Volker Bühler

Polyvinylpyrrolidone Excipients for Pharmaceuticals

Povidone, Crospovidone and Copovidone

Springer

Volker Bühler
In den Weingärten 14
67157 Wachenheim/Weinstraße
Germany

ISBN 3-540-23412-8 Springer Berlin Heidelberg New York

Library of Congress Control Number: 2004112897

Springer is a part of Springer Science+Business Media
springeronline.com

Printed in Germany

Typesetting: medionet AG, Berlin
Coverdesign: Design & Production, Heidelberg

Printed on acid-free paper 2/M – 5 4 3 2 1 0 –

Contents

1 General notes on synthesis

1.1 Soluble polyvinylpyrrolidone (Povidone)

Modern acetylene chemistry is based on the work of Reppe. One of the many products of this work is N-vinylpyrrolidone (Fig. 1).

The first polymerization product of N-vinylpyrrolidone was soluble polyvinylpyrrolidone, which was patented in 1939. Fig. 2 and 3 show mechanisms of polymerization: free-radical polymerization in water using hydrogen peroxide as initiator or in 2-propanol using an organic peroxide as initiator [1, 141].

The mechanism for terminating the polymerization reaction makes it possible to produce soluble polyvinylpyrrolidone of almost any molecular weight.

Apart from the method of production in water shown in Fig. 2, it is also possible to conduct the polymerization in an organic solvent, e.g. 2-propanol, an with

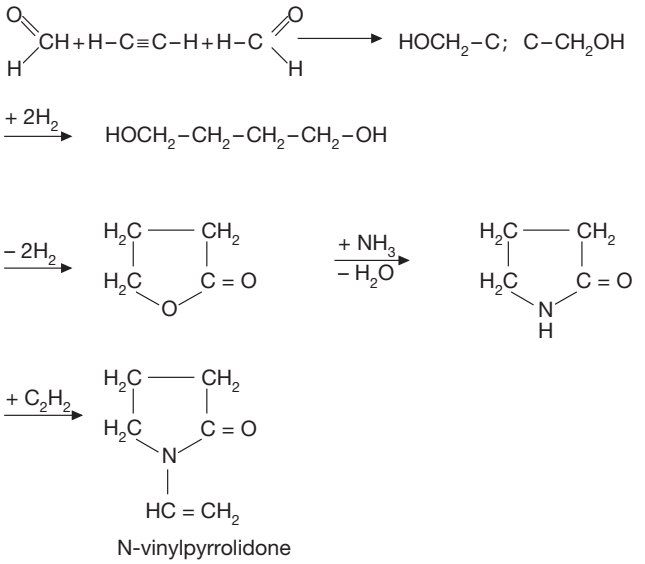

Fig. 1. Reppe's synthesis of N-vinylpyrrolidone (C_6H_9NO; Mr 111.1)

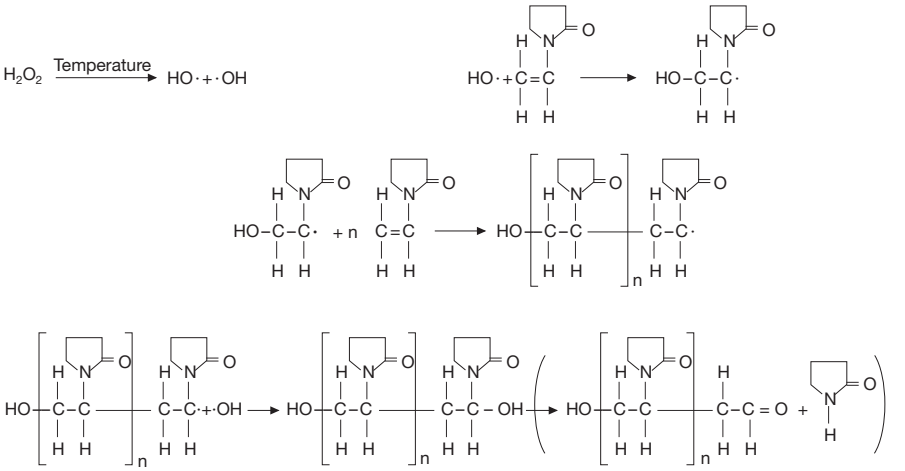

Fig. 2. The reaction mechanism for the radical polymerization of N-vinylpyrrolidone in water

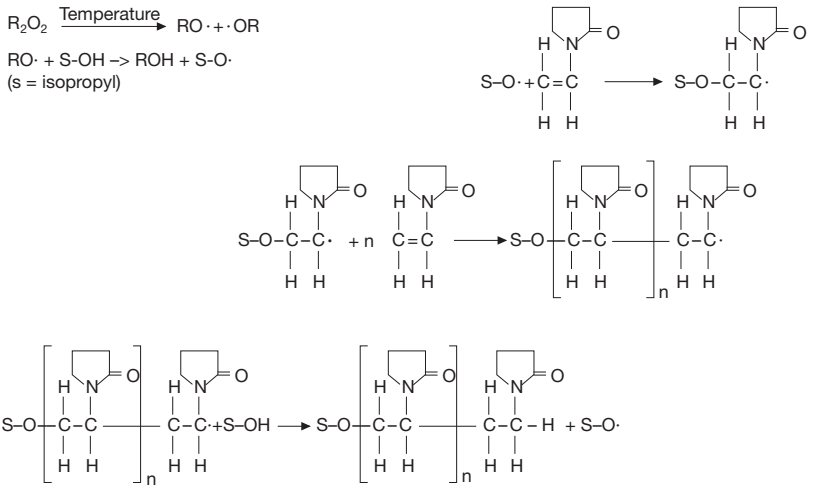

Fig. 3. The reaction mechanism for the radical polymerization of N-vinylpyrrolidone in 2-propanol

an organic peroxide as initiator (Fig. 3). This technology is used today in the production of low-molecular polyvinylpyrrolidone.

