Technical Information

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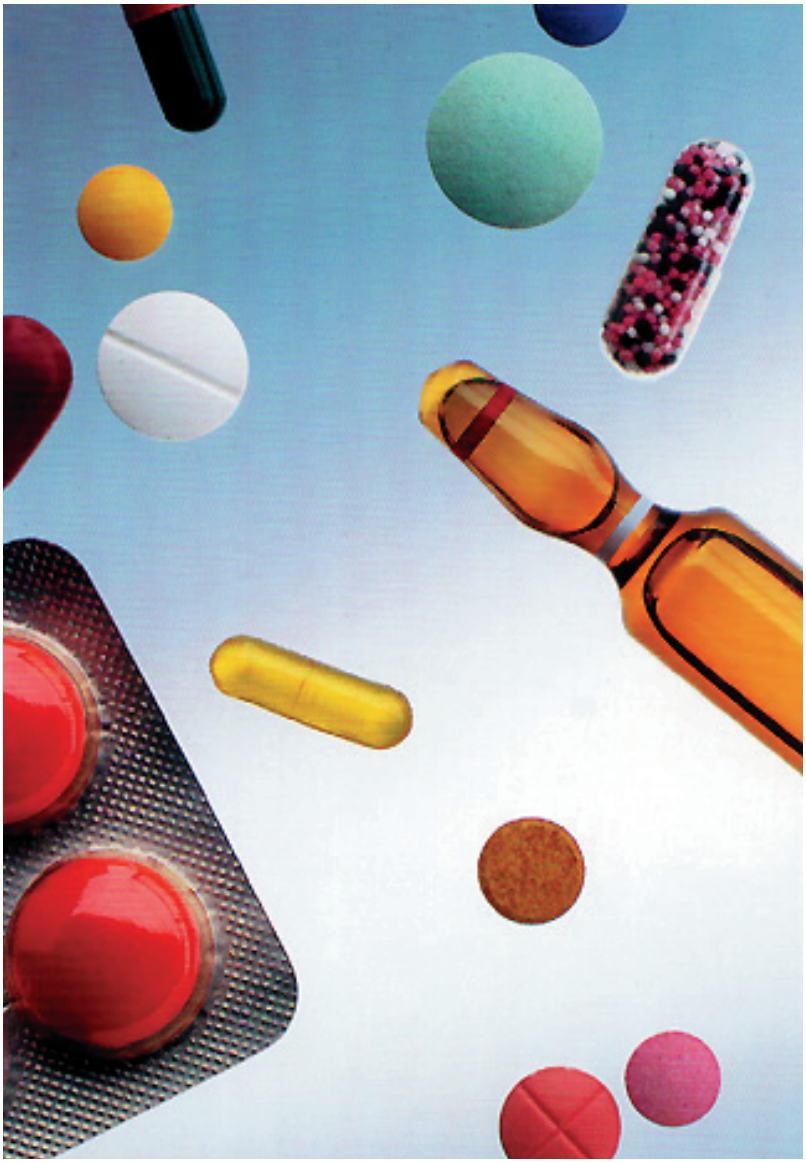
Soluble Kollidon® grades

Povidone Ph. Eur., USP, JP

Soluble polyvinylpyrrolidone for the pharmaceutical industry



BASF
The Chemical Company

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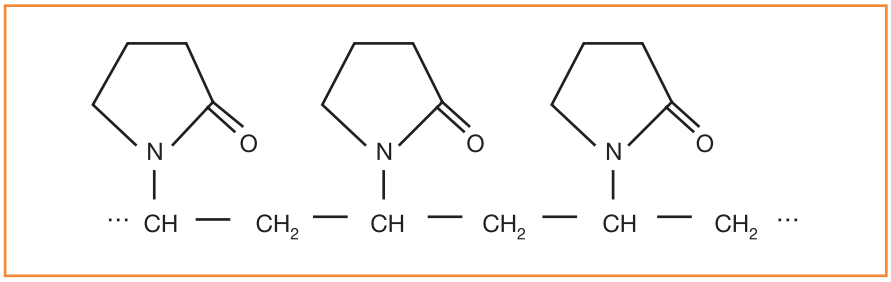
1. Introduction

