

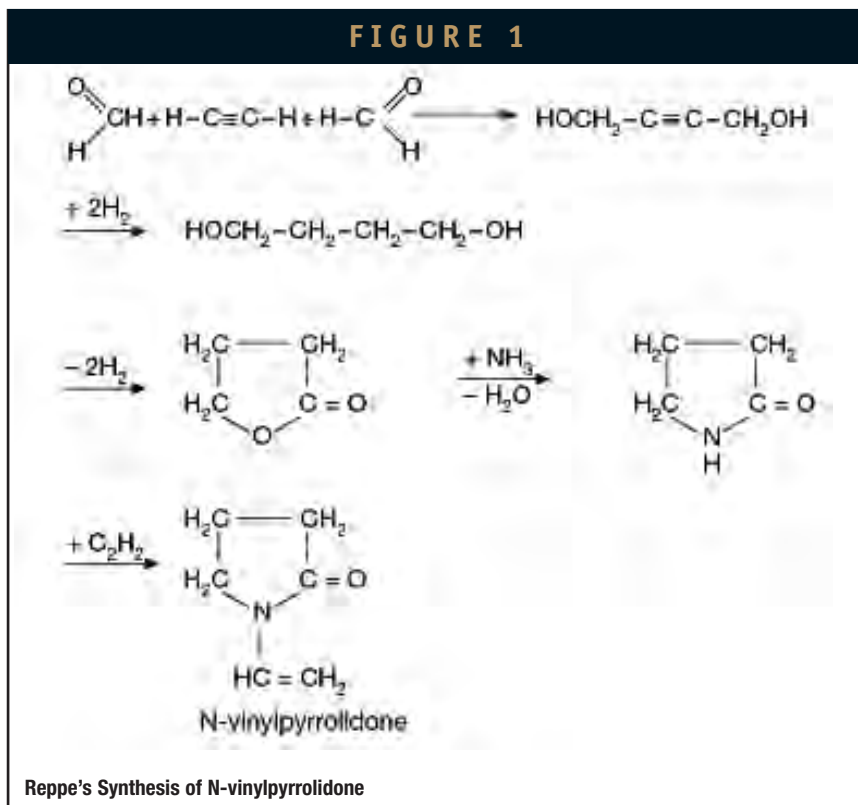
# EXCIPIENT UPDATE

## Polyvinylpyrrolidone (PVP) – One of the Most Widely Used Excipients in Pharmaceuticals: An Overview

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The chemistry of acetylene, developed at BASF in the 1920s by Walter Reppe, opened up numerous application possibilities, especially in the young field of plastics. In 1938, the year Nylon and Perlon were discovered, BASF succeeded in using acetylene chemistry to develop a highly interesting derivative: by reacting acetylene with pyrrolidone, vinylpyrrolidone was obtained, which in turn was used to form polyvinylpyrrolidone (PVP). The process patent was granted on January 1, 1939.

It soon became apparent that PVP was an all-around talent. It is readily soluble in water, physiologically compatible, non-toxic, essentially chemically inert, temperature-resistant, pH-stable, non-ionic, and colorless. This remarkable combination of properties predestined its use in numerous applications in medicine, pharmaceutical technology, cosmetics, and in the technical industry. Even as early as 1939, PVP was used as a plasma expander and was widely used in this form during World War II. During the 1950s, PVP replaced the schellac hitherto used in hair sprays. This article, however, deals with the applications of PVP in the pharmaceutical industry.



### POLYVINYLPIRROLIDONE (POVIDONE)

#### Structure, Properties & Product Range

Soluble PVP products are obtained by the radical polymerization of vinylpyrrolidone, giving the structure in Figure 2. Drying is carried out either by spray- or drum-drying. This results in a white-to-yellow-white powder. Soluble PVP in aqueous solution has a very slight taste of its own.

The soluble PVP products of pharmaceutical quality are designated as Povidone in the USP. Today's range

comprises products of different K-values. The K-value characterizes the mean molecular weight (eg, Povidone K 12, Povidone K 17, Povidone K 25, Povidone K 30, and Povidone K 90). BASF markets these products under the brand name Kollidon®; ISP is marketed as Plasdone®. As these products are widely used, they are monographed in numerous pharmacopoeias, eg, Ph Eur, USP, and JP/JPE. Table 1 lists the current pharmacopoeial requirements.