The low and medium-molecular weight grades of soluble polyvinylpyrrolidone are spray-dried to produce the pharmaceutical-grade povidone powders, while the high-molecular weight grades are roller-dried.

Soluble polyvinylpyrrolidone was first used during World War II as a blood-plasma substitute. Although it has excellent properties for this purpose, it has no longer been used for a number of decades. The organism does not metabolize the polymer, with the result that after parenteral administration, small quantities of high-molecular components may remain within the body. This problem does not exist with oral administration.

Today, soluble polyvinylpyrrolidone (povidone) is one of the most versatile and widely used pharmaceutical auxiliaries (see Section 2.4).

It is also used in the production of one of the most important topical disinfectants, povidone-Iodine.

1.2 Insoluble polyvinylpyrrolidone (Crospovidone)

Insoluble polyvinylpyrrolidone (crospovidone) is obtained by popcorn polymerization of N-vinylpyrrolidone [2], which yields a mainly physically crosslinked polymer [4–6]. The process is illustrated in Fig. 4 and uses either an alkali hydroxide at temperatures over 100°C, which yields some bifunctional monomer, or a small percentage of bifunctional monomer in water to initiate crosslinking of the polymer.

A comparison of the infrared spectra of the main physically crosslinked popcorn polymer obtained as shown in Fig. 4 and that of soluble polyvinylpyrrolidone shows practically no difference, while the infrared spectrum of a chemically crosslinked insoluble polyvinylpyrrolidone polymer prepared in the laboratory is quite different, which proves that the crosslinking in the crospovidone polymer is essentially of a physical nature.

Insoluble polyvinylpyrrolidone finds extensive applications in the pharmaceutical and beverage industries as a swelling popcorn polymer with selective adsorp-

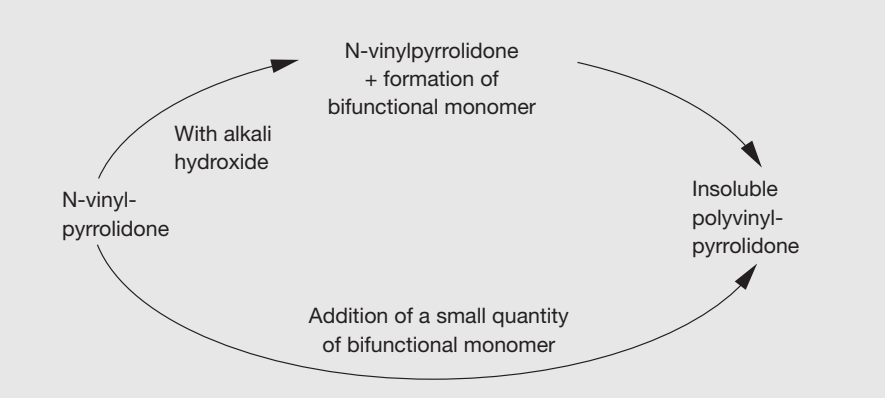

Fig. 4. Production processes for insoluble N-vinylpyrrolidone popcorn polymers (crospovidone)

tive properties. Its disintegration effect in tablets, its ability to hydrophylize insoluble active ingredients and to adsorb and form complexes are the main properties that make it useful as a pharmaceutical auxiliary. Today, crospovidone is regarded as one of the "superdisintegrants" for tablets.

Further, micronized crospovidone is of considerable significance as an active substance against diarrhoea in certain parts of the world. Micronized crospovidone grades of different bulk densities and different applications are available in the market.

1.3 Vinylpyrrolidone-vinyl acetate copolymer (Copovidone)

Water-soluble vinylpyrrolidone-vinyl acetate copolymer contains the two components in a ratio of 6 : 4. It is produced in the same way as soluble polyvinylpyrrolidone, by free-radical polymerization reaction with an organic peroxide as initiator (Fig. 5). As vinyl acetate is not soluble in water, the synthesis is conducted in an organic solvent such as 2-propanol.

Because of its vinyl acetate component, copovidone is somewhat more hydrophobic and gives less brittle films. This gives the product its favourable properties as a soluble binder and film-forming agent, particularly for solid dosage forms.

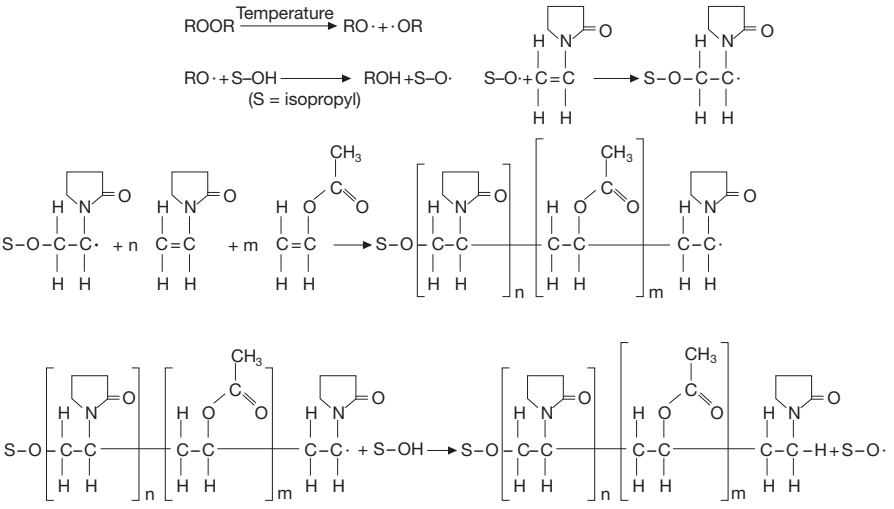

Fig. 5. Free-radical polymerization of vinylpyrrolidone-vinyl acetate copolymer (n +1) : m = 6 : 4

2 Soluble polyvinylpyrrolidone (Povidone)

2.1 Structure, product range and synonyms

Soluble polyvinylpyrrolidone is obtained by free-radical polymerization of vinylpyrrolidone in water or 2-propanol, yielding the chain structure of Fig. 6 [1, 141].

