

Handbook of Pharmaceutical Excipients

Handbook of Pharmaceutical Excipients

FIFTH EDITION

Edited by

Raymond C Rowe

BPharm, PhD, DSc, FRPharmS, CChem,
FRSC, CPhys, MInstP

Chief Scientist

Intelligensys Ltd
Billingham, UK

Paul J Sheskey

BSc, RPh

Technical Services Leader

The Dow Chemical Company
Midland
MI, USA

Siân C Owen

BSc, MA

Development Editor

Royal Pharmaceutical Society of Great Britain
London, UK



London • Chicago

Published by the Pharmaceutical Press

Publications division of the Royal Pharmaceutical Society of Great Britain

1 Lambeth High Street, London SE1 7JN, UK
100 South Atkinson Road, Suite 206, Grayslake, IL 60030-7820, USA

and the American Pharmacists Association

2215 Constitution Avenue, NW, Washington, DC 20037-2985, USA

© Pharmaceutical Press and American Pharmacists Association 2006

 is a trademark of Pharmaceutical Press

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

Printed in Great Britain by Butler & Tanner, Frome, Somerset
Typeset by Data Standards Ltd, Frome, Somerset

ISBN 0 85369 618 7 (UK)
ISBN 1 58212 058 7 (USA)

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, without the prior written permission of the copyright holder.

The publisher makes no representation, express or implied, with regard to the accuracy of the information contained in this book and cannot accept any legal responsibility or liability for any errors or omissions that may be made.

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

Library of Congress Cataloging-in-Publication Data

Handbook of pharmaceutical excipients.—5th ed. / edited by Raymond C. Rowe, Paul J. Sheskey, Siân C. Owen.

p. ; cm.

Includes bibliographical references and index.

ISBN 1-58212-058-7 (USA) – ISBN 0-85369-618-7 (UK)

1. Excipients—Handbooks, manuals, etc.

[DNLM: 1. Excipients—Handbooks. 2. Technology, Pharmaceutical—Handbooks. QV 735 H236 2006] I. Rowe, Raymond C. II. Sheskey, Paul J. III. Owen, Siân C. IV. American Pharmacists Association.

RS201.E87H36 2006
615'.19—dc22

2005028523

Povidone

1 Nonproprietary Names

BP: Povidone
JP: Povidone
PhEur: Povidonum
USP: Povidone

2 Synonyms

E1201; *Kollidon*; *Plasdone*; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer.

3 Chemical Name and CAS Registry Number

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

4 Empirical Formula and Molecular Weight

(C₆H₉NO)_n 2500–3 000 000

The USP 28 describes povidone as a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the differing degree of polymerization of which results in polymers of various molecular weights. It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a *K*-value, in the range 10–120. The *K*-value is calculated using Fikentscher's equation:⁽¹⁾

$$\log z = c \left[\frac{75k^2}{1 + 1.5kc} \right] + k$$

where *z* is the relative viscosity of the solution of concentration *c* (in % w/v), and *k* is the *K*-value $\times 10^{-3}$.

Alternatively, the *K*-value may be determined from the following equation:

$$K\text{-value} = \sqrt{\frac{300c \log z (c + 1.5c \log z)^2 + 1.5}{0.15c + 0.003c^2}}$$

where *z* is the relative viscosity of the solution of concentration *c* (in % w/v).

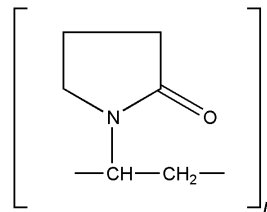
Approximate molecular weights for different povidone grades are shown in Table I.

Table I: Approximate molecular weights for different grades of povidone.

K-value	Approximate molecular weight
12	2 500
15	8 000
17	10 000
25	30 000
30	50 000
60	400 000
90	1 000 000
120	3 000 000

See also Section 8.

5 Structural Formula



6 Functional Category

Disintegrant; dissolution aid; suspending agent; tablet binder.

7 Applications in Pharmaceutical Formulation or Technology

Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet-granulation processes.^(2,3) Povidone is also added to powder blends in the dry form and granulated *in situ* by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms.^(4–6) Povidone solutions may also be used as coating agents.

Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone. See Table II.

