.007%	—	≤0.007%
Sulfate	≤ 0.002%	—	≤ 0.006%
Heavy metals	≤ 5 ppm	≤ 5 ppm	≤ 5 ppm
Organic volatile impurities	—	—	+
Refractive index	—	1.431-1.433	—
Oxidizing substances	—	+	—
Reducing substances	—	+	—
Arsenic	≤ 2 ppm	—	—
Glycerin	+	—	—
Distilling range	184-189°C	—	—
Assay	—	—	99.5%

10. Typical Properties

Autoignition temperature: 371°C
Boiling point: 188°C
Density: 1.038 g/cm^3 at 20°C
Flammability: upper limit, 12.6% v/v in air; lower limit, 2.6% v/v in air.
Flash point: 99°C (open cup)
Heat of combustion: 1803.3 kJ/mol (431.0 kcal/mol)
Heat of vaporization: 705.4 J/g (168.6 cal/g) at b.p.
Melting point: -59°C
Osmolarity: a 2.0% v/v aqueous solution is iso-osmotic with serum.
Refractive index: n_D^{20} = 1.4324
Specific rotation $[\alpha]_D^{20}$:
-15.0° (neat) for (*R*)-form;
+15.8° (neat) for (*S*)-form.
Solubility: miscible with acetone, chloroform, ethanol (95%), glycerin, and water; soluble 1 in 6 parts of ether; not miscible with light mineral oil or fixed oils, but will dissolve some essential oils.
Specific heat: 2.47 J/g (0.590 cal/g) at 20°C
Surface tension: 40.1 mN/m (40.1 dynes/cm) at 25°C
Vapor density (relative): 2.62 (air = 1)
Vapor pressure: 9.33 Pa (0.07 mmHg) at 20°C
Viscosity (dynamic): 58.1 mPa s (0.581 P) at 20°C

11. Stability and Storage Conditions

At cool temperatures, propylene glycol is stable in a well-closed container, but at high temperatures, in the open, it tends to oxidize, giving rise to products such as propionaldehyde, lactic acid, pyruvic acid, and acetic acid. Propylene glycol is chemically stable when mixed with ethanol (95%), glycerin, or water; aqueous solutions may be sterilized by autoclaving.

Propylene glycol is hygroscopic and should be stored in a well-closed container, protected from light, in a cool, dry, place.

12. Incompatibilities

Propylene glycol is incompatible with oxidizing reagents such as potassium permanganate.

13. Method of Manufacture

Propylene is converted to chlorohydrin by chlorine water and hydrolyzed to 1,2-propylene oxide. With further hydrolysis, 1,2-propylene oxide is converted to propylene glycol.

14. Safety

Propylene glycol is used in a wide variety of pharmaceutical formulations and is generally regarded as a nontoxic material. Probably as a consequence of its metabolism and excretion, propylene glycol is less toxic than other glycols.

In topical preparations, propylene glycol is regarded as minimally irritant although it is more irritant than glycerin. Some local irritation is produced upon application to mucous membranes or when used under occlusive conditions.[1] Parenteral administration may cause pain or irritation when used in high concentration.

Propylene glycol is estimated to be one third as intoxicating as ethanol, with administration of large volumes being associated with adverse effects most commonly on the central nervous system, especially in neonates and children.[2-4] Other adverse reactions reported, though generally isolated, include: ototoxicity;[5] cardiovascular effects; seizures; hyperosmolarity[6] and lactic acidosis, both of which occur most frequently in patients with renal impairment.

Based on metabolic and toxicological data, the WHO has set an acceptable daily intake of propylene glycol at up to 25 mg/kg body-weight.[7] Formulations containing 35% propylene glycol can cause hemolysis in humans.