The current range of povidone consists of pharmaceutical grade products with different nominal K-values given in Table 1. All povidone grades are produced in according to the cGMP regulations.

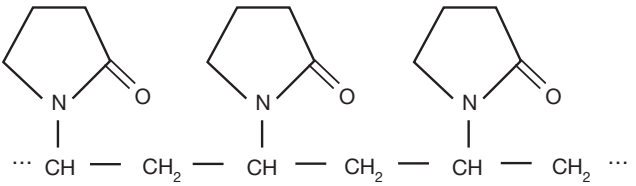

Fig. 6. Chemical structure of soluble polyvinylpyrrolidone (povidone) Mr $(111.1)_x$

Table 1. Povidone grades available in the market

Povidone grade	Trade names	Manufacturer
Povidone K 12*	Kollidon® 12PF	BASF
Povidone K 17*	Kollidon® 17PF, Plasdone® C-15	BASF, ISP
Povidone K 25	Kollidon® 25, Plasdone® K-25	BASF, ISP
Povidone K 30	Kollidon® 30, Plasdone® K-29/32	BASF, ISP
Povidone K 90	Kollidon® 90F, Plasdone® K-90	BASF, ISP
	Plasdone® K-90 D**, Plasdone® K-90 M**	ISP

* endotoxin or pyrogen free grades; ** D = densified, M = milled

Kollidon® is a registered trademark of BASF AG, Ludwigshafen, Germany
Plasdone® is a registered trademark of ISP Investments Inc., Wilmington, Delaware, USA

Table 2. Official names and abbreviations for soluble polyvinylpyrrolidone

Name/abbreviation	Origin/area of application
Povidone	Current valid Pharmacopoeias (e.g. USP 26, Ph.Eur. 5, JP 14)
Polyvidon(e)	Former editions of Pharmacopoeias (e.g. Ph.Fr. IX)
Povidonum	Pharmacopoeias (e.g. Ph.Eur. 5)
Polyvidonum solubile	Former edition of the DAC (1986)
Poly(1-vinyl-2-pyrrolidon)	Deutsches Arzneimittelgesetz 1984 § 10 (6)
PVP	General abbreviation, commercial name for cosmetics/technical grade

Spray drying technology is used in the production of all povidone grades with the exception of povidone 90. Because of its very high average molecular weight, it has to be dried on a roller.

Soluble polyvinylpyrrolidone is known under the names and abbreviations given in Table 2, most of which are specific to the pharmaceutical industry.

The CAS number of polyvinylpyrrolidone is 9003-39-8.

This book subsequently uses the name "Povidone".

2.2 Product properties

2.2.1 Description, specifications, pharmacopoeias

2.2.1.1 *Description*

All povidone grades are of pharmaceutical purity. They are free-flowing white or yellowish-white powders with different particle sizes (see Section 2.2.4).

The typical odour of the individual products depends on their method of synthesis and is therefore not the same for all the grades of povidone. Povidone K 25 and Povidone K 30, for instance, always have a typical amine or ammonia odour, as ammonia is used for neutralisation.

All the povidone types give aqueous solutions with very little taste.

2.2.1.2
Pharmacopoeial requirements, test methods

The products are tested according to the corresponding monographs for "Povidone" in the supplements of Ph.Eur. 5 and in USP 26. Their release for sale depends on fulfilment of the requirements of these monographs.

Table 3 contains the current pharmacopoeial requirements. The testing and guarantee of a particular microbial status and absence of pyrogens or endotoxins are not required by the pharmacopoeias in the povidone monographs.

The low-molecular grades povidone K 12 and povidone K 17 are tested for absence of bacterial endotoxins according to Ph.Eur. Method 2.6.14. A 6% solution in 0.9% sodium chloride solution is used. The validation of the endotoxin test (Ph.Eur. method 2.6.14) was done with povidone K 17 [609].

Low-molecular povidone can be polymerized in 2-propanol and in such case it contains the radical 2-propanol-vinylpyrrolidone adduct (hydroxy-methyl)-butylpyrrolidone as impurity (structure and determination see Section 2.3.3.8). The level of this impurity depends on the average molecular weight.

The products meet the ICH requirements on residual solvents according to Ph.Eur., 5.4: Only Class 3 solvents (2-propanol or formic acid) are likely to be present (<0.5%)

The microbial status can be determined according to Ph.Eur. methods 2.6.12 and 2.6.13 The usual limits (see Table 4) given in the European Pharmacopoeia apply to the categories 2 and 3A.

Table 3 see next page.

Table 4. Microbial purity requirements (Ph.Eur. 5, 5.1.4, Categories 2 + 3A)

– Max. 10^2 aerobic bacteria and fungi/g
– No Escherichia coli/g
– Max. 10^1 enterobacteria and other gramnegative bacteria/g
– No Pseudomonas aeruginosa/g
– No Staphylococcus aureus/g