Special grades of pyrogen-free povidone are available and have been used in parenteral formulations; see Section 14.

Table II: Uses of povidone.

Use	Concentration (%)
Carrier for drugs	10–25
Dispersing agent	Up to 5
Eye drops	2–10
Suspending agent	Up to 5
Tablet binder, tablet diluent, or coating agent	0.5–5

8 Description

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with *K*-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K-90 and higher *K*-value povidones are manufactured by drum drying and occur as plates.

9 Pharmacopeial Specifications

See Table III.

Table III: Pharmacopeial specifications for povidone.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	—	+	—
pH	—	+	3.0–7.0
$K \leq 30$	3.0–5.0	3.0–5.0	—
$K > 30$	4.0–7.0	4.0–7.0	—
Appearance of solution	+	+	—
Viscosity	—	+	—
Water	$\leq 5.0\%$	$\leq 5.0\%$	$\leq 5.0\%$
Residue on ignition	$\leq 0.1\%$	$\leq 0.1\%$	$\leq 0.1\%$
Lead	—	—	≤ 10 ppm
Aldehydes	≤ 500 ppm ^(a)	≤ 500 ppm ^(a)	$\leq 0.05\%$
Hydrazine	≤ 1 ppm	≤ 1 ppm	≤ 1 ppm
Vinylpyrrolidinone	≤ 10 ppm	≤ 10 ppm	$\leq 0.2\%$
Peroxides	≤ 400 ppm ^(b)	≤ 400 ppm ^(b)	—
K-value	25–90	—	10–120
≤ 15	90.0–108.0%	85.0–115.0%	85.0–115.0%
> 15	90.0–108.0%	90.0–108.0%	90.0–108.0%
Heavy metals	≤ 10 ppm	≤ 10 ppm	—
Assay (nitrogen content)	11.5–12.8%	11.5–12.8%	11.5–12.8%

^(a) Expressed as acetaldehyde.^(b) Expressed as hydrogen peroxide.

10 Typical Properties

Acidity/alkalinity: pH = 3.0–7.0 (5% w/v aqueous solution).

Density (bulk): 0.29–0.39 g/cm³ for *Plasdone*.

Density (tapped): 0.39–0.54 g/cm³ for *Plasdone*.

Density (true): 1.180 g/cm³

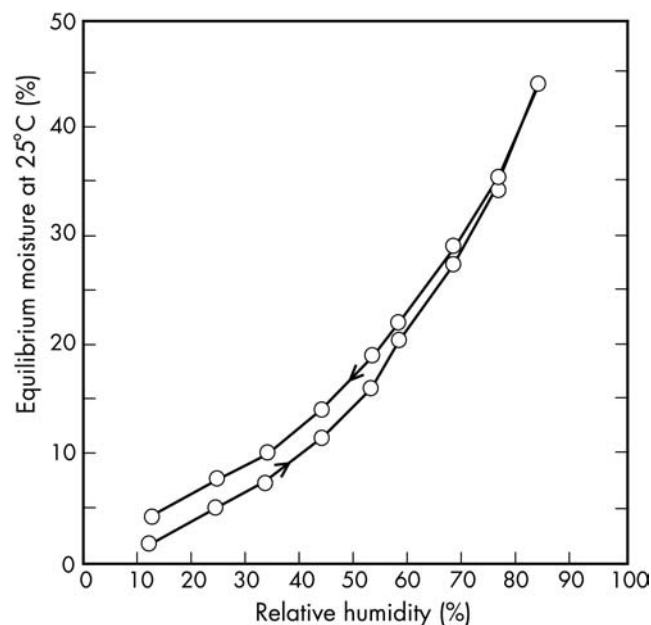
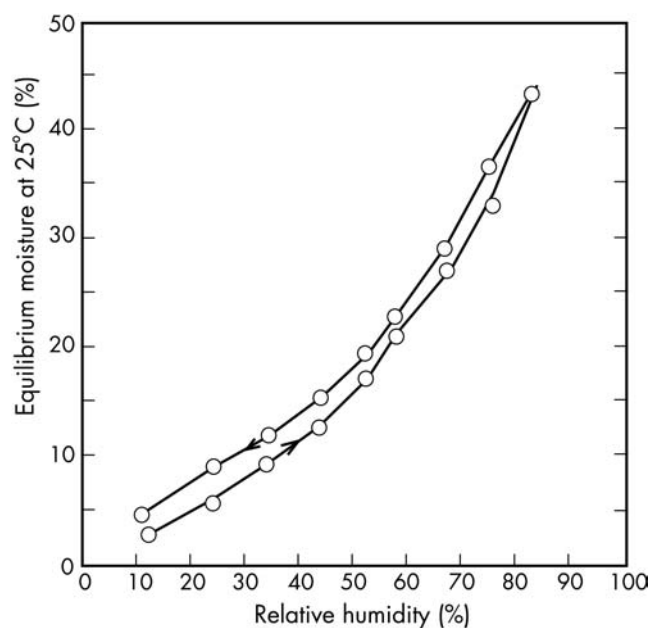
Flowability:

20 g/s for povidone K-15;

16 g/s for povidone K-29/32.

Melting point: softens at 150°C.

Moisture content: povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humidities. See Figures 1 and 2.

**Figure 1:** Sorption-desorption isotherm of povidone K-15 (*Plasdone* K-15).**Figure 2:** Sorption-desorption isotherm of povidone K-29/32 (*Plasdone* K-29/32).

Particle size distribution:

Kollidon 25/30: 90% >50 μm, 50% >100 μm, 5% >200 μm;

Kollidon 90: 90% >200 μm, 95% >250 μm.⁽⁷⁾

Solubility: freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the K-value.

Viscosity (dynamic): the viscosity of aqueous povidone solutions depends on both the concentration and the molecular weight of the polymer employed. See Tables IV and V.⁽⁷⁾

Table IV: Dynamic viscosity of 10% w/v aqueous povidone (*Kollidon*) solutions at 20°C.⁽⁷⁾

Grade	Dynamic viscosity (mPa s)
K-11/14	1.3–2.3
K-16/18	1.5–3.5
K-24/27	3.5–5.5
K-28/32	5.5–8.5
K-85/95	300–700

Table V: Dynamic viscosity of 5% w/v povidone (*Kollidon*) solutions in ethanol (95%) and propan-2-ol at 25°C.⁽⁷⁾

Grade	Dynamic viscosity (mPa s)	
	Ethanol (95%)	Propan-2-ol
K-12PF	1.4	2.7
K-17PF	1.9	3.1
K-25	2.7	4.7
K-30	3.4	5.8
K-90	53.0	90.0

SEM: 1

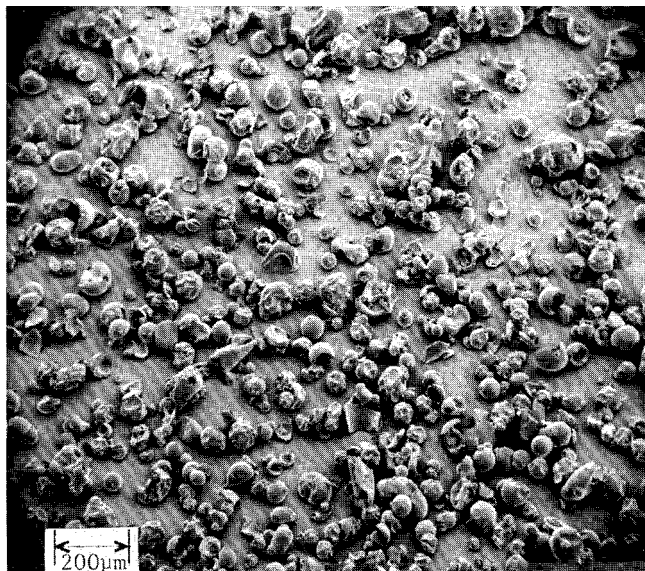
Excipient: Povidone K-15 (Plasdone K-15)