In animal studies, there has been no evidence that propylene glycol is teratogenic or mutagenic. Rats can tolerate a repeated oral daily dose of up to 30 mL/kg in the diet over 6 months, while the dog is unaffected by a repeated oral daily dose of 2 g/kg in the diet for 2 years.[8]

LD_{50} (dog, IV): 25.9 g/kg[8-10]
LD_{50} (dog, oral): 10-20 g/kg
LD_{50} (guinea pig, oral): 18.4-19.6 g/kg
LD_{50} (guinea pig, SC): 13-15.5 g/kg
LD_{50} (mouse, IP): 6.8-13.6 g/kg
LD_{50} (mouse, IV): 7.6-8.3 g/kg
LD_{50} (mouse, oral): 23.9 g/kg
LD_{50} (mouse, SC): 15.5-19.2 g/kg
LD_{50} (rabbit, IM): 6 g/kg
LD_{50} (rabbit, IV): 5-6.5 g/kg
LD_{50} (rabbit, oral): 15.7-19.2 g/kg
LD_{50} (rat, IM): 13-20.7 g/kg
LD_{50} (rat, IP): 13-16.8 g/kg
LD_{50} (rat, IV): 6.2-12.7 g/kg
LD_{50} (rat, oral): 21-33.7 g/kg
LD_{50} (rat, SC): 21.7-29 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Propylene glycol should be handled in a well-ventilated environment; eye protection is recommended. In the UK, the long-term (8-hour TWA) occupational exposure limit for propylene glycol vapor and particulates is 470 mg/m^3 (150 ppm) and 10 mg/m^3 for particulates.[11]

16. Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe (does not have a code number). Included in the FDA Inactive Ingredients Guide (dental preparations, IM and IV injections, inhalations, ophthalmic, oral, otic, percutaneous, rectal, topical, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK.

17. Pharmacopeias

Eur, Jpn, Pol, and US.

18. Related Substances

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19. Comments

In addition to its uses as an excipient, propylene glycol is used in veterinary medicine as an oral glucogenic in ruminants.[12]

20. Specific References

1. Motoyoshi K, Nozawa S, Yoshimura M, Matsuda K. The safety of propylene glycol and other humectants. *Cosmet Toilet* 1984; 99(10): 83-91.
2. Arulanantham K, Genel M. Central nervous system toxicity associated with ingestion of propylene glycol. *J Pediatr* 1978; 93: 515-516.
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12. Bishop Y, editor. *The Veterinary Formulary,* 4th edition. London, Pharmaceutical Press, 1998; 480-481.

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Yu CD, Kent JS. Effect of propylene glycol on subcutaneous absorption of a benzimidazole hydrochloride. *J Pharm Sci* 1982; 71: 476-478.

22. Authors

Y Dandiker.

Sodium Phosphate, Dibasic

1. Nonproprietary Names

BP: Sodium phosphate
JP: Dibasic sodium phosphate
PhEur: Dinatrii phosphas dihydricus
Dinatrii phosphas dodecahydricus
USP: Dibasic sodium phosphate

Note that the PhEur contains two separate monographs for dihydrate and the dodecahydrate; the JP contains one monograph for the dodecahydrate; and the USP contains one monograph for the heptahydrate.

2. Synonyms

Disodium hydrogen phosphate; disodium phosphate; E339; secondary sodium phosphate; sodium orthophosphate; phosphoric acid, disodium salt.

3. Chemical Name and CAS Registry Number

Anhydrous dibasic sodium phosphate [7558-79-4]
Dibasic sodium phosphate dihydrate [10028-24-7]
Dibasic sodium phosphate heptahydrate [7782-85-6]
Dibasic sodium phosphate dodecahydrate [10039-32-4]

4. Empirical Formula and Molecular Weight

Empirical Formula	Molecular Weight
Na_2HPO_4	141.96
$Na_2HPO_4.2H_2O$	177.98
$Na_2HPO_4.7H_2O$	268.03
$Na_2HPO_4.12H_2O$	358.08

5. Structural Formula

$Na_2HPO_4.xH_2O$

Where x = 0, 2, 7, or 12.

6. Functional Category

Buffering agent; sequestering agent.

7. Applications in Pharmaceutical Formulation or Technology

Dibasic sodium phosphate is used in a wide variety of pharmaceutical formulations as a buffering agent and as a sequestering agent. Therapeutically, dibasic sodium phosphate is used as a mild laxative and in the treatment of hypophosphatemia.[1,2] Dibasic sodium phosphate is also used in food products, e.g., as an emulsifier in processed cheese.

