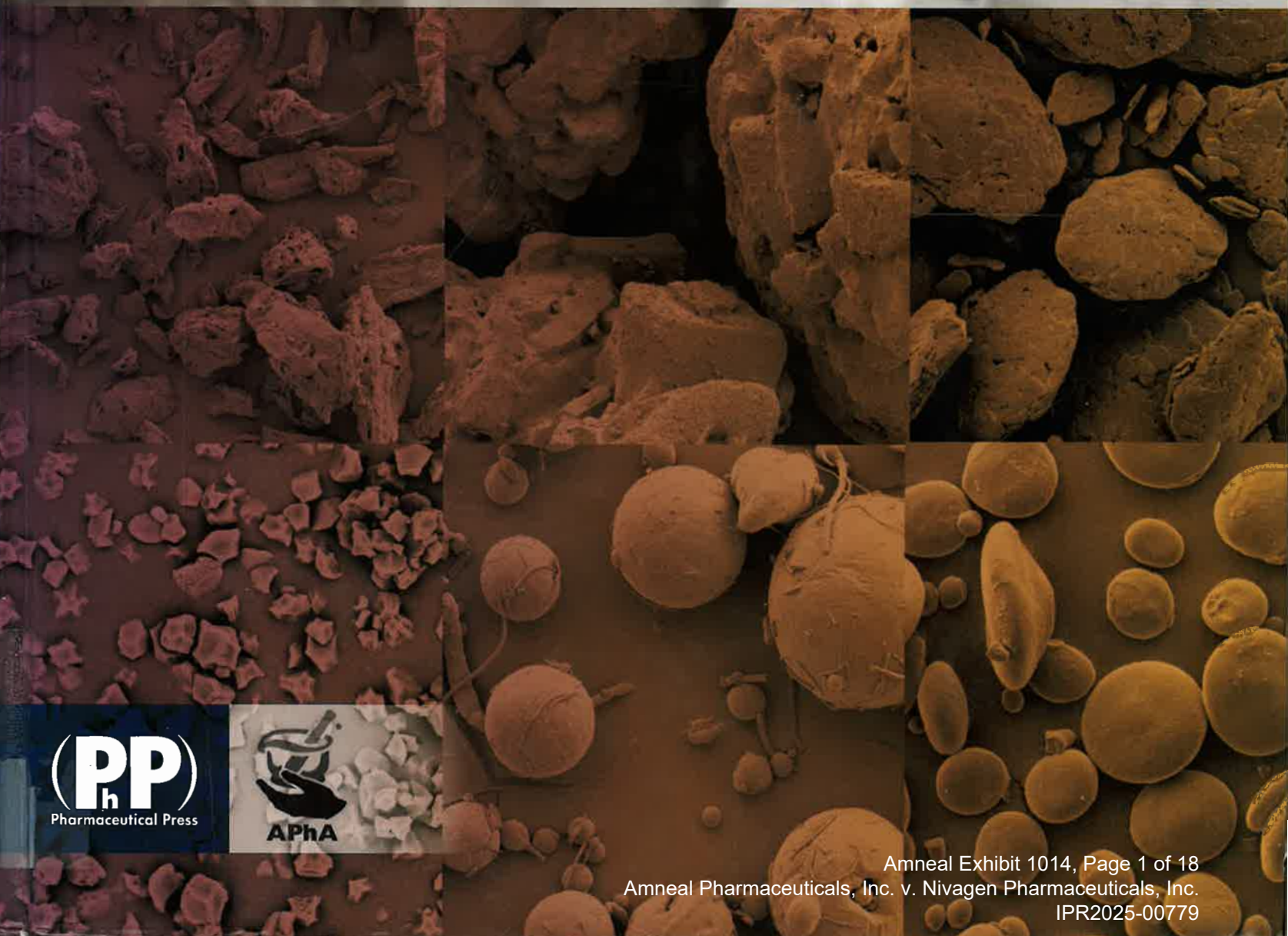
Handbook of Pharmaceutical Excipients

Sixth edition

Edited by
Raymond C Rowe, Paul J Sheskey and Marian E Quinn



Pharmaceutical Press
APhA

Amneal Exhibit 1014, Page 1 of 18
Amneal Pharmaceuticals, Inc. v. Nivagen Pharmaceuticals, Inc.
IPR2025-00779

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SIXTH EDITION

Edited by

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London • Chicago Pharmaceutical Press

Amneal Exhibit 1014, Page 2 of 18
Amneal Pharmaceuticals, Inc. v. Nivagen Pharmaceuticals, Inc.
IPR2025-00779

Published by the Pharmaceutical Press
An imprint of RPS Publishing

1 Lambeth High Street, London SE1 7JN, UK
100 South Atkinson Road, Suite 200, Grayslake, IL 60030-7820, USA

and the American Pharmacists Association
2215 Constitution Avenue, NW, Washington, DC 20037-2985, USA

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(PP) is a trade mark of RPS Publishing

RPS Publishing is the publishing organisation of the Royal Pharmaceutical Society of Great Britain

First published 1986
Second edition published 1994
Third edition published 2000
Fourth edition published 2003
Fifth edition published 2006
Sixth edition published 2009

Typeset by Data Standards Ltd, Frome, Somerset
Printed in Italy by L.E.G.O. S.p.A.

ISBN 978 0 85369 792 3 (UK)
ISBN 978 1 58212 135 2 (USA)

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

HBLNG
QV
735
8145610

Contents

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2009
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Preface x
Arrangement xi
Acknowledgments xiii
Notice to Readers xiii
International Steering Committee xiv
Editorial Staff xv
Contributors xvi
About the Editors xx
New Monographs xxi
Related Substances xxii
Bibliography xxiv
Abbreviations xxv
Units of Measurement xxvii

Monographs

A

Acacia 1
Acesulfame Potassium 3
Acetic Acid, Glacial 5
Acetone 7
Acetyltributyl Citrate 8
Acetyltriethyl Citrate 10
Adipic Acid 11
Agar 13
Albumin 14
Alcohol 17
Alginic Acid 20
Aliphatic Polyesters 23
Alitame 28
Almond Oil 29
Alpha Tocopherol 31
Aluminum Hydroxide Adjuvant 34
Aluminum Monostearate 35
Aluminum Oxide 37
Aluminum Phosphate Adjuvant 38
Ammonia Solution 39
Ammonium Alginate 41
Ammonium Chloride 42
Ascorbic Acid 43
Ascorbyl Palmitate 46
Aspartame 48
Attapulgite 51