One of the outstanding properties of the soluble PVP products is their universal solubility in hydrophilic and hydrophobic solvents. Povidone, for

example, is practically infinitely soluble in standard pharmaceutical solvents, although at high concentrations, the solution becomes highly viscous. The mean molecular weight of the Povidone grades is characterized by the K-value in the European and US pharmacopoeias. It is always included as part of the tradename and is calculated from the relative viscosity in water. Povidone is hygroscopic, a particular advantage in its main application as a tablet binding agent.

The following  $M_w$  values (weight average molecular weight) were determined for different grades of Povidone in recent measurements: Povidone K 12 (2000-3000),

Povidone K 17 (7000-11000), Povidone K 25 (28000-34000), Povidone K 30 (44000-54000), and Povidone K 90 (1000000-1500000). With the exception of very few particles, the particle size distribution of the products is within the range 50  $\mu\text{m}$  to 250  $\mu\text{m}$ . The bulk density is approximately 400-600 g/l.

Povidone can form fairly stable association compounds or complexes with a number of active substances. The best-known example is PVP-iodine, one of the most important disinfectants in current use. The ability of Povidone to form a water-soluble complex with insoluble active substances can be used in pharmaceuticals to improve the release rate and solubility of drugs. It must be noted, however, that if Povidone is combined with strongly alkaline substances, such as lithium carbonate or sodium hydroxide, it can cross-link and become insoluble, particularly at elevated temperatures. In extreme cases, this can increase the viscosity of liquid presentation forms and delay bioavailability in solid forms.

Povidone possesses the following properties that make it ideal for numerous applications in drug manufacture:

- Solubility in all conventional solvents
- Adhesive and binding powers
- Film formation
- Affinity to hydrophilic and hydrophobic surfaces

<b>Specifications of the Povidone grades</b>					
	<b>Povidone K 12</b>	<b>Povidone K 17</b>	<b>Povidone K 25</b>	<b>Povidone K 30</b>	<b>Povidone K 90</b>
Colour (10% in water)	lighter than B6/BY6/R6	lighter than B6/BY6/R6	lighter than B6/BY6/R6	lighter than B6/BY6/R6	lighter than B6/BY6/R6
Clarity (10% in water)	clear	clear	clear	clear	clear
K-value	10.2-13.8	15.3-18.0	22.5-27.0	27.0-32.4	81.0-96.3
Nitrogen content (%)	11.5-12.8	12.0-12.8	12.0-12.8	12.0-12.8	12.0-12.8
Water (Karl Fischer, %)	≤ 5.0	≤ 5.0	≤ 5.0	≤ 5.0	≤ 5.0
pH value (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, HPLC)	≤ 10.0	≤ 10.0	≤ 10.0	≤ 10.0	≤ 10.0
Sulfated ash (%)	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1
Aldehyde (ppm)	≤ 500	≤ 500	≤ 500	≤ 500	≤ 500
Heavy metals (ppm)	≤ 10.0	≤ 10.0	≤ 10.0	≤ 10.0	≤ 10.0
Hydrazine (ppm)	≤ 1.0	≤ 1.0	≤ 1.0	≤ 1.0	≤ 1.0
Peroxides (ppm H <sub>2</sub> O <sub>2</sub> )	≤ 400	≤ 400	≤ 400	≤ 400	≤ 400
Microbial status (see Table 3)	passes test	passes test	passes test	passes test	passes test
Endotoxins (Ph.Eur.) (6% solution)	≤ 6 I.U./ml (≤ 0.1 I.U./mg)	≤ 6 I.U./ml (≤ 0.1 I.U./mg)	not tested	not tested	not tested
Residual solvents (Ph. Eur. 5.4)	≤ 0.5% 2-propanol	≤ 0.5% 2-propanol	≤ 0.5% formic acid	≤ 0.5% formic acid	≤ 0.5% formic acid
2-pyrrolidone (%)	≤ 3.0	≤ 3.0	≤ 3.0	≤ 3.0	≤ 3.0

- Ability to form complexes
- Availability in different mean molecular weights
- Thickening properties

The main applications of Povidone (including functions and dosage forms) in the pharmaceutical industry can be seen in Table 2.