8. Description

Anhydrous dibasic sodium phosphate occurs as a white powder. The dihydrate occurs as white or almost white, odorless, crystals. The heptahydrate occurs as colorless crystals or as a white, granular, or caked salt that effloresces in warm, dry air. The dodecahydrate occurs as strongly efflorescent, colorless, or transparent crystals.

9. Pharmacopeial Specifications

Test	JP	PhEur	USP
Identification	+	+	+
Characters	+	+	—
pH (2% solution)	9.0-9.4	—	—
Appearance of solution	+	+	—
Loss on drying			
(anhydrous)	—	—	≤ 5.0%
(monohydrate)	—	—	10.3-12.0%
(dihydrate)	—	19.5-21.0%	18.5-21.5%
(heptahydrate)	—	—	43.0-50.0%
(dodecahydrate)	57.0-61.0%	57.0-61.0%	55.0-64.0%
Insoluble substances	—	—	≤ 0.4%
Reducing substances	—	+	—
Monosodium phosphate	—	+	—
Carbonate	+	—	—
Chloride			
(dihydrate)	—	≤ 400 ppm	—
(heptahydrate)	—	—	≤ 0.06%
(dodecahydrate)	≤ 0.014%	≤ 200 ppm	—
Sulfate			
(dihydrate)	≤ 0.014%	≤ 0.1%	—
(heptahydrate)	—	—	≤ 0.2%
(dodecahydrate)	≤ 0.038%	≤ 500 ppm	—
Arsenic			
(dihydrate)	—	≤ 4 ppm	—
(heptahydrate)	≤ 16 ppm	—	≤ 16 ppm
(dodecahydrate)	≤ 2 ppm	≤ 2 ppm	—
Heavy metals			
(dihydrate)	—	≤ 20 ppm	—
(heptahydrate)	≤ 10 ppm	—	≤ 0.002%
Iron			
(dihydrate)	≤ 10 ppm	≤ 40 ppm	—
(dodecahydrate)	—	≤ 20 ppm	—
Assay (dried basis)	≥ 98.0%	98.0-101.0%	98.0-100.5%

10. Typical Properties

Acidity/alkalinity: pH = 9.1 for a 1% w/v aqueous solution of the anhydrous material at 25°C. A saturated aqueous solution of the dodecahydrate has a pH of about 9.5.

Ionization constants:[3]
pK_{a1} = 2.15 at 25°C;
pK_{a2} = 7.20 at 25°C.
pK_{a3} = 12.38 at 25°C.

Hygroscopicity: the anhydrous form is hygroscopic and will absorb 2-7 moles of water on exposure to air, whereas the heptahydrate is stable in air.

Osmolarity: a 2.23% w/v aqueous solution of the dihydrate is iso-osmotic with serum; a 4.45% w/v aqueous solution of the dodecahydrate is iso-osmotic with serum.

Solubility: very soluble in water, more so in hot or boiling water; practically insoluble in ethanol (95%). The anhydrous material is soluble 1 in 8 parts of water, the heptahydrate 1 in 4 parts of water, and the dodecahydrate 1 in 3 parts of water.

11. Stability and Storage Conditions

The anhydrous form of dibasic sodium phosphate is hygroscopic. When heated to 40°C, the dodecahydrate fuses; at 100°C it loses its water of crystallization and at a dull-red heat, about 240°C, it is converted into the pyrophosphate,

$Na_4P_2O_7$. Aqueous solutions of dibasic sodium phosphate are stable and may be sterilized by autoclaving.

The bulk material should be stored in an airtight container, in a cool, dry, place.

12. Incompatibilities

Dibasic sodium phosphate is incompatible with alkaloids, antipyrine, chloral hydrate, lead acetate, pyrogallol, resorcinol and calcium gluconate, and ciprofloxacin.[4] Interaction between calcium and phosphate, leading to the formation of insoluble calcium-phosphate precipitates, is possible in parenteral admixtures.

13. Method of Manufacture

Either bone phosphate (bone ash), obtained by heating bones to whiteness, or the mineral phosphorite is used as a source of tribasic calcium phosphate, which is the starting material in the industrial production of dibasic sodium phosphate.

Tribasic calcium phosphate is finely ground and digested with sulfuric acid. This mixture is then leached with hot water, neutralized with sodium carbonate, and dibasic sodium phosphate crystallized from the filtrate.