Manufacturer: ISP

Lot No.: 82A-1

Magnification: 60×

Voltage: 5 kV

**SEM: 3**

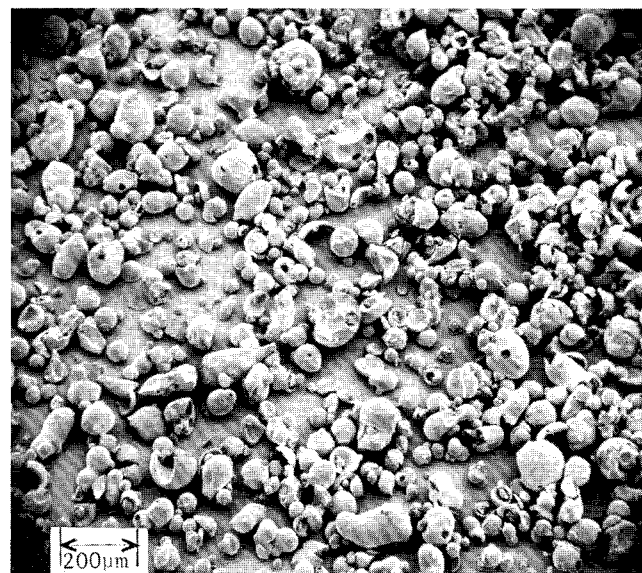
Excipient: Povidone K-26/28 (Plasdone K-26/28)

Manufacturer: ISP

Lot No.: 82A-2

Magnification: 60×

Voltage: 5 kV

**SEM: 2**

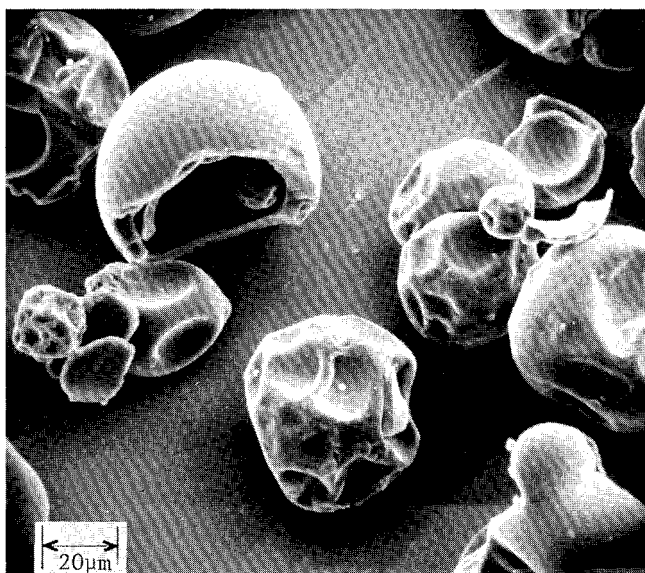
Excipient: Povidone K-15 (Plasdone K-15)

Manufacturer: ISP

Lot No.: 82A-1

Magnification: 600×

Voltage: 5 kV

**SEM: 4**

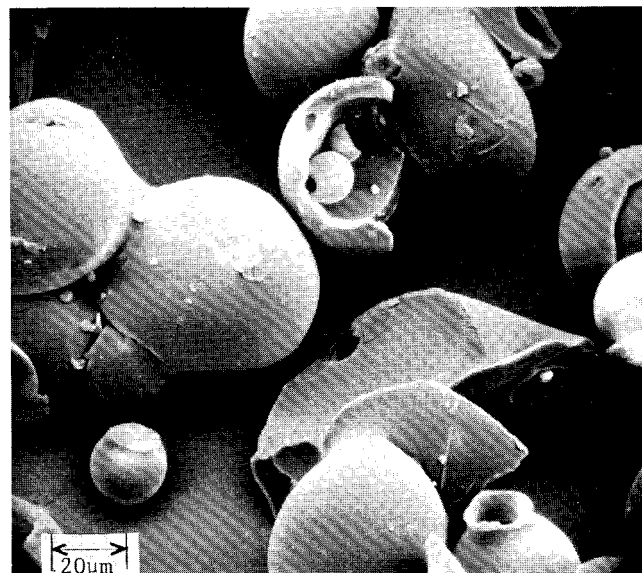
Excipient: Povidone K-26/28 (Plasdone K-26/28)