B

Bentonite 53
Benzalkonium Chloride 56
Benzethonium Chloride 59
Benzoic Acid 61
Benzyl Alcohol 64
Benzyl Benzoate 66
Boric Acid 68
Bronopol 70
Butylated Hydroxyanisole 73
Butylated Hydroxytoluene 75
Butylene Glycol 77
Butylparaben 78

C

Calcium Acetate 82
Calcium Alginate 83
Calcium Carbonate 86
Calcium Chloride 89
Calcium Hydroxide 91
Calcium Lactate 92
Calcium Phosphate, Dibasic Anhydrous 94
Calcium Phosphate, Dibasic Dihydrate 96
Calcium Phosphate, Tribasic 99
Calcium Silicate 101
Calcium Stearate 103
Calcium Sulfate 105
Canola Oil 108
Carbomer 110
Carbon Dioxide 115
Carboxymethylcellulose Calcium 117
Carboxymethylcellulose Sodium 118
Carrageenan 122
Castor Oil 126
Castor Oil, Hydrogenated 128
Cellulose, Microcrystalline 129
Cellulose, Microcrystalline and Carboxymethylcellulose Sodium 134
Cellulose, Powdered 136
Cellulose, Silicified Microcrystalline 139
Cellulose Acetate 141
Cellulose Acetate Phthalate 143
Ceratonia 146
Ceresin 148

Cetostearyl Alcohol 150
Cetrimide 152
Cetyl Alcohol 155
Cetylpyridinium Chloride 157
Chitosan 159
Chlorhexidine 162
Chlorobutanol 166
Chlorocresol 168
Chlorodifluoroethane (HCFC) 171
Chlorofluorocarbons (CFC) 173
Chloroxylenol 176
Cholesterol 178
Citric Acid Monohydrate 181
Coconut Oil 184
Colloidal Silicon Dioxide 185
Coloring Agents 189
Copovidone 196
Corn Oil 199
Corn Starch and Pregelatinized Starch 200
Cottonseed Oil 202
Cresol 203
Croscarmellose Sodium 206
Crospovidone 208
Cyclodextrins 210
Cyclomethicone 215

D

Denatonium Benzoate 217
Dextrates 218
Dextrin 220
Dextrose 222
Dibutyl Phthalate 225
Dibutyl Sebacate 227
Diethanolamine 228
Diethyl Phthalate 230
Difluoroethane (HFC) 232
Dimethicone 233
Dimethyl Ether 235
Dimethyl Phthalate 236
Dimethyl Sulfoxide 238
Dimethylacetamide 241
Disodium Edetate 242
Docusate Sodium 244

E

Edetic Acid 247
Erythorbic Acid 250
Erythritol 251
Ethyl Acetate 253
Ethyl Lactate 256
Ethyl Maltol 257
Ethyl Oleate 259
Ethyl Vanillin 261
Ethylcellulose 262
Ethylene Glycol Stearates 267
Ethylene Vinyl Acetate 268
Ethylparaben 270

F

Fructose 273
Fumaric Acid 276

G

Gelatin 278
Glucose, Liquid 282
Glycerin 283
Glyceryl Behenate 286
Glyceryl Monooleate 288
Glyceryl Monostearate 290
Glyceryl Palmitostearate 293
Glycine 295
Glycofurol 297
Guar Gum 298

H

Hectorite 301
Heptafluoropropane (HFC) 303
Hexetidine 304
Hydrocarbons (HC) 306
Hydrochloric Acid 308
Hydrophobic Colloidal Silica 309
Hydroxyethyl Cellulose 311
Hydroxyethylmethyl Cellulose 314
Hydroxypropyl Betadex 315
Hydroxypropyl Cellulose 317
Hydroxypropyl Cellulose, Low-substituted 322
Hydroxypropyl Starch 325
Hypromellose 326
Hypromellose Acetate Succinate 330
Hypromellose Phthalate 333

I

Imidurea 337
Inulin 339

Iron Oxides 340
Isomalt 342
Isopropyl Alcohol 346
Isopropyl Myristate 348
Isopropyl Palmitate 350

K

Kaolin 352

L

Lactic Acid 355
Lactitol 357
Lactose, Anhydrous 359
Lactose, Inhalation 362
Lactose, Monohydrate 364
Lactose, Monohydrate and Corn Starch 370
Lactose, Monohydrate and Microcrystalline Cellulose 371
Lactose, Monohydrate and Povidone 373
Lactose, Monohydrate and Powdered Cellulose 374
Lactose, Spray-Dried 376
Lanolin 378
Lanolin, Hydrous 380
Lanolin Alcohols 382
Lauric Acid 383
Lecithin 385
Leucine 387
Linoleic Acid 389

M

Macrogol 15 Hydroxystearate 391
Magnesium Aluminum Silicate 393
Magnesium Carbonate 397
Magnesium Oxide 400
Magnesium Silicate 402
Magnesium Stearate 404
Magnesium Trisilicate 408
Maleic Acid 410
Malic Acid 411
Maltitol 414
Maltitol Solution 416
Maltodextrin 418
Maltol 421
Maltose 422
Mannitol 424
Medium-chain Triglycerides 429
Meglumine 431
Menthol 433
Methionine 436
Methylcellulose 438
Methylparaben 441
Mineral Oil 445
Mineral Oil, Light 447
Mineral Oil and Lanolin Alcohols 449
Monoethanolamine 450
Monosodium Glutamate 452
Monothioglycerol 454
Myristic Acid 455
Myristyl Alcohol 456

N

Neohesperidin Dihydrochalcone 458
Neotame 460
Nitrogen 461
Nitrous Oxide 463

O

Octyldodecanol 465
Oleic Acid 466
Oleyl Alcohol 468
Olive Oil 470

P

Palmitic Acid 473
Paraffin 474
Peanut Oil 476
Pectin 478
Pentetic Acid 480
Petrolatum 481
Petrolatum and Lanolin Alcohols 484
Phenol 485
Phenoxyethanol 488
Phenylethyl Alcohol 490
Phenylmercuric Acetate 492
Phenylmercuric Borate 494
Phenylmercuric Nitrate 496
Phospholipids 499
Phosphoric Acid 503
Polacrilin Potassium 504
Poloxamer 506
Polycarbophil 509
Polydextrose 513
Poly (DL-Lactic Acid) 515
Polyethylene Glycol 517
Polyethylene Oxide 522