14. Safety

Dibasic sodium phosphate is widely used as an excipient in parenteral, oral, and topical pharmaceutical formulations.

Phosphate occurs extensively in the body and is involved in many physiological processes since it is the principal anion of intracellular fluid. Most foods contain adequate amounts of phosphate and hence deficiency, hypophosphatemia,[1] is virtually unknown except for certain disease states[2] or in patients receiving total parenteral nutrition. Treatment is usually by the oral administration of up to 100 mmol of phosphate daily.

Approximately two-thirds of ingested phosphate is absorbed from the gastrointestinal tract, virtually all of it being excreted in the urine, the remainder being excreted in the feces.

Excessive administration of phosphate, particularly intravenously, rectally, or in patients with renal failure, can cause hyperphosphatemia which may lead to hypocalcemia or other severe electrolyte imbalances.[5,6] Adverse effects occur less frequently following oral consumption although phosphates act as mild saline laxatives when administered by this route or rectally. Consequently, gastrointestinal disturbances including diarrhea, nausea, and vomiting may occur following the use of dibasic sodium phosphate as an excipient in oral formulations. Generally however, the level of dibasic sodium phosphate used as an excipient in a pharmaceutical formulation is not usually associated with adverse effects.

LD_{50} (rat, oral): 17 g/kg[7]

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Dibasic sodium phosphate may be irritating to the skin, eyes, and mucous membranes. Eye protection and gloves are recommended.

16. Regulatory Status

GRAS listed. Accepted in Europe as a food additive. Included in the FDA Inactive Ingredients Guide (injections, infusions, nasal, ophthalmic, oral, otic, topical, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK.

17. Pharmacopeias

Eur, Jpn, Pol, and US.

These pharmacopeias may specify one or more states of hydration for dibasic sodium phosphate. Monographs or specifications can be found for the anhydrous form, the dihydrate, the dodecahydrate and the heptahydrate, although not all forms may necessarily be found in any one pharmacopeia.

18. Related Substances

Dibasic potassium phosphate; sodium phosphate, monobasic; tribasic sodium phosphate.

Dibasic potassium phosphate: K_2HPO_4

Molecular weight: 174.15

CAS number: [7758-11-4]

Synonyms: dipotassium hydrogen orthophosphate; dipotassium hydrogen phosphate; dipotassium phosphate; E340; potassium phosphate.

Appearance: colorless or white, granular, hygroscopic powder.

Pharmacopeias: Eur and US.

Acidity/alkalinity: pH = 8.5-9.6 for a 5% w/v aqueous solution at 25°C.

Osmolarity: a 2.08% w/v aqueous solution of dibasic potassium phosphate is iso-osmotic with serum.

Solubility: freely soluble in water; very slightly soluble in ethanol (95%).

Comments: each gram of dibasic potassium phosphate contains approximately 11.5 mmol of potassium and 5.7 mmol of phosphate.

Tribasic sodium phosphate: $Na_3PO_4.xH_2O$

Molecular weight: 163.94 for the anhydrous material; 380.06 for the dodecahydrate ($12H_2O$).

CAS number: [7601-54-9] for the anhydrous material.

Synonyms: E339; trisodium orthophosphate; trisodium phosphate; TSP.

Acidity/alkalinity: pH = 12.1 for a 1% w/v aqueous solution of the anhydrous material at 25°C. A 1% w/v aqueous solution of the dodecahydrate, at 25°C, has a pH of 12-12.2.

Density:

1.3 g/cm^3 for the anhydrous material;

0.9 g/cm^3 for the dodecahydrate.

Solubility: the anhydrous material is soluble 1 in 8 parts of water, while the dodecahydrate is soluble 1 in 5 parts of water at 20°C.

19. Comments

Each gram of anhydrous dibasic sodium phosphate represents approximately 14.1 mmol of sodium and 7.0 mmol of phosphate. Each gram of dibasic sodium phosphate dihydrate represents approximately 11.2 mmol of sodium and 5.6 mmol of phosphate. Each gram of dibasic sodium phosphate heptahydrate represents approximately 7.5 mmol of sodium and 3.7 mmol of phosphate. Each gram of dibasic sodium phosphate dodecahydrate represents approximately 5.6 mmol of sodium and 2.8 mmol of phosphate.