Manufacturer: ISP

Lot No.: 82A-2

Magnification: 600×

Voltage: 10 kV



SEM: 5

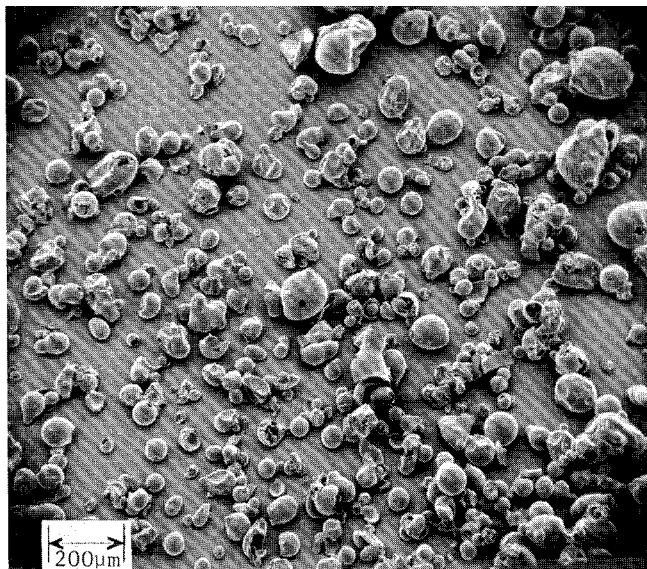
Excipient: Povidone K-30 (Plasdone K-30)

Manufacturer: ISP

Lot No.: 82A-4

Magnification: 60×

Voltage: 10 kV



SEM: 7

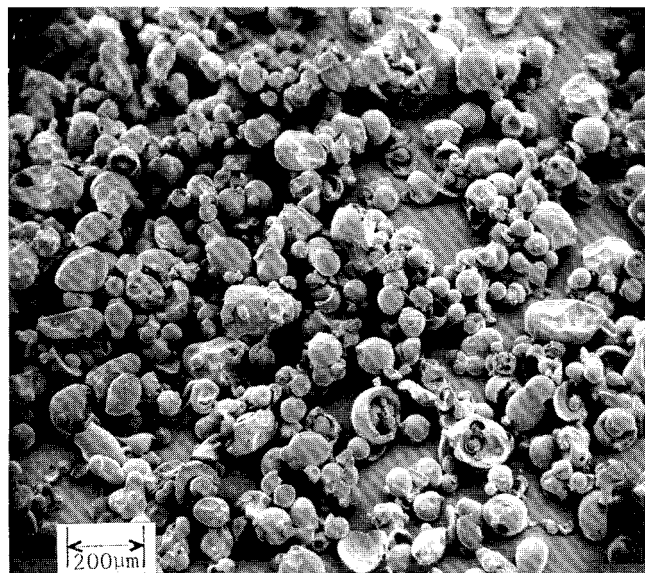
Excipient: Povidone K-29/32 (Plasdone K-29/32)

Manufacturer: ISP

Lot No.: 82A-3

Magnification: 60×

Voltage: 5 kV



SEM: 6

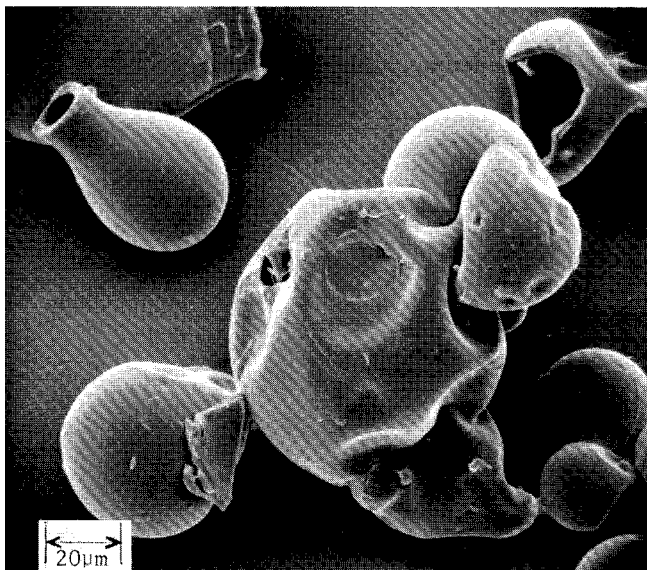
Excipient: Povidone K-30 (Plasdone K-30)