Polymethacrylates 525
Poly(methyl vinyl ether/maleic anhydride) 534
Polyoxyethylene Alkyl Ethers 536
Polyoxyethylene Castor Oil Derivatives 542
Polyoxyethylene Sorbitan Fatty Acid Esters 549
Polyoxyethylene Stearates 554
Polyoxylglycerides 557
Polyvinyl Acetate Phthalate 562
Polyvinyl Alcohol 564
Potassium Alginate 566
Potassium Alum 567
Potassium Benzoate 569
Potassium Bicarbonate 570
Potassium Chloride 572
Potassium Citrate 574
Potassium Hydroxide 576
Potassium Metabisulfite 577
Potassium Sorbate 579
Povidone 581
Propionic Acid 586
Propyl Gallate 587
Propylene Carbonate 590
Propylene Glycol 592
Propylene Glycol Alginate 594
Propylparaben 596
Propylparaben Sodium 599
Pyrrolidone 600

R

Raffinose 603

S

Saccharin 605
Saccharin Sodium 608
Safflower Oil 610
Saponite 612
Sesame Oil 614
Shellac 616
Simethicone 619
Sodium Acetate 620
Sodium Alginate 622
Sodium Ascorbate 625
Sodium Benzoate 627
Sodium Bicarbonate 629
Sodium Borate 633
Sodium Carbonate 635
Sodium Chloride 637
Sodium Citrate Dihydrate 640
Sodium Cyclamate 643
Sodium Formaldehyde Sulfoxylate 645
Sodium Hyaluronate 646
Sodium Hydroxide 648
Sodium Lactate 650
Sodium Lauryl Sulfate 651
Sodium Metabisulfite 654
Sodium Phosphate, Dibasic 656
Sodium Phosphate, Monobasic 659
Sodium Propionate 661
Sodium Starch Glycolate 663
Sodium Stearyl Fumarate 667
Sodium Sulfite 669
Sodium Thiosulfate 671
Sorbic Acid 672
Sorbitan Esters (Sorbitan Fatty Acid Esters) 675
Sorbitol 679
Soybean Oil 682
Starch 685
Starch, Pregelatinized 691
Starch, Sterilizable Maize 695
Stearic Acid 697
Stearyl Alcohol 700
Sucralose 701
Sucrose 703
Sucrose Octaacetate 707
Sugar, Compressible 709
Sugar, Confectioner's 710
Sugar Spheres 712
Sulfobutylether β-Cyclodextrin 714
Sulfur Dioxide 718
Sulfuric Acid 719
Sunflower Oil 721
Suppository Bases, Hard Fat 722

T

Tagatose 727
Talc 728
Tartaric Acid 731
Tetrafluoroethane (HFC) 733
Thaumatin 735
Thimerosal 736
Thymol 739
Titanium Dioxide 741
Tragacanth 744

Trehalose 746
Triacetin 748
Tributyl Citrate 749
Tricaprylin 751
Triethanolamine 754
Triethyl Citrate 756
Triolein 757

V

Vanillin 760
Vegetable Oil, Hydrogenated 762
Vitamin E Polyethylene Glycol Succinate 764

W

Water 766
Wax, Anionic Emulsifying 770
Wax, Carnauba 772
Wax, Cetyl Esters 774
Wax, Microcrystalline 775
Wax, Nonionic Emulsifying 777
Wax, White 779
Wax, Yellow 780

X

Xanthan Gum 782
Xylitol 786

Z

Zein 790
Zinc Acetate 791
Zinc Stearate 793

Appendix I: Suppliers Directory 795
Appendix II: List of Excipient 'E' Numbers 847
Appendix III: List of Excipient 'EINECS' Numbers 849
Appendix IV: List of Excipient Molecular Weights 852
Index 855

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Sodium Chloride

1 Nonproprietary Names

BP: Sodium Chloride
JP: Sodium Chloride
PhEur: Sodium Chloride
USP: Sodium Chloride

2 Synonyms

Alberger; chlorure de sodium; common salt; hopper salt; natrii chloridum; natural halite; rock salt; saline; salt; sea salt; table salt.

3 Chemical Name and CAS Registry Number

Sodium chloride [7647-14-5]

4 Empirical Formula and Molecular Weight

NaCl 58.44

5 Structural Formula

See Section 4.

6 Functional Category

Tablet and capsule diluent; tonicity agent.

7 Applications in Pharmaceutical Formulation or Technology

Sodium chloride is widely used in a variety of parenteral and nonparenteral pharmaceutical formulations, where the primary use is to produce isotonic solutions.

Sodium chloride has been used as a lubricant and diluent in capsules and direct-compression tablet formulations in the past,[1–5] although this practice is no longer common. Sodium chloride has also been used as a channeling agent[6,7] and as an osmotic agent[8,9] in the cores of controlled-release tablets. It has been used as a porosity modifier in tablet coatings,[10] and to control drug release from microcapsules.[11,12]

The addition of sodium chloride to aqueous spray-coating solutions containing hydroxypropyl cellulose or hypromellose suppresses the agglomeration of crystalline cellulose particles.[13] Sodium chloride can also be used to modify drug release from gels[14] and from emulsions.[15] It can be used to control micelle size,[16–18] and to adjust the viscosity of polymer dispersions by altering the ionic character of a formulation.[19,20]

See Table I.

Table I: Uses of sodium chloride.

Use	Concentration (%)
Capsule diluent	10–80
Controlled flocculation of suspensions	≤1
Direct compression tablet diluent	10–80
To produce isotonic solutions in intravenous or ophthalmic preparations	≤0.9
Water-soluble tablet lubricant	5–20

8 Description

Sodium chloride occurs as a white crystalline powder or colorless crystals; it has a saline taste. The crystal lattice is a face-centered cubic structure. Solid sodium chloride contains no water of crystallization although, below 0°C, salt may crystallize as a dihydrate.

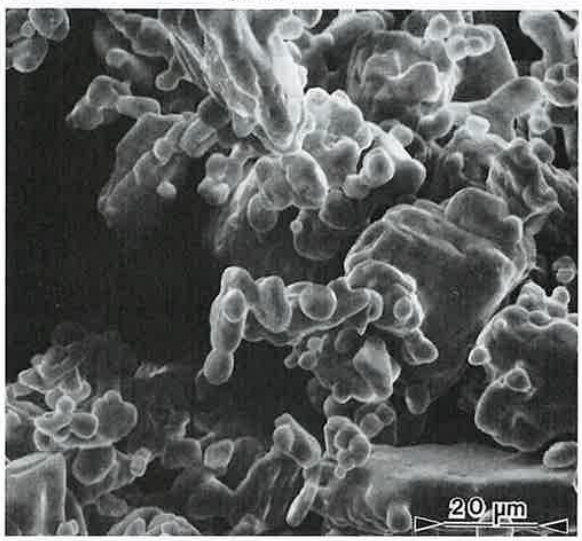
9 Pharmacopeial Specifications

See Table II. *See also* Section 18.