20. Specific References

1. Lloyd CW, Johnson CE. Management of hypophosphatemia. *Clin Pharm* 1988; 7: 123-128.
2. Holland PC, Wilkinson AR, Diez J, Lindsell DRM. Prenatal deficiency of phosphate, phosphate supplementation, and rickets in very-low-birthweight infants. *Lancet* 1990; 335: 697-701.
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21. General References

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22. Authors

AS Kearney.

Sodium Phosphate, Monobasic

1. Nonproprietary Names

BP: Sodium dihydrogen phosphate dihydrate.

PhEur: Natrii dihydrogenophosphas dihydricus

USP: Monobasic sodium phosphate

See also Section 17.

2. Synonyms

E339; monosodium orthophosphate; monosodium phosphate; phosphoric acid, monosodium salt; primary sodium phosphate; sodium biphosphate; sodium dihydrogen orthophosphate; sodium dihydrogen phosphate; acid sodium phosphate.

3. Chemical Name and CAS Registry Number

Anhydrous monobasic sodium phosphate [7558-80-7]

Monobasic sodium phosphate monohydrate [10049-21-5]

Monobasic sodium phosphate dihydrate [10028-24-7] or [13472-35-0]

4. Empirical Formula and Molecular Weight

Empirical Formula	Molecular Weight
NaH_2PO_4	119.98
$NaH_2PO_4.H_2O$	137.99
$NaH_2PO_4.2H_2O$	156.01

5. Structural Formula

$NaH_2PO_4.xH_2O$

Where x = 0, 1, or 2.

6. Functional Category

Buffering agent; emulsifying agent; sequestering agent.

7. Applications in Pharmaceutical Formulation or Technology

Monobasic sodium phosphate is used in a wide variety of pharmaceutical formulations as a buffering agent and as a sequestering agent. Therapeutically, monobasic sodium phosphate is used as a mild saline laxative and in the treatment of hypophosphatemia.[1,2]

Monobasic sodium phosphate is also used in food products, e.g., in baking powders, and as a dry acidulant and sequestrant.

8. Description

The hydrated forms of monobasic sodium phosphate occur as odorless, colorless or white-colored, slightly deliquescent, crystals. The anhydrous form occurs as a white crystalline powder or granules.

9. Pharmacopeial Specifications

Test	PhEur	USP
Identification	+	+
Characters	+	—
pH	4.2-4.5	4.1-4.5
Appearance of solution	+	—
Water		
(anhydrous form)	—	≤ 2.0%
(monohydrate)	—	10.0-15.0%
(dihydrate)	21.5-24.0%	18.0-26.5%
Insoluble substances	—	≤ 0.2%
Reducing substances	+	—
Chloride	≤ 200 ppm	≤ 0.014%
Sulfate	≤ 300 ppm	≤ 0.15%
Aluminum, cadmium and related elements	—	+
Arsenic	≤ 2 ppm	≤ 8 ppm
Heavy metals	≤ 10 ppm	≤ 0.002%
Iron	≤ 10 ppm	—
Organic volatile impurities	—	+
Assay (dried basis)	98.0-100.5%	98.0-103.0%

10. Typical Properties

Acidity/alkalinity: pH = 4.1-4.5 for a 5% w/v aqueous solution of the monohydrate at 25°C.

Density: 1.915 g/cm^3 for the dihydrate.

Dissociation constant: pK_a = 2.15 at 25°C.

Solubility: soluble 1 in 1 of water; very slightly soluble in ethanol (95%).

11. Stability and Storage Conditions

Monobasic sodium phosphate is chemically stable although it is slightly deliquescent. On heating at 100°C, the dihydrate loses all of its water of crystallization. On further heating, it melts with decomposition at 205°C forming sodium hydrogen pyrophosphate, $Na_2H_2P_2O_7$, and at 250°C it leaves a final residue of sodium metaphosphate, $NaPO_3$.

Aqueous solutions are stable and may be sterilized by autoclaving.

Monobasic sodium phosphate should be stored in an airtight container in a cool, dry, place.