Manufacturer: ISP

Lot No.: 82A-4

Magnification: 600×

Voltage: 10 kV



SEM: 8

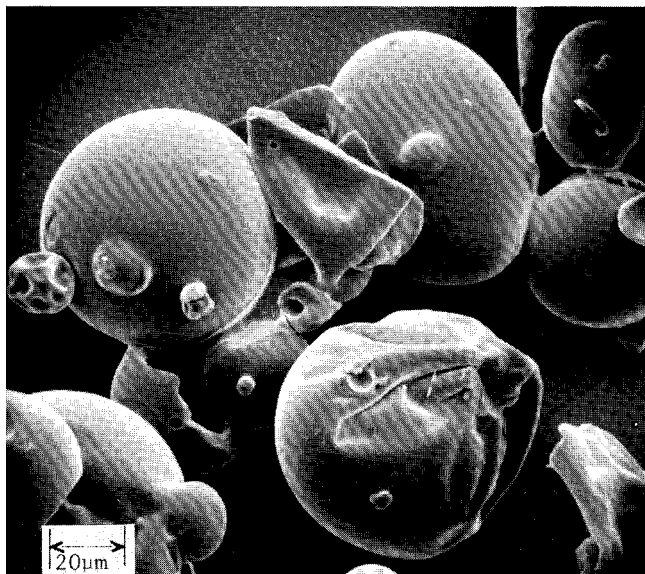
Excipient: Povidone K-29/32 (Plasdone K-29/32)

Manufacturer: ISP

Lot No.: 82A-3

Magnification: 600×

Voltage: 10 kV



11 Stability and Storage Conditions

Povidone darkens to some extent on heating at 150°C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110–130°C; steam sterilization of an

aqueous solution does not alter its properties. Aqueous solutions are susceptible to mold growth and consequently require the addition of suitable preservatives.

Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds; *see* Section 18. The efficacy of some preservatives, e.g. thimerosal, may be adversely affected by the formation of complexes with povidone.

13 Method of Manufacture

Povidone is manufactured by the Reppe process. Acetylene and formaldehyde are reacted in the presence of a highly active copper acetylide catalyst to form butynediol, which is hydrogenated to butanediol and then cyclodehydrogenated to form butyrolactone. Pyrrolidone is produced by reacting butyrolactone with ammonia. This is followed by a vinylation reaction in which pyrrolidone and acetylene are reacted under pressure. The monomer, vinylpyrrolidone, is then polymerized in the presence of a combination of catalysts to produce povidone.

14 Safety

Povidone has been used in pharmaceutical formulations for many years, being first used in the 1940s as a plasma expander, although it has now been superseded for this purpose by dextran.⁽⁸⁾

Povidone is widely used as an excipient, particularly in oral tablets and solutions. When consumed orally, povidone may be regarded as essentially nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes.⁽⁸⁾ Povidone additionally has no irritant effect on the skin and causes no sensitization.

Reports of adverse reactions to povidone primarily concern the formation of subcutaneous granulomas at the injection site of intramuscular injections formulated with povidone.⁽⁹⁾ Evidence also exists that povidone may accumulate in the organs of the body following intramuscular injection.⁽¹⁰⁾

A temporary acceptable daily intake for povidone has been set by the WHO at up to 25 mg/kg body-weight.⁽¹¹⁾

LD₅₀ (mouse, IP): 12 g/kg⁽¹²⁾

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

16 Regulatory Status

Accepted for use in Europe as a food additive. Included in the FDA Inactive Ingredients Guide (IM and IV injections; ophthalmic preparations; oral capsules, drops, granules, suspensions, and tablets; sublingual tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in

the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Crospovidone.

18 Comments

The molecular adduct formation properties of povidone may be used advantageously in solutions, slow-release solid-dosage forms, and parenteral formulations. Perhaps the best-known example of povidone complex formation is povidone-iodine, which is used as a topical disinfectant.

For accurate standardization of solutions, the water content of the solid povidone must be determined before use and taken into account for any calculations. A specification for povidone is contained in the Food Chemicals Codex (FCC).