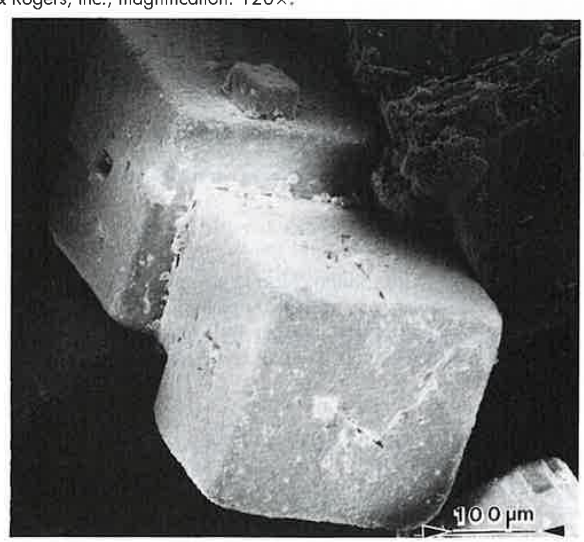
10 Typical Properties

Acidity/alkalinity pH = 6.7–7.3 (saturated aqueous solution)
Angle of repose 38° for cubic crystals
Boiling point 1413°C

SEM 1: Excipient: sodium chloride, powder; manufacturer: Mallinckrodt Speciality Chemicals Co.; magnification: 600×.



SEM 2: Excipient: sodium chloride, granular; manufacturer: Van Waters & Rogers, Inc.; magnification: 120×.



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Amneal Exhibit 1014, Page 9 of 18
Amneal Pharmaceuticals, Inc. v. Nivagen Pharmaceuticals, Inc.
IPR2025-00779

SEM 3: Excipient: sodium chloride, granular; manufacturer: Van Waters & Rogers, Inc.; magnification: 600×.

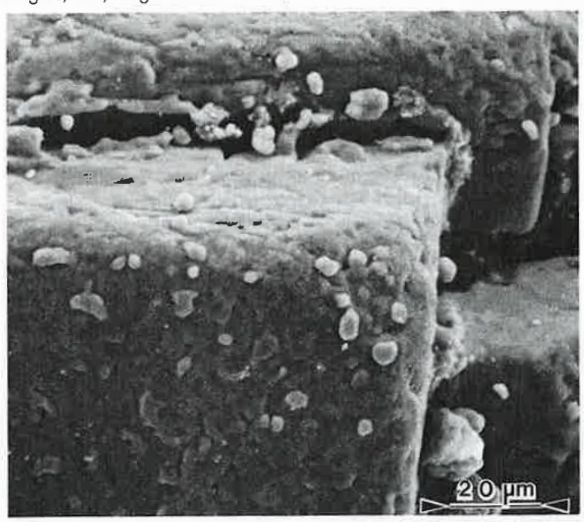

Table II: Pharmacopeial specifications for sodium chloride.

Test	JP XV	PhEur 6.0	USP 32
Identification	+	+	+
Characters	+	+	−
Appearance of solution	+	+	+
Acidity or alkalinity	+	+	+
Loss on drying	≤0.5%	≤0.5%	≤0.5%
Arsenic	≤2 ppm	≤1 ppm	≤1 µg/g
Bromides	+	≤100 ppm	≤0.01%
Chloride	−	−	+
Barium	+	+	+
Nitrites	−	+	+
Aluminum	−	≤0.2 ppm[a]	≤0.2 µg/g[a]
Magnesium and alkaline earth metals	+	≤100 ppm	≤0.01%
Iodide	+	+	+
Iron	+	≤2 ppm	≤2 µg/g
Sulfate	+	≤200 ppm	≤0.02%
Ferrocyanides	+	+	+
Heavy metals	≤3 ppm	≤5 ppm	≤5 ppm
Phosphate	+	≤25 ppm	≤0.0025%
Potassium	−	≤500 ppm[a] [b]	≤0.05%[a] [b]
Sterility	−	−	+
Bacterial endotoxins	−	≤5 IU/g[b]	+
Assay (dried basis)	99.0–100.5%	99.0–100.5%	99.0–100.5%

(a) If for use in peritoneal dialysis, hemodialysis or hemofiltration solutions.
(b) If for parenteral use.

Compressibility With sodium chloride powder of less than 30 µm particle size, tablets are formed by plastic deformation; above this size, both plastic deformation and fracture occur.[1,3,4] *See also* Figure 1.

Density

2.17 g/cm^3;

1.20 g/cm^3 for saturated aqueous solution.

Density (bulk) 0.93 g/cm^3

Density (tapped) 1.09 g/cm^3

Dielectric constant 5.9 at 1 MHz

Freezing point depression *see* Table III.

Table III: Freezing point depression values of aqueous sodium chloride.

Aqueous sodium chloride solution (% w/v)	Freezing point depression (°C)
11.69	6.90
17.53	10.82
23.38	15.14
30.39	21.12

Hardness (Mohs) 2–2.5

Hygroscopicity Hygroscopic above 75% relative humidity.

Melting point 804°C

NIR spectra *see* Figure 2.

Osmolarity A 0.9% w/v aqueous solution is iso-osmotic with serum.

Refractive index n_D^{20} = 1.343 for a 1 M aqueous solution.

Solubility *see* Table IV.

Thermal conductivity 1.15 Wm/K at 273 K

Specific heat capacity 854 J/kg/K

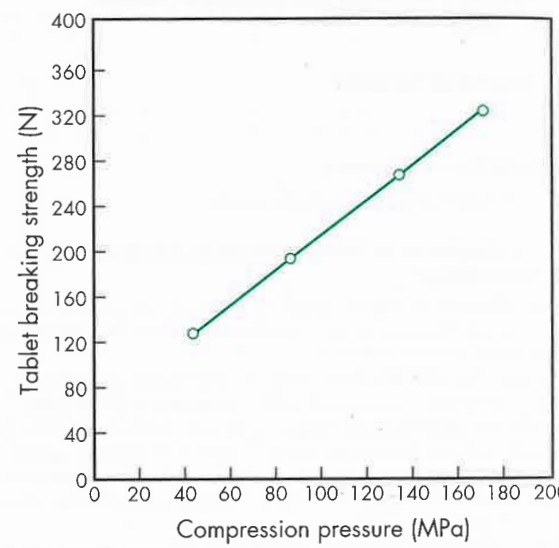

Figure 1: Compression characteristics of sodium chloride (cubic crystals).[3] Tablet diameter = 12 mm.