Table 3. Pharmacopoeial requirements of povidone

	Povidone K 12	Povidone K 17	Povidone K 25	Povidone K 30	Povidone K 90
Clarity and colour (10% in water)	Clear and lighter than B6/BY6/R6	Clear and lighter than B6/BY6/R6	Clear and lighter than B6/BY6/R6	Clear and lighter than B6/BY6/R6	Clear and lighter than B6/BY6/R6
K-value (see 2.3.2.1)	10.2–13.8	15.3–18.4	22.5–27.0	27.0–32.4	81.0–97.2
Nitrogen content (%, see 2.3.3.6)	11.5–12.8	11.5–12.8	11.5–12.8	11.5–12.8	11.5–12.8
Water (K. Fischer, %)	≤ 5.0	≤ 5.0	≤ 5.0	≤ 5.0	≤ 5.0
pH (5% in water)	3.0–5.0	3.0–5.0	3.0–5.0	3.0–5.0	4.0–7.0
Vinylpyrrolidone (ppm, see 2.3.3.2)	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10
Sulfated ash (%)	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1
Aldehyde (%, see 2.3.3.3)	≤ 0.05	≤ 0.05	≤ 0.05	≤ 0.05	≤ 0.05
Heavy metals (ppm)	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10
Hydrazine (ppm)	≤ 1	≤ 1	≤ 1	≤ 1	≤ 1
Peroxides (ppm H_2O_2)	≤ 400	≤ 400	≤ 400	≤ 400	≤ 400
2-Pyrrolidone (%, see 2.3.3.2)	≤ 3.0	≤ 3.0	≤ 3.0	≤ 3.0	≤ 3.0
Formic acid (%, see 2.3.3.4)	–	–	≤ 0.5	≤ 0.5	≤ 0.5
2-Propanol (%, see 2.3.3.4)	≤ 0.5	≤ 0.5	–	–	–
Organic volatile impurities (USP)	Passes test	Passes test	Passes test	Passes test	Passes test
Bacterial endotoxins (Ph.Eur. 5)*	= ≤0.1 I.U./mg	= ≤0.1 I.U./mg			

* monograph "Substances for pharmaceutical use"

Table 5. Countries in which povidone fulfil the requirements of the pharmacopoeias

Country	Pharmacopoeia
More than 30 european countries (Examples)	Ph.Eur. 5, Suppl. 4.7
Austria	ÖAB
Belgium	Ph.Belg.
France	Ph.Fr.
Germany	DAB
Great Britain	BP
Italy	F.U.
Netherlands	Ph.Ned.
Scandinavia	Ph.Nord.
Spain	F.E.
USA	USP 26
Japan (only Kollidon® 25, 30 and 90 F)	J.P. 14
Japan (only Kollidon® 17 PF)	JPE

2.2.1.3
Pharmacopoeias

Povidone complies with the harmonized monographs in the pharmacopoeias of the countries listed in Table 5. The list is not comprehensive.

2.2.2
Solubility, dissolution

One of salient features of povidone is its universal solubility, which extends from extremely hydrophilic solvents, such as water, to hydrophobic liquids, such as butanol.

Today, the use of organic solvents, such as methylene chloride or chloroform is severely restricted, but nevertheless, small quantities of organic solvents are still used by most pharmaceutical companies. The most commonly used are ethanol, propylene glycol or low-molecular polyethylene glycol. Povidone is miscible in practically all proportions in these solvents and in water, though, above a certain concentration, the solution obtained has a high viscosity (see Section 2.2.3).

Table 6 lists a number of solvents that are capable of forming solutions containing either more than 10% or not more than 1% of povidone. The solubility in acetone is 1–2%.

The dissolution behaviour and dissolution rate are typical for a polymer. It is recommended to add the powder slowly and in small portions to the solvent with vigorous stirring to ensure that it disperses and dissolves rapidly without forming lumps. Larger lumps dissolve rather slowly. This applies particularly to povidone K 90, as this high-molecular grade dissolves more slowly than the low-molecular grades.

Table 6. Solubility of povidone

More than 10% in:	Less than 1% in:
Water	
Diethylene glycol	Ethyl acetate
Methanol	Dioxane
Ethanol	Diethyl ether
n-Propanol	Pentane
Isopropanol	Cyclohexane
n-Butanol	Carbon tetrachloride
Chloroform	Toluene
Methylene chloride	Xylene
2-Pyrrolidone	Liquid paraffin
Polyethylene glycol 400	Cyclohexanol
Propylene glycol	
1,4-Butanediol	
Glycerol	
Triethanolamine	
Propionic acid	
Acetic acid	

The surface tension and the conductivity of solutions with surfactants is not affected by the addition of povidone [492, 616].

2.2.3 Viscosity, K-value

2.2.3.1 *Viscosity in water*

The viscosity of aqueous solutions of povidone depends on their average molecular weight. This can therefore be calculated from the viscosity, giving the viscosity-average molecular weight (see Section 2.2.6). Fig. 7 shows the very considerable differences in viscosity between solutions of the different povidones in water, as a function of their concentration. A 20% aqueous solution of povidone K 12 shows hardly any visible difference to pure water, while a 20% solution of povidone K 90 in water gives high viscosities until 5000 mPa·s.

Differentiations between the individual types of different molecular weight are made on the basis of their relative viscosity in water and their K-value, which can be calculated from the former according to the Ph.Eur. and USP monographs, "Povidone". The tolerance limits for the K-value given in Table 9 can similarly be calculated from the viscosity limits given in Table 7 using the methods given in these monographs.