### *As a Binder in Tablets, Granulates & Capsules*

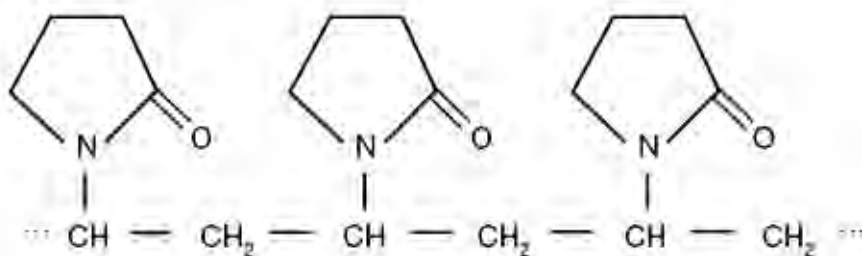
The main application area for Povidone K 25, K 30, and K 90 is as a binder in tablets and granulates (Table 3). The binding effect is achieved both in wet and dry granulation and in direct tablet compression.

While Povidone K 25 and K 30 are very similar, the binding effect of Povidone K 90 is considerably greater; this means that only about half the concentration of Povidone K 90 needs to be used. Due to their excellent solubility in water, the Povidone grades, in spite of their excellent binding qualities, have hardly any negative effect on the

disintegration time of the tablets. Wet granulation with Povidone K 25, K 30, or K 90 results generally in hard granulates with excellent flow properties. Povidone can be used with all current granulation techniques. Povidone K 25 and K 30 are suitable for the manufacture of effervescent tablets as they, due to their high degree of solubility, rapidly form clear solutions. Interesting applications for K 25, K 30, and K 90 as binders are the wet granulation of excipients for direct tablet compression (eg, Ludipress<sup>®</sup>, Kollidon<sup>®</sup> SR) and the granulation of directly compressible active substances for tablets. Active substances marketed in pre-granulated form for direct tablet compression are usually those substances that are difficult to compress or that are subject to hydrolysis. Typical examples are vitamins and acetaminophen.

Apart from wet granulation, the Povidone grades are also used in dry granulation (eg, drum compression) or in direct tablet compression. However, for direct tablet compression, the more plastic and less hygroscopic Copovidone is the more suitable.

**FIGURE 2**



**The Chemical Structure of Polyvinylpyrrolidone (Povidone)**

**TABLE 2**

<u>Function</u>	<u>Dosage Form</u>
Binder	Tablets, Capsules & Granules
Bioavailability Enhancer	Tablets, Capsules, Granules, Pellets, Suppositories & Transdermal Systems
Film Former	Ophthalmic Solutions, Tablet Cores & Medical Plastics
Solubilizer	Oral, Parenteral & Topical Solutions
Taste-Masker	Oral Solutions & Chewable Tablets
Lyophilization Agent	Injectables & Oral Lyophilizates
Suspension Stabilizer	Suspensions, Instant Granules & Dry Syrups
Hydrophilizer	Medical Plastics, Sustained Release Forms & Suspensions
Adhesive	Transdermal Systems & Adhesive Gels
Stabilizer	Enzymes in Diagnostics & Different Drug Forms
Toxicity Reducer	Injectables, Oral Preparations, etc

**Main Applications of Povidone**

**Improvement of the Release & Bioavailability of Active Substances**

Two problems are frequently encountered with many active substances: their low degree of solubility in water and their limited bioavailability. One simple method to improve solubility is to add a solubilizer such as Povidone. With many active substances, Povidone forms soluble complexes. In some cases, a physical mixture of an API and Povidone is quite adequate. Apart from that, several methods have been used to increase the surface interface between active substance and solubilizer. In such cases, solid dispersions or solid solutions are suitable. In solid dispersions, the active substance is embedded in a hydrophilic carrier (eg,

Povidone), possibly in fine crystalline form. In solid solutions, the active substance is in an amorphous, molecular-disperse form within the matrix (Povidone). Povidone is suitable for the manufacture of solid dispersions or solid solutions as it possesses hydrophylic properties, is available in various molecular weights and viscosities, forms water-soluble complexes with many active substances, and is almost universally soluble.