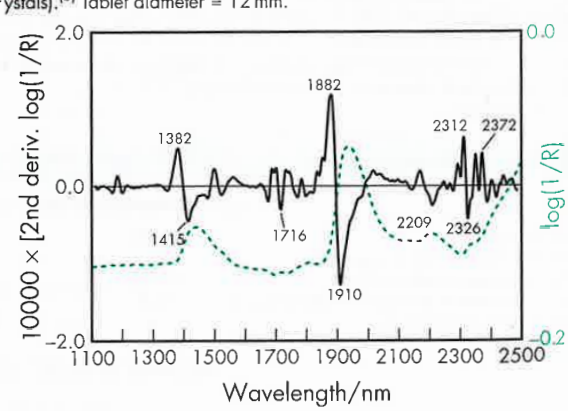

Figure 2: Near-infrared spectrum of sodium chloride measured by reflectance. Sodium chloride does not absorb in the near-infrared region; however, it will generally show some peaks due to traces of moisture (approx. 1450 nm and 1950 nm).

Table IV: Solubility of sodium chloride.

Solvent	Solubility at 20°C unless otherwise stated
Ethanol	Slightly soluble
Ethanol (95%)	1 in 250
Glycerin	1 in 10
Water	1 in 2.8
	1 in 2.6 at 100°C

Vapor pressure

133.3 Pa at 865°C for solid;

1759.6 Pa at 20°C for a saturated aqueous solution (equivalent to 75.3% relative humidity).

Viscosity A 10% w/v solution has a viscosity of 1.19 mPa s (1.19 cP).

11 Stability and Storage Conditions

Aqueous sodium chloride solutions are stable but may cause the separation of glass particles from certain types of glass containers. Aqueous solutions may be sterilized by autoclaving or filtration. The solid material is stable and should be stored in a well-closed container, in a cool, dry place.

It has been shown that the compaction characteristics and the mechanical properties of tablets are influenced by the relative humidity of the storage conditions under which sodium chloride was kept.[21,22]

12 Incompatibilities

Aqueous sodium chloride solutions are corrosive to iron. They also react to form precipitates with silver, lead, and mercury salts. Strong oxidizing agents liberate chlorine from acidified solutions of sodium chloride. The solubility of the antimicrobial preservative methylparaben is decreased in aqueous sodium chloride solutions[23] and the viscosity of carbomer gels and solutions of hydroxyethyl cellulose or hydroxypropyl cellulose is reduced by the addition of sodium chloride.

13 Method of Manufacture

Sodium chloride occurs naturally as the mineral halite. Commercially, it is obtained by the solar evaporation of sea water, by mining, or by the evaporation of brine from underground salt deposits.

14 Safety

Sodium chloride is the most important salt in the body for maintaining the osmotic tension of blood and tissues. About 5–12 g of sodium chloride is consumed daily, in the normal adult diet, and a corresponding amount is excreted in the urine. As an excipient, sodium chloride may be regarded as an essentially nontoxic and nonirritant material. However, toxic effects following the oral ingestion of 0.5–1.0 g/kg body-weight in adults may occur. The oral ingestion of larger quantities of sodium chloride, e.g. 1000 g in 600 mL of water,[24] is harmful and can induce irritation of the gastrointestinal tract, vomiting, hypernatremia, respiratory distress, convulsions, or death.

In rats, the minimum lethal intravenous dose is 2.5 g/kg body-weight.

LD_{50} (mouse, IP): 6.61 g/kg[25]

LD_{50} (mouse, IV): 0.65 g/kg

LD_{50} (mouse, oral): 4.0 g/kg

LD_{50} (mouse, SC): 3.0 g/kg

LD_{50} (rat, oral): 3.0 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. If heated to high temperatures, sodium chloride evolves a vapor irritating to the eyes.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Database (injections; inhalations; nasal, ophthalmic, oral, otic, rectal, and topical preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Potassium chloride.

18 Comments

Sodium chloride is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32–NF27, the General Chapter 5.8 in PhEur 6.0, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

Domestic table salt may contain sodium iodide (as a prophylactic substance against goiter) and agents such as magnesium carbonate, calcium phosphate, or starch, which reduce the hygroscopic characteristics of the salt and maintain the powder in a free-flowing state.

Food-grade dendritic salt, which is porous, can be used as an absorbent for liquid medications, and as a tablet diluent in specific formulations.

Each gram of sodium chloride represents approximately 17.1 mmol of sodium and 17.1 mmol of chloride; 2.54 g of sodium chloride is approximately equivalent to 1 g of sodium.

A saturated solution of sodium chloride can be used as a constant-humidity solution; at 25°C, a relative humidity of 75% is produced. A specification for sodium chloride is contained in the Food Chemicals Codex (FCC).[26]

The EINECS number for sodium chloride is 231-598-3. The PubChem Compound ID (CID) for sodium chloride is 5234.

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20 General References

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Heng PW *et al.* Influence of osmotic agents in diffusion layer on drug release from multilayer coated pellets. *Drug Dev Ind Pharm* 2004; 30(2): 213–220.

21 Author

JS Maximilien.

22 Date of Revision

3 February 2009.

Sodium Citrate Dihydrate

S

1 Nonproprietary Names

BP: Sodium Citrate
JP: Sodium Citrate Hydrate
PhEur: Sodium Citrate
USP: Sodium Citrate

2 Synonyms

Citric acid trisodium salt; E331; natrii citras; sodium citrate tertiary; trisodium citrate.

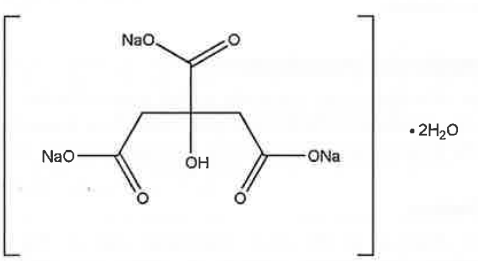
3 Chemical Name and CAS Registry Number

Trisodium 2-hydroxypropane-1,2,3-tricarboxylate dihydrate [6132-04-3]

4 Empirical Formula and Molecular Weight

$C_6H_5Na_3O_7 \cdot 2H_2O$ 294.10

5 Structural Formula



6 Functional Category

Alkalizing agent; buffering agent; emulsifying agent; sequestering agent.

7 Applications in Pharmaceutical Formulation or Technology

Sodium citrate, as either the dihydrate or anhydrous material, is widely used in pharmaceutical formulations; *see* Table I.

It is used in food products, primarily to adjust the pH of solutions. It is also used as a sequestering agent. The anhydrous material is used in effervescent tablet formulations.[1] Sodium citrate is additionally used as a blood anticoagulant either alone or in combination with other citrates such as disodium hydrogen citrate.