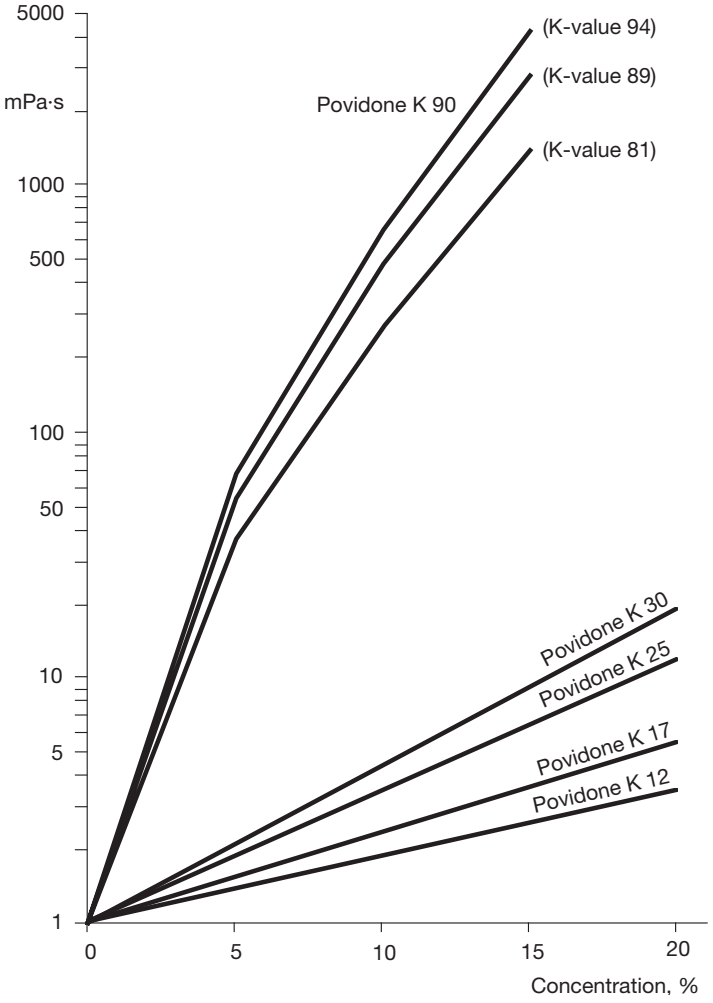

Fig. 7. Viscosity curves for the povidone grades in water (capillary viscometer, 25 °C)

Table 7. Relative viscosity values for povidone in water for calculating the K-value according to Ph.Eur. and USP (capillary viscometer, 25 °C)

Nominal K-value	Concentration	Relative viscosity USP and Ph.Eur. limits
12	5%	1.222–1.361
17	5%	1.430–1.596
25	1%	1.146–1.201
30	1%	1.201–1.281
90	1%	3.310–5.195

If the concentrations of the solutions are increased, the viscosity ranges become even greater, as can be seen from the values given in Table 8 for 10% (g/ml) solutions in water. These typical values have been taken from the former monograph "Lösliches Polyvidon" in Deutscher Arzneimittel-Codex 1986.

The viscosity, e. g. of povidone K 30 in water at concentrations up to 10%, is hardly affected by temperature (Fig. 8). At higher concentrations, however, the viscosity decreases rapidly with increasing temperature.

It was reported that most cations increase the viscosity and most of anions decrease the viscosity of povidone K 90 solutions [530]. Some polymers such as carragheenan show a synergistic viscosity increasing effect with the high-molecular povidone K 90.

It must be emphasized that the viscosity of povidone solutions is independent of their pH over a wide range. Only in extreme cases does this rule not apply: concentrated hydrochloric acid increases their viscosity; strong alkali precipitates povidone. However, it usually redissolves on addition of water.

Highly concentrated solutions of povidone K 90 demonstrate a certain degree of associative thickening and their viscosity is reduced by strong shear forces.

Table 8. Typical viscosity values for 10 % (g/ml) solutions of povidone in water at 20°C (DAC 1986)

Product	K-value range	Typical viscosity range
Povidone K 12	11–14	1.3–2.3 mPa s
Povidone K 17	16–18	1.5–3.5 mPa s
Povidone K 25	24–27	3.5–5.5 mPa s
Povidone K 30	28–32	5.5–8.5 mPa s
Povidone K 90	85–95	300–700 mPa s

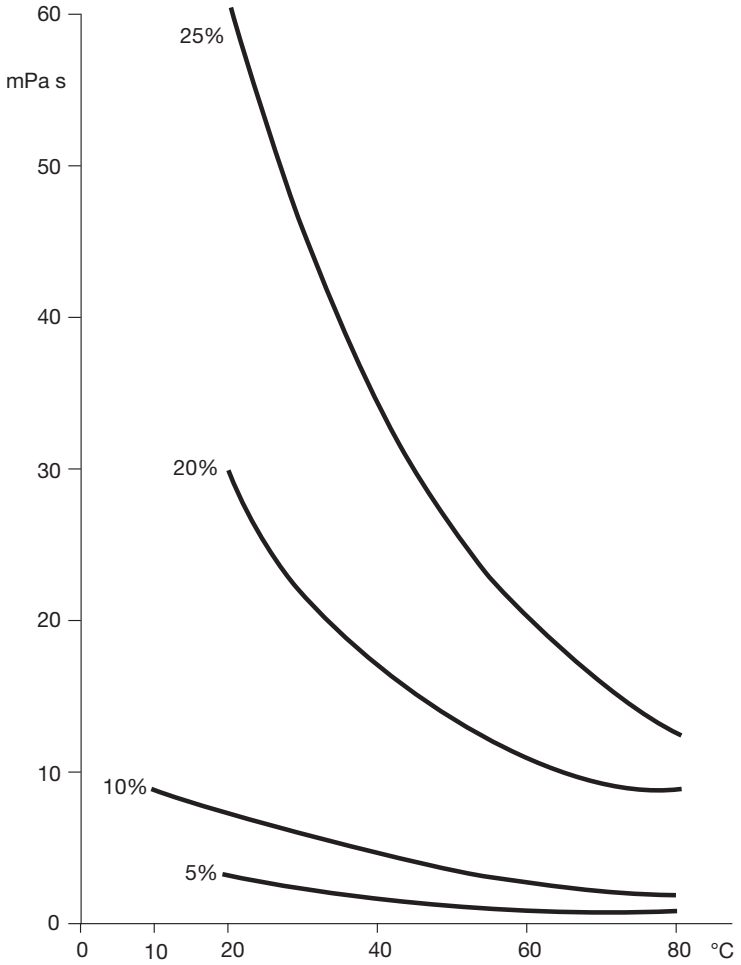

Fig. 8. The viscosity of different povidone K 30 solutions in water as a function of temperature

2.2.3.2 *K-value*

The average molecular weight of povidone is expressed in terms of the K-value in the pharmacopoeias valid in Europe, the USA and Japan [13]. It is calculated from the relative viscosity in water and always forms a part of the commercial name. The K-values specified in Section 2.2.1.2 are the ranges specified in the European Pharmacopoeia (Ph.Eur.). As can be seen from Table 9, the K-value ranges specified in the USP are identical. The USP and Ph.Eur. specify harmonized limits of 85–115% for nominal (= stated) K-values up to 15, while for nominal K-values