19 Specific References

- 1 Fikentscher H, Herrle K. Polyvinylpyrrolidone. *Modern Plastics* 1945; 23(3): 157-161, 212, 214, 216, 218.
- 2 Becker D, Rigassi T, Bauer-Brandl A. Effectiveness of binders in wet granulation: comparison using model formulations of different tableability. *Drug Dev Ind Pharm* 1997; 23(8): 791-808.
- 3 Stubberud L, Arwidsson HG, Hjortsberg V, Graffner C. Water-solid interactions. Part 3. Effect of glass transition temperature, T_g and processing on tensile strength of compacts of lactose and lactose/polyvinyl pyrrolidone. *Pharm Dev Technol* 1996; 1(2): 195-204.
- 4 Iwata M, Ueda H. Dissolution properties of glibenclamide in combinations with polyvinylpyrrolidone. *Drug Dev Ind Pharm* 1996; 22: 1161-1165.
- 5 Lu WG, Zhang Y, Xiong QM, *et al.* Development of nifedipine (NE) pellets with a high bioavailability. *Chin Pharm J Zhongguo Yaoxue Zazhi* 1995; 30(Nov Suppl): 24-26.
- 6 Chowdary KP, Ramesh KV. Microencapsulation of solid dispersions of nifedipine-novel approach for controlling drug release. *Indian Drugs* 1995; 32(Oct): 477-483.
- 7 BASF Corporation. Technical literature: *Soluble Kollidon Grades, Soluble Polyvinylpyrrolidone for the Pharmaceutical Industry*, 1997.
- 8 Wessel W, Schoog M, Winkler E. Polyvinylpyrrolidone (PVP), its diagnostic, therapeutic and technical application and consequences thereof. *Arzneimittelforschung* 1971; 21: 1468-1482.
- 9 Hizawa K, Otsuka H, Inaba H, *et al.* Subcutaneous pseudosarcomatous polyvinylpyrrolidone granuloma. *Am J Surg Pathol* 1984; 8: 393-398.
- 10 Christensen M, Johansen P, Hau C. Storage of polyvinylpyrrolidone (PVP) in tissues following long-term treatment with a PVP containing vasopressin preparation. *Acta Med Scand* 1978; 204: 295-298.
- 11 FAO/WHO. Evaluation of certain food additives and contaminants. Twenty-seventh report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1983; No. 696.
- 12 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 3016-3017.

20 General References

- Adeyeye CM, Barabas E. Povidone. In: Brittain HG, ed. *Analytical Profiles of Drug Substances and Excipients*, vol. 22. London: Academic Press, 1993: 555-685.
- Genovesi A, Spadoni A, Funaro C, Vecchio C. Binder evaluation in tableting. *Manuf Chem* 2004; 175(6): 29-30.
- Horn D, Ditter W. Chromatographic study of interactions between polyvinylpyrrolidone and drugs. *J Pharm Sci* 1982; 71: 1021-1026.

- Hsiao CH, Rhodes HJ, Blake MI. Fluorescent probe study of sulfonamide binding to povidone. *J Pharm Sci* 1977; **66**: 1157–1159.
- ISP. Technical literature: *Plasdone povidone USP*, 1999.
- Jager KF, Bauer KH. Polymer blends from PVP as a means to optimize properties of fluidized bed granulates and tablets. *Acta Pharm Technol* 1984; **30**(1): 85–92.
- Plaizier-Vercammen JA, DeNève RE. Interaction of povidone with aromatic compounds III: thermodynamics of the binding equilibria and interaction forces in buffer solutions at varying pH values and varying dielectric constant. *J Pharm Sci* 1982; **71**: 552–556.
- Robinson BV, Sullivan FM, Borzelleca JF, Schwartz SL. *PVP: A Critical Review of the Kinetics and Toxicology of Polyvinylpyrrolidone (Povidone)*. Chelsea, MI: Lewis Publishers, 1990.

- Shefter E, Cheng KC. Drug–polyvinylpyrrolidone (PVP) dispersions. A differential scanning calorimetric study. *Int J Pharm* 1980; **6**: 179–182.
- Smolinske SC. *Handbook of Food, Drug, and Cosmetic Excipients*. Boca Raton, FL: CRC Press, 1992: 303–305.

21 Authors

AH Kibbe.

22 Date of Revision

30 August 2005.