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20 General References

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21 Authors

MA Kabir, JP Reo.

22 Date of Revision

5 February 2009.

Sodium Phosphate, Dibasic

1 Nonproprietary Names

BP: Anhydrous Disodium Hydrogen Phosphate
Disodium Hydrogen Phosphate Dihydrate
Disodium Hydrogen Phosphate Dodecahydrate

JP: Dibasic Sodium Phosphate Hydrate

PhEur: Disodium Phosphate, Anhydrous
Disodium Phosphate Dihydrate
Disodium Phosphate Dodecahydrate

USP: Dibasic Sodium Phosphate

Note that the BP 2009 and PhEur contain three separate monographs for the anhydrous (PhEur 6.3), the dihydrate (PhEur 6.0), and the dodecahydrate (PhEur 6.1); the JP XV contains one monograph for the dodecahydrate; and the USP 32 contains one monograph that includes the anhydrous, the monohydrate, the dihydrate, the heptahydrate, and the dodecahydrate. *See also* Section 8.

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2 Synonyms

Dinatrii phosphas anhydricus; dinatrii phosphas dihydricus; dinatrii phosphas dodecahydricus; disodium hydrogen phosphate; disodium phosphate; E339; phosphoric acid, disodium salt; secondary sodium phosphate; sodium orthophosphate.

3 Chemical Name and CAS Registry Number

Anhydrous dibasic sodium phosphate [7558-79-4]
Dibasic sodium phosphate dihydrate [10028-24-7]
Dibasic sodium phosphate dodecahydrate [10039-32-4]
Dibasic sodium phosphate heptahydrate [7782-85-6]
Dibasic sodium phosphate hydrate [10140-65-5]
Dibasic sodium phosphate monohydrate [118830-14-1]

4 Empirical Formula and Molecular Weight

Na_2HPO_4	141.96
$Na_2HPO_4 \cdot H_2O$	159.94
$Na_2HPO_4 \cdot 2H_2O$	177.98
$Na_2HPO_4 \cdot 7H_2O$	268.03
$Na_2HPO_4 \cdot 12H_2O$	358.08

5 Structural Formula

See Section 4.

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; for example as an emulsifier in processed cheese.

8 Description

The USP 32 states that dibasic sodium phosphate is dried or contains, 1, 2, 7, or 12 molecules of water of hydration.

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

See Table I.

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

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

Moisture content The anhydrous form is hygroscopic and will absorb up to 7 moles of water on exposure to air, whereas the heptahydrate is stable in air.

NIR spectra *see* Figure 1.

Osmolarity A 2.23% w/v aqueous solution of the dihydrate is isoosmotic with serum; a 4.45% w/v aqueous solution of the dodecahydrate is isoosmotic with serum.

Solubility Very soluble in water, more so in hot or boiling water; practically insoluble in ethanol (95%). The anhydrous material

Table I: Pharmacopeial specifications for sodium phosphate, dibasic.

Test	JP XV[a]	PhEur 6.0,[b] 6.1,[a] 6.3[c]	USP 32
Identification	+	+	+
Characters	+	+	–
Appearance of solution	+	+	–
pH	9.0–9.4	–	–
Reducing substances	–	+	–
Insoluble substances	–	–	⩽0.4%
Monosodium phosphate	–	⩽2.5%	–
Carbonate	+	–	–
Chloride	⩽0.014%	+	⩽0.06%
Anhydrous	–	⩽200 ppm	–
Dihydrate	–	⩽400 ppm	–
Dodecahydrate	–	⩽200 ppm	–
Water	–	+	–
Anhydrous	–	–	–
Dihydrate	–	–	–
Dodecahydrate	–	57.0–61.0%	–
Sulfates	⩽0.038%	+	⩽0.2%
Anhydrous	–	⩽500 ppm	–
Dihydrate	–	⩽0.1%	–
Dodecahydrate	–	⩽500 ppm	–
Arsenic	⩽2 ppm	+	⩽16 ppm
Anhydrous	–	⩽2 ppm	–
Dihydrate	–	⩽4 ppm	–
Dodecahydrate	–	⩽2 ppm	–
Heavy metals	⩽10 ppm	+	⩽0.002%
Anhydrous	–	⩽10 ppm	–
Dihydrate	–	⩽20 ppm	–
Dodecahydrate	–	⩽10 ppm	–
Iron	–	+	–
Anhydrous	–	⩽20 ppm	–
Dihydrate	–	⩽40 ppm	–
Dodecahydrate	–	⩽20 ppm	–
Loss on drying	57.0–61.0%	+	+
Anhydrous	–	⩽1.0%	⩽5.0%
Monohydrate	–	–	10.3–12.0%
Dihydrate	–	19.5–21.0%	18.5–21.5%
Heptahydrate	–	–	43.0–50.0%
Dodecahydrate	–	–	55.0–64.0%
Assay (dried basis)	⩾98.0%	98.0–101.0% 98.5–102.5%[a]	98.0–100.5%

(a) JP XV and PhEur 6.1 for the dodecahydrate.
(b) PhEur 6.0 for the dihydrate;
(c) PhEur 6.3 for the anhydrous.

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.

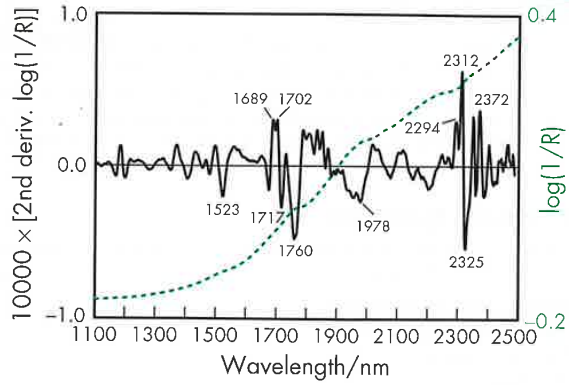

Figure 1: Near-infrared spectrum of dibasic sodium phosphate measured by reflectance.

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 and neutralized with sodium carbonate, and dibasic sodium phosphate is 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, making hypophosphatemia (phosphate deficiency)[1] 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, and the remainder is excreted in the feces.

Excessive administration of phosphate, particularly intravenously, rectally, or in patients with renal failure, can cause hyperphosphatemia that 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 orally 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. 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.

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16 Regulatory Status

GRAS listed. Accepted in Europe for use as a food additive. Included in the FDA Inactive Ingredients Database (injections; infusions; nasal, ophthalmic, oral, otic, topical, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

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

Dibasic potassium phosphate

Empirical formula 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.
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 isoosmotic with serum.
Solubility Freely soluble in water; very slightly soluble in ethanol (95%).
Comments One gram of dibasic potassium phosphate contains approximately 11.5 mmol of potassium and 5.7 mmol of phosphate.