Table 9. Pharmacopoeia requirements for the K-values of povidone (calculated from Table 7)

Nominal K-value	USP and Ph.Eur. specification
12	10.2–13.8
17	15.3–18.4
25	22.5–27.0
30	27.0–32.4
90	81.0–97.2

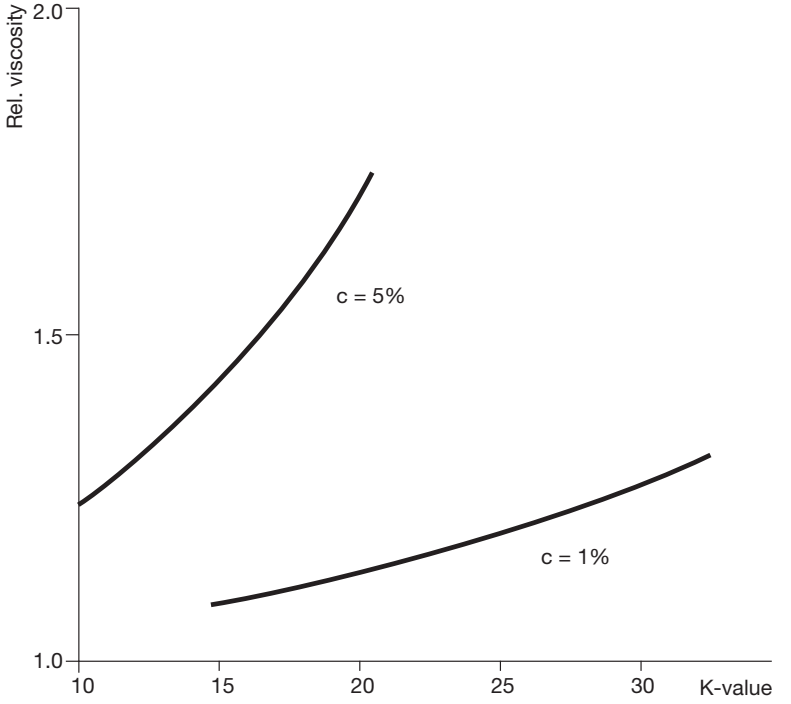

Fig. 9. Relative viscosity in water between K-values 10 and 33 [13]

above 15, they allow limits of 90–108% of the K-value. The values in Table 9 were calculated from the data in Table 7 (formula: see Section 2.3.2.1).

Figures 9 and 10 show the relative viscosity as a function of the K-value for 1% and 5% solutions in water.

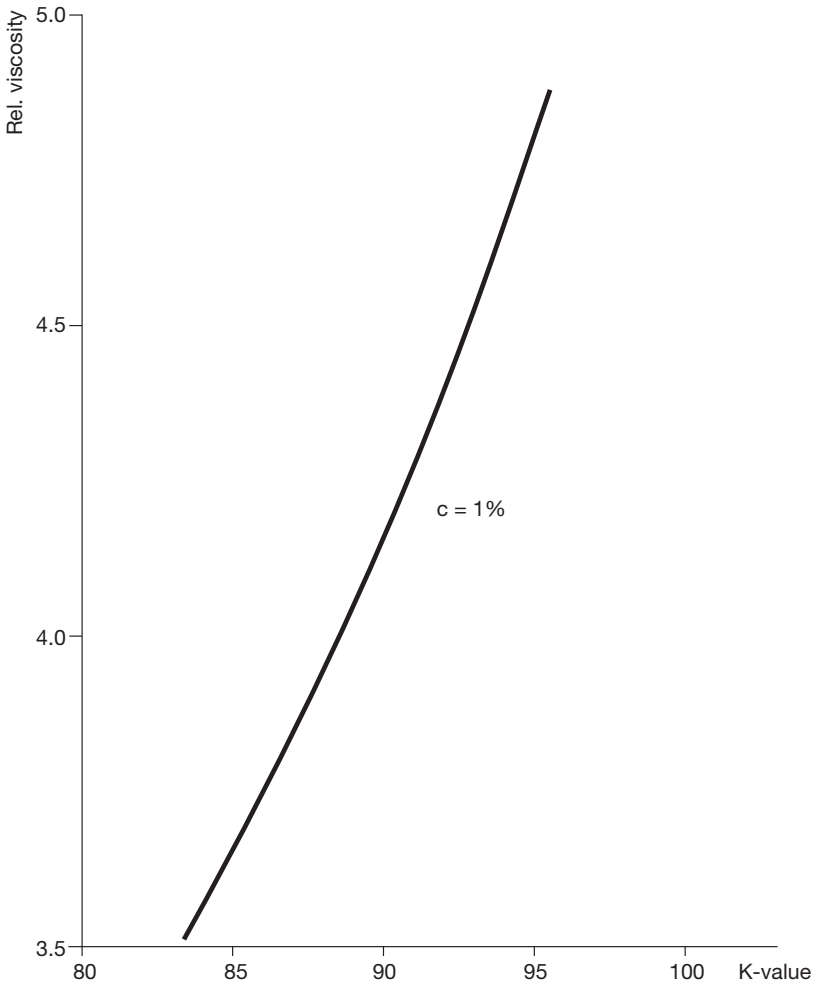

Fig. 10. Relative viscosity in water between K-values 83 – 95 [13]

2.2.3.3 *Viscosity in alcohols*

The viscosity of alcoholic solutions of povidone is significantly higher than that of aqueous solutions, as can be seen from the values in Table 10. The solvents most commonly used in tablet granulation, ethanol and 2-propanol, have been selected as examples.

The values given in Table 10 vary, of course, according to the K-value range of the individual product. Major deviations are found particularly with the high-molecular povidone K 90.