12. Incompatibilities

Monobasic sodium phosphate is an acid salt and is therefore generally incompatible with alkaline materials and carbonates; aqueous solutions of monobasic sodium phosphate are acidic and will cause carbonates to effervesce.

Monobasic sodium phosphate should not be administered concomitantly with aluminum, calcium, or magnesium salts since they bind phosphate and could impair its absorption from the gastrointestinal tract. Interaction between calcium and phosphate, leading to the formation of insoluble calcium-phosphate precipitates, is possible in parenteral admixtures.[3,4]

13. Method of Manufacture

Monobasic sodium phosphate is prepared by adding phosphoric acid to a hot, concentrated solution of disodium phosphate until the liquid ceases to form a precipitate with barium chloride. This

solution is then concentrated and the monobasic sodium phosphate crystallized.

14. Safety

Monobasic sodium phosphate is widely used as an excipient in parenteral, oral, and topical pharmaceutical formulations.

Phosphate occurs extensively in the body and is involved in many physiological processes since it is the principal anion of intracellular fluid. Most foods contain adequate amounts of phosphate and hence deficiency, hypophosphatemia,[1] is virtually unknown except for certain disease states[2] or in patients receiving total parenteral nutrition. Treatment is usually by the oral administration of up to 100 mmol of phosphate daily.

Approximately two-thirds of ingested phosphate is absorbed from the gastrointestinal tract, virtually all of it being excreted in the urine, the remainder being excreted in the feces.

Excessive administration of phosphate, particularly intravenously, rectally, or in patients with renal failure, can cause hyperphosphatemia which may lead to hypocalcemia or other severe electrolyte imbalances.[5-7] Adverse effects occur less frequently following oral consumption although phosphates act as mild saline laxatives when administered by this route or rectally (2-4 g of monobasic sodium phosphate in an aqueous solution is used as a laxative). Consequently, gastrointestinal disturbances including diarrhea, nausea, and vomiting may occur following the use of monobasic sodium phosphate as an excipient in oral formulations. Generally however, the level of monobasic sodium phosphate used as an excipient in a pharmaceutical formulation is not usually associated with adverse effects.

LD_{50} (rat, IM): 0.25 g/kg[8]
LD_{50} (rat, oral): 8.29 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Monobasic sodium phosphate may be irritant to the skin, eyes, and mucous membranes. Eye protection and gloves are recommended.

16. Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (injections, infusions, ophthalmic, oral, topical, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK.

17. Pharmacopeias

China, Eur, Pol, and US.

Eur and Pol specify the dihydrate.

China specifies the monohydrate.

Br specifies the anhydrous form or monohydrate.

US specifies either the dihydrate, monohydrate, or anhydrous form.

18. Related Substances

Dibasic sodium phosphate; monobasic potassium phosphate.

Monobasic potassium phosphate: KH_2PO_4
Molecular weight: 136.09
CAS number: [7778-77-0]
Synonyms: E340; monopotassium phosphate; potassium acid phosphate; potassium biphosphate; potassium dihydrogen orthophosphate.
Appearance: colorless crystals or a white, odorless, granular, or crystalline powder.
Pharmacopeias: Eur and US.
Acidity/alkalinity: pH ≈ 4.5 for a 1% w/v aqueous solution at 25°C.
Solubility: freely soluble in water; practically insoluble in ethanol (95%).
Comments: each gram of monobasic potassium phosphate represents approximately 7.3 mmol of potassium and of phosphate.

19. Comments

Each gram of anhydrous monobasic sodium phosphate represents approximately 8.3 mmol of sodium and of phosphate. Each gram of monobasic sodium phosphate monohydrate represents approximately 7.2 mmol of sodium and of phosphate. Each gram of monobasic sodium phosphate dihydrate represents approximately 6.4 mmol of sodium and of phosphate.

20. Specific References

1. Lloyd CW, Johnson CE. Management of hypophosphatemia. *Clin Pharm* 1988; 7: 123-128.
2. Holland PC, Wilkinson AR, Diez J, Lindsell DRM. Prenatal deficiency of phosphate, phosphate supplementation, and rickets in very-low-birthweight infants. *Lancet* 1990; 335: 697-701.
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