Tribasic sodium phosphate

Empirical formula $Na_3PO_4 \cdot xH_2O$
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 12.0–12.2.
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.

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18 Comments

One gram of anhydrous dibasic sodium phosphate represents approximately 14.1 mmol of sodium and 7.0 mmol of phosphate.

One gram of dibasic sodium phosphate dihydrate represents approximately 11.2 mmol of sodium and 5.6 mmol of phosphate.

One gram of dibasic sodium phosphate heptahydrate represents approximately 7.5 mmol of sodium and 3.7 mmol of phosphate.

One gram of dibasic sodium phosphate dodecahydrate represents approximately 5.6 mmol of sodium and 2.8 mmol of phosphate.

A specification for sodium phosphate, dibasic is contained in the Food Chemicals Codex (FCC).[8]

The PubChem Compound ID (CID) for anhydrous dibasic sodium phosphate is 24203, and for dibasic sodium phosphate dodecahydrate is 61456.

19 Specific References

1 Lloyd CW, Johnson CE. Management of hypophosphatemia. *Clin Pharm* 1988; 7: 123–128.
2 Holland PC *et al.* Prenatal deficiency of phosphate, phosphate supplementation, and rickets in very-low-birthweight infants. *Lancet* 1990; 335: 697–701.
3 Albert A, Serjeant EP. *Ionization Constants of Acids and Bases*, 2nd edn. Edinburgh: Chapman and Hall, 1971.
4 Benjamin BE. Ciprofloxacin and sodium phosphates not compatible during actual Y-site injection [letter]. *Am J Health Syst Pharm* 1996; 53: 1850–1851.
5 Haskell LP. Hypocalcaemic tetany induced by hypertonic-phosphate enema [letter]. *Lancet* 1985; ii: 1433.
6 Martin RR *et al.* Fatal poisoning from sodium phosphate enema: case report and experimental study. *J Am Med Assoc* 1987; 257: 2190–2192.
7 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004; 3273.
8 *Food Chemicals Codex*, 6th edn. Bethesda, MD: United States Pharmacopeia, 2008; 900.

20 General References

Sweetman SC, ed. *Martindale: The Complete Drug Reference*, 36th edn. London: Pharmaceutical Press, 2009; 1682.

21 Author

AS Kearney.

22 Date of Revision

12 February 2009.

Sodium Phosphate, Monobasic

1 Nonproprietary Names

BP: Anhydrous Sodium Dihydrogen Phosphate
Sodium Dihydrogen Phosphate Monohydrate
Sodium Dihydrogen Phosphate Dihydrate

PhEur: Sodium Dihydrogen Phosphate Dihydrate

USP: Monobasic Sodium Phosphate

Note that the BP 2009 contains three separate monographs for the anhydrous, the monohydrate, and the dihydrate; the PhEur 6.0 contains a single monograph for the dihydrate; and the USP 32 contains one monograph for the anhydrous, the monohydrate and the dihydrate. *See also* Section 8.

2 Synonyms

Acid sodium phosphate; E339; *Kalipol 32*; monosodium orthophosphate; monosodium phosphate; natrii dihydrogenophosphas dihydricus; phosphoric acid, monosodium salt; primary sodium phosphate; sodium biphosphate; sodium dihydrogen orthophosphate; sodium dihydrogen 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 [13472-35-0]

4 Empirical Formula and Molecular Weight

NaH_2PO_4	119.98
$NaH_2PO_4 \cdot H_2O$	137.99
$NaH_2PO_4 \cdot 2H_2O$	156.01

5 Structural Formula

See Section 4.

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.[1–3]

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

8 Description

The USP 32 states that monobasic sodium phosphate contains one or two molecules of water of hydration or is anhydrous.

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

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium phosphate, monobasic.

Test	PhEur 6.0	USP 32
Identification	+	+
Characters	+	–
Appearance of solution	+	–
Aluminum, calcium and related elements	–	+
Arsenic	≤2 ppm	≤8 ppm
Chloride	≤200 ppm	≤0.014%
Insoluble substances	–	≤0.2%
Heavy metals	≤10 ppm	≤0.002%
Iron	≤10 ppm	–
pH	4.2–4.5	4.1–4.5
Reducing substances	+	–
Sulfate	≤300 ppm	≤0.15%
Water	+	+
Anhydrous	–	≤2.0%
Monohydrate	–	10.0–15.0%
Dihydrate	21.5–24.0%	18.0–26.5%
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
NIR spectra *see* Figures 1 and 2.
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, $Na_2H_2P_2O_7$. 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.[4–6]

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

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Amneal Exhibit 1014, Page 16 of 18
Amneal Pharmaceuticals, Inc. v. Nivagen Pharmaceuticals, Inc.
IPR2025-00779

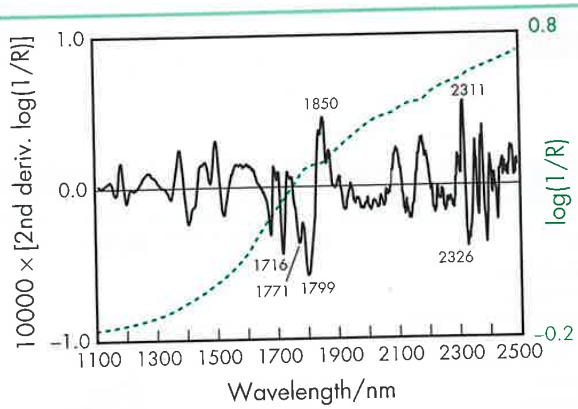

Figure 1: Near-infrared spectrum of anhydrous monobasic sodium phosphate measured by reflectance.

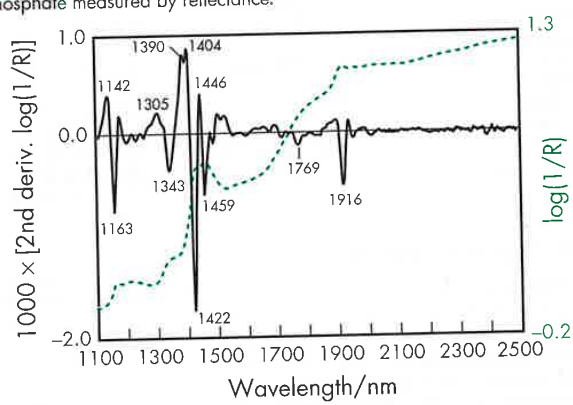

Figure 2: Near-infrared spectrum of monobasic sodium phosphate dihydrate measured by reflectance.

solution is then concentrated and the monobasic sodium phosphate is crystallized.