Table 10. Viscosity of 5 % organic solutions of povidone at 25 °C (typical values)

	Ethanol	Isopropanol
Povidone K 12	1.4 mPa s	2.7 mPa s
Povidone K 17	1.9 mPa s	3.1 mPa s
Povidone K 25	2.7 mPa s	4.7 mPa s
Povidone K 30	3.4 mPa s	5.8 mPa s
Povidone K 90	55.0 mPa s	90.0 mPa s

2.2.3.4 *Intrinsic viscosity*

The intrinsic viscosity of unfractionated povidone can be determined by various methods [212]. In Fig. 11, the intrinsic viscosity of povidone K 30 is determined by extrapolation to zero concentration of measurements at different concentrations, giving a value of 0.207 dl/g.

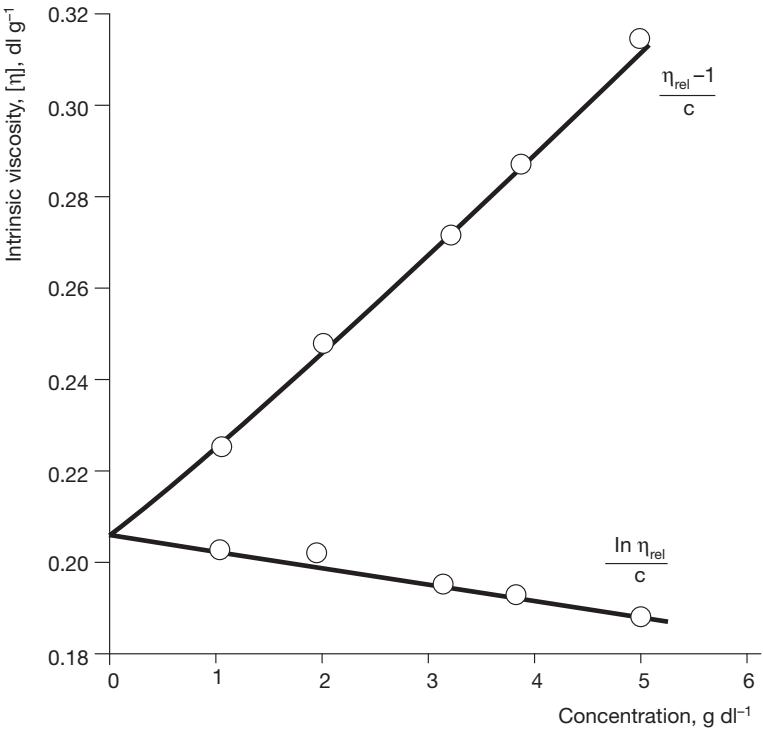

Fig. 11. Determination of the intrinsic viscosity [h] of povidone K 30 in water by extrapolation [212]

A simpler method for determining the intrinsic viscosity is to calculate it from the relative viscosity at a single concentration [16]:

$$[\eta] = \frac{\eta_{rel} - 1}{c + 0.28\ c\ (\eta_{rel} - 1)}\ (dl/g)$$

Figure 12 shows the intrinsic viscosity values obtained with this equation for povidone K 17, povidone K 25 and povidone K 30 at different concentrations in water [212]. Povidone K 17 is the only grade in which there is any significant variation in the viscosity between concentrations of 2% and 5%.
The values obtained in Fig. 11 by extrapolation agree well with the results in Fig 12.

A further method of determining the intrinsic viscosity from a single measurement is to calculate it from the K-value [223]:

$$[\eta] = 2.303\ (0.001\ K + 0.000075\ K^2)$$

The values obtained with this equation at different concentrations of povidone K 17, povidone K 25 and povidone K 30 largely agree with those in Fig. 12 [212].

A further method for determining the intrinsic viscosity from a measurement at a single concentration has been adopted in the former monographs of Japanese

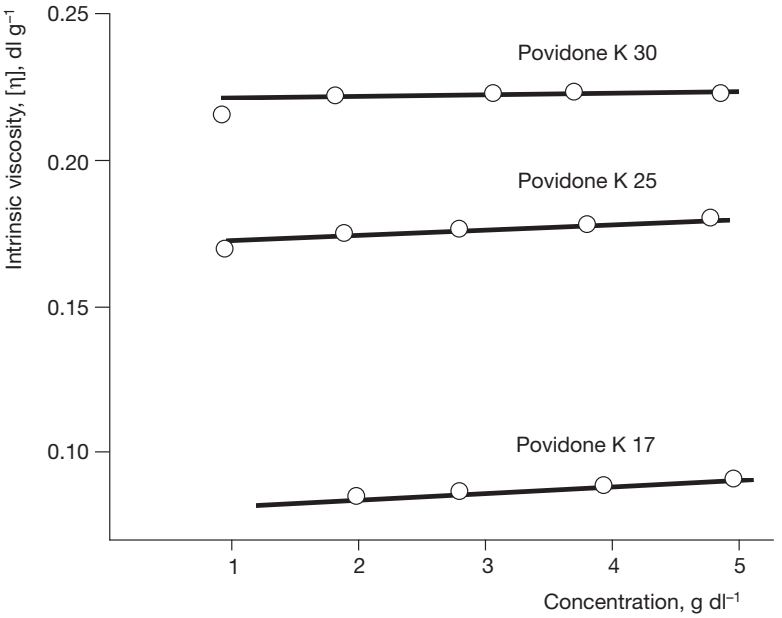

Fig. 12. Influence of the concentration of povidone K 17, povidone K 25 and povidone K 30 on their intrinsic viscosities, calculated according to [16]

Table 11. Intrinsic viscosity of povidone from Jap.Ph. XII

Povidone K 25	0.15 – 0.19
Povidone K 30	0.19 – 0.25
Povidone K 90	1.30 – 1.60

Pharmacopoeia (e. g. Jap.Ph. XII). It is based on the relative viscosity of a 1% solution of povidone in water and is calculated with the following equation:

$$\text{Intrinsic viscosity} = \frac{\ln \eta_{rel}}{\text{Sample concentration (g/dl)}}$$

Table 11 shows the ranges prescribed for the intrinsic viscosity in the former monographs of Jap.Ph. XII.