Suitable processes include mixing, co-milling, or melt-extrusion of the Povidone-drug mixture, co-precipitation, granulation onto a carrier, or spray-drying a solution containing the drug and Povidone. Numerous drugs are available

on the market as solid dispersions or solid solutions. In some cases, a positive influence on bioavailability is described in the literature. The most frequently tested drug mentioned is most likely Nifedipine.

The low-molecular grades, Povidone K 12 and K 17, are used as solubilizing agents, dispersants, and crystallization inhibitors, particularly for injectables. This application is used in particular for antibiotics in solution or in lyophilized form. Povidones with higher K-values may not be administered parenterally as, due to their high molecular weights, they cannot be excreted by the kidneys and hence accumulate within the body. The use of Povidone grades K 12 and K 17 as solubilizers in parenteral applications is a frequent one for veterinary drugs; however, it has not been approved for use in humans in all countries.

Povidone K 25 and K 30 can be used as solubilizers in preparations for oral or topical applications in the same way as Povidone K 12 and K 17 are used in injectables. One typical example is the formulation of acetaminophen syrup, in which Povidone K 25 increases the solubility of the drug and also reduces its bitter taste.

**Other Applications**

**STABILIZER OF SUSPENSIONS:** The Povidone grades can be used in suspensions, dry granulates, and dry syrups as physical stabilizers. The most important function of these hydrophylic polymers in such cases is as a protective colloid; the individual solid particles are rendered hydrophylic and separated sterically. In this way, dispersibility is improved and the sediment volume can be increased. A further general function of Povidone is that it can prevent crystallization of the dissolved active substance by forming soluble complexes with it. The low-molecular Povidones K 12 and K 17 can also be used to stabilize parenteral suspensions.

**OPHTHALMIC PREPARATIONS:** Because of its solubilizing, film-forming, and

thickening properties, Povidone is used in ophthalmic preparations. This ensures that the preparation remains in the eye for a certain amount of time to lubricate it or to solubilize the active ingredient. This application requires between 2% and 10% Povidone. The bioavailability of some APIs in ophthalmic preparations can be improved by adding Povidone. Povidone is also used in cleaning fluids for contact lenses.

**SUGAR COATING:** In sugar coating, Povidone K 25 or K 30 is mostly used due to their following properties:

- Prevention of micro-cracks on the coating
- Adhesion of the sugar coating onto the core when hydrophobic active substances are being used
- Homogeneous distribution of the pigment or lacquer in the coating
- Stabilization of the sugar suspension
- Slower and more homogeneous crystallization of the sugar

The prevention of micro-cracks is extremely important if large batches are to be prepared or if rapid drying is important. As most active substances are hydrophobic, Povidone helps to prevent the sugar coating from cracking.

**FILM COATING:** Due to its already mentioned film-forming and adhesive properties in sugar coating and its ability to form dispersions with pigments, Povidone is also used in film coating. However, it is never used as the sole film-former due to its hygroscopicity. Povidone, when added to other soluble film coatings increases the dissolution speeds of the other film-formers, resulting in the disintegration of the tablet and the release of active substance being accelerated.

**MISCELLANEOUS APPLICATIONS:** Apart from the aforementioned applications, the

**TABLE 3**

Povidone Grade	Concentration in Tablets/Granules
Povidone K 25	2%-5%
Povidone K 30	2%-5%
Povidone K 90	1%-3%

**Usual Concentrations as a Binder**

soluble grades of Povidone can be used for the following purposes:

- As adhesives in gels (eg, dentures)
- Stabilization of nitroglycerine in transdermal systems
- Regulation of the release of active substances in controlled-release preparations and transdermal systems
- Hydrophilization and pore formation in plastics for medical applications (eg, hollow fibers)
- Reduction of the toxicity of certain active substances
- Cryoprotection, lyophilization
- Enzyme stabilization (eg, diagnostics)
- Vitamin stabilization

## CONCLUSION

The unique properties of Povidone, such as its high solubility in solvents of differing polarities, its solubilizing and film-forming abilities, its suspension and emulsion-stabilizing effects and, last but not least, its binding properties, make it one of the most important excipients in pharmaceutical technology. Scientists keep working on numerous alternative applications of Povidone.

## MORE LITERATURE

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## BIOGRAPHIES



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