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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, making hypophosphatemia[1] virtually unknown except in 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, and the remainder is excreted in the feces.

Excessive administration of phosphate, particularly intravenously, rectally, or in patients with renal failure, can cause hyperphosphatemia that may lead to hypocalcemia or other severe electrolyte imbalances.[7–9] Adverse effects occur less frequently following oral consumption, although phosphates act as mild saline laxatives when administered orally 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. 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[10]
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 for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (injections; infusions; ophthalmic, oral, topical, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Dibasic sodium phosphate; monobasic potassium phosphate.

Monobasic potassium phosphate

Empirical formula 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.
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 1 g of monobasic potassium phosphate represents approximately 7.3 mmol of potassium and of phosphate.

The EINECS number for monobasic potassium phosphate is 231-913-4.

18 Comments

One gram of anhydrous monobasic sodium phosphate represents approximately 8.3 mmol of sodium and of phosphate.

One gram of monobasic sodium phosphate monohydrate represents approximately 7.2 mmol of sodium and of phosphate.

One gram of monobasic sodium phosphate dihydrate represents approximately 6.4 mmol of sodium and of phosphate.

A specification for sodium phosphate monobasic is contained in the Food Chemicals Codex (FCC).[11]

The EINECS number for monobasic sodium phosphate is 231-449-2. The PubChem Compound ID (CID) for monobasic sodium phosphate dihydrate is 23673460.

19 Specific References

1 Lloyd CW, Johnson CE. Management of hypophosphatemia. *Clin Pharm* 1988; 7: 123–128.
2 Holland PC *et al.* Prenatal deficiency of phosphate, phosphate supplementation, and rickets in very-low-birthweight infants. *Lancet* 1990; 335: 697–701.
3 Rosen GH *et al.* Intravenous phosphate repletion regimen for critically ill patients with moderate hypophosphatemia. *Crit Care Med* 1995; 23: 1204–1210.
4 Eggert LD *et al.* Calcium and phosphorus compatibility in parenteral nutrition solutions for neonates. *Am J Hosp Pharm* 1982; 39: 49–53.
5 Niemiec PW, Vanderveen TW. Compatibility considerations in parenteral nutrient solutions. *Am J Hosp Pharm* 1984; 41: 893–911.

6 Pereira-da-Silva L *et al.* Compatibility of calcium and phosphate in four parenteral nutrition solutions for preterm neonates. *Am J Health Syst Pharm* 2003; **60**: 1041–1044.
7 Haskell LP. Hypocalcaemic tetany induced by hypertonic-phosphate enema [letter]. *Lancet* 1985; **ii**: 1433.
8 Larson JE *et al.* Laxative phosphate poisoning: pharmacokinetics of serum phosphorus. *Hum Toxicol* 1986; **5**: 45–49.
9 Martin RR *et al.* Fatal poisoning from sodium phosphate enema: case report and experimental study. *J Am Med Assoc* 1987; **257**: 2190–2192.
10 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004; 3274.
11 *Food Chemicals Codex*, 6th edn. Bethesda, MD: United States Pharmacopeia, 2008; 901.

20 General References

Sweetman SC, ed. *Martindale: The Complete Drug Reference*, 36th edn. London: Pharmaceutical Press, 2009; 1682.

21 Authors

ME Quinn, PJ Sheskey.

22 Date of Revision

7 January 2009.

Sodium Propionate

1 Nonproprietary Names

BP: Sodium Propionate
PhEur: Sodium Propionate
USP-NF: Sodium Propionate

2 Synonyms

E281; ethylformic acid, sodium salt, hydrate; methylacetic acid, sodium salt, hydrate; natrii propionas; sodium propanoate hydrate; sodium propionate hydrate.

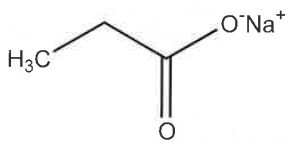
3 Chemical Name and CAS Registry Number

Propionic acid, sodium salt, hydrate [6700-17-0]
Propionic acid, sodium salt, anhydrous [137-40-6]

4 Empirical Formula and Molecular Weight

$C_3H_5NaO_2 \cdot xH_2O$ 114.06 (for monohydrate)
$C_3H_5NaO_2$ 96.06 (for anhydrous)

5 Structural Formula



6 Functional Category

Antimicrobial preservative.

7 Applications in Pharmaceutical Formulation or Technology

As an excipient, sodium propionate is used in oral pharmaceutical formulations as an antimicrobial preservative. Like propionic acid, sodium propionate and other propionic acid salts are fungistatic and bacteriostatic against a number of Gram-positive cocci. Propionates are more active against molds than is sodium benzoate, but have essentially no activity against yeasts; *see* Section 10.

Therapeutically, sodium propionate has been used topically in concentrations up to 10% w/w alone or in combination with other propionates, caprylates, or other antifungal agents, in the form of ointments or solutions for the treatment of dermatophyte infections. Eye drops containing 5% w/v sodium propionate have also been used. *See* Section 18.

In food processes, particularly baking, sodium propionate is used as an antifungal agent; it may also be used as a flavoring agent in food products. In veterinary medicine, sodium propionate is used therapeutically as a glucogenic substance in ruminants.[1]

8 Description

Sodium propionate occurs as colorless transparent crystals or as a granular, free-flowing, crystalline powder. It is odorless, or with a slight characteristic odor, and is deliquescent in moist air. Sodium propionate has a characteristic, slightly cheeselike taste, although by itself it is unpalatable.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium propionate.

Test	PhEur 6.0	USP32–NF27
Identification	+	+
Characters	+	–
Appearance of solution	+	–
Alkalinity	–	+
pH	7.8–9.2	–
Water	–	⩽1.0%
Heavy metals	⩽10 ppm	⩽0.001%
Related substances	+	–
Readily oxidizable substances	+	–
Iron	⩽10 ppm	–
Loss on drying	0.5%	–
Assay (dried basis)	99.0–101.0%	99.0–100.5%

10 Typical Properties

Antimicrobial activity Sodium propionate, propionic acid, and other propionates possess mainly antifungal activity and are used as preservatives primarily against molds; they exhibit essentially no activity against yeasts. Although, in general, propionates exhibit little activity against bacteria, sodium propionate is effective against *Bacillus mesenterium*, the organ-

Amneal Exhibit 1014, Page 18 of 18
Amneal Pharmaceuticals, Inc. v. Nivagen Pharmaceuticals, Inc.
IPR2025-00779