2.2.4
Particle size, particle structure, bulk density

2.2.4.1
Particle size distribution

In the manufacture of solid dosage forms, the particle size distribution of auxiliaries such as povidone can play a major role. This applies particularly to direct compression. However, the particle size of medium or high-molecular polymers also plays a role when they are used in liquid dosage forms. Table 12 lists a number of important factors related to the particle size, that must be considered in the manufacture of pharmaceuticals.

For these reasons, the fine fraction below 50 µm and the coarse fraction above 500 µm have been kept as small as possible in the non-micronized povidone types. Table 13 shows typical values for some individual povidone grades based on measurements with an air-jet screen.

Table 12. Important effects of particle size on the manufacture of pharmaceuticals

- A high proportion of fines spoils the flow properties.
- Fines produce dust.
- A high proportion of coarse particles leads to demixing.
- The coarse fraction is unevenly distributed in tablets.
- With high-molecular polymers, a large coarse fraction seriously delays dissolution.
- In direct compression, the coarse particles of a binder demonstrate a weaker binding effect.

Table 13. Typical sieve analysis of some povidone grades available on the market

Trade name	Fine fraction smaller than 74 µm	Coarse fraction larger than 297 µm
Kollidon® 25	less than 20 %	less than 5 %
Kollidon® 30	less than 20 %	less than 5 %
Kollidon® 90F	less than 10 %	less than 20 %
Plasdone® K-90	less than 5 %	less than 20 %
Plasdone® K-90D	less than 5 %	about 30 %
Plasdone® K-90M	about 30 %	less than 1 %

2.2.4.2
Particle structure

All povidone types with exception of roller dried povidone K 90 are spray dried powders and have therefore the typical particle structure of this technoloy.

Figure 13 shows an example of spray dried povidone. The structure are holow and mainly spherical particles. Figure 14 shows the completely different particle structure of the roller dried povidone K 90.

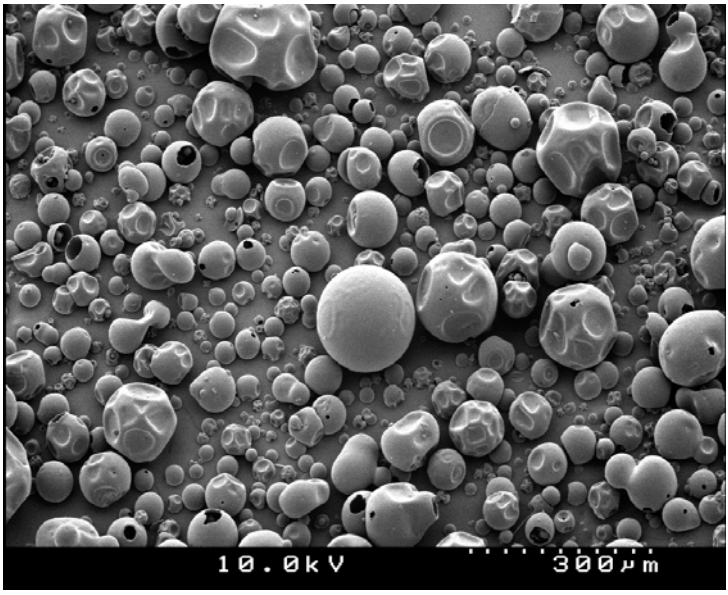

Fig. 13. Typical particle structure of spray-dried povidone (e.g. Kollidon® 30)

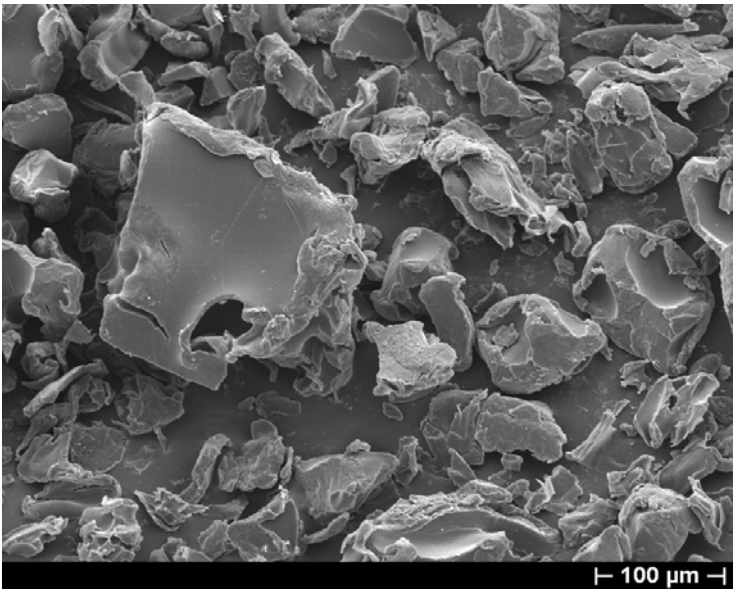

Fig. 14. Typical particle structure of roller-dried povidone K 90 (e.g. Kollidon® 90F)

2.2.4.3 *Bulk density, tap density*

The bulk densities of the spray-dried povidones are very similar. Table 14 gives typical values for the bulk and tap densities of the products on the market.

Table 14. Typical bulk and tap densities of povidone grades available on the market

Trade name	Bulk density (g/ml)	Tap density (g/ml)
Kollidon® 12PF	about 0.6	about 0.7
Kollidon® 17PF	about 0.45	about 0.55
Kollidon® 25	about 0.45	about 0.55
Kollidon® 30	about 0.45	about 0.55
Kollidon® 90F	about 0.45	about 0.6
Plasdone® C-15	about 0.34	about 0.44
Plasdone® K-25	about 0.34	about 0.44
Plasdone® K-29/32	about 0.34	about 0.43
Plasdone® K-90	about 0.29	about 0.39
Plasdone® K-90D	about 0.39	about 0.54
Plasdone® K-90M	about 0.56	about 0.72