1.1 General

The foundations of modern acetylene chemistry were laid by Reppe at BASF. One of the many products to emerge from this work was soluble polyvinylpyrrolidone, which is obtained by radical polymerization of N-vinylpyrrolidone



Monomer unit: 111.14

Because of its solubility in water and in many organic solvents, its high binding power and its ability to form complexes, soluble polyvinylpyrrolidone is a very valuable synthetic polymer for the pharmaceutical industry.

Separate Technical Data Sheets are available for the insoluble Kollidon® grades (crospovidone) and for Kollidon® VA 64, a copolymer of N-vinylpyrrolidone and vinyl acetate (copovidone).

More information on Kollidon® Grades may be found in the book, “Kollidon®, Polyvinylpyrrolidone for the Pharmaceutical Industry”.

1.2 Synonyms

Soluble polyvinylpyrrolidone is also known as povidon(e), povidonum, polyvidone, poly(1-vinyl-2-pyrrolidone) and PVP.

1.3 Product range

As the requirements differ considerably in the various fields of application, it has been found necessary to create different product lines: The Kollidon® grades for pharmaceutical products, the Luviskol® grades for the cosmetic industry and the Luvitec® grades for technical applications.

The Kollidon® range consists of the following products

– Kollidon® 12
– Kollidon® 12 PF
– Kollidon® 17 PF
– Kollidon® 25
– Kollidon® 30
– Kollidon® 30 LP
– Kollidon® 90 F

2. Specifications and stability

2.1 Specifications

See separate document: “Standard Specification (not for regulatory purposes)“ available via BASF’s WorldAccount: https://worldaccount.basf.com (registered access).

2.2 Regulatory status

Kollidon® 12 and Kollidon® 12 PF meet current Ph. Eur. and USP/NF povidone monograps.
Kollidon® 17 PF, Kollidon® 25, Kollidon® 30, Kollidon® 90 F meet current Ph. Eur., USP/NF and JP/JPE povidone monographs.

2.3 Microbiological Status, endotoxins

The microbiological status is determined according to the harmonized methods of the European Pharmacopoeia (Ph.Eur., latest edtion). The limits compiled in table 1 apply to all the soluble Kollidon® grades.

Total aerobic microbiological count (TAMC) max. 200 cfu/g
Total combined yeasts and moulds count (TYMC) max. 20 cfu/g

Kollidon® 12 PF and Kollidon® 17 PF are tested for bacterial endotoxins by method 2.6.14 d as published in the latest edition of the Ph. Eur.

The limit of the test is set to max. 100 IU/g.

2.4 Residual solvents

The Kollidon® grades fulfill the requirements for residual solvents (Class 3, Ph. Eur. 5, 5.4)

3. Physical and chemical properties

3.1 Description

All grades of Kollidon® are supplied in the form of an almost white free-flowing powder. They have a slight characteristic odour.

3.2 Molecular weight

With polymers generally, the average molecular weight can be expressed in three forms: weight, number and viscosity average.

The molecular weight of povidone is usually expressed as the K-value, from which it is possible to calculate the viscosity average molecular weight (M_v).

However, the weight average molecular weight (M_w) is found more frequently in the literature. It is determined by methods such as light scattering that measure the weight of the molecules.

The following M_w values were determined for different grades of Kollidon® in recent measurements.

Table 1:	
Kollidon® 12	2 000 – 3 000
Kollidon® 12 PF	2 000 – 3 000
Kollidon® 17 PF	7 000 – 11 000
Kollidon® 25	28 000 – 34 000
Kollidon® 30 Origin Germany	44 000 – 54 000
Kollidon® 90 F	1 000 000 – 1 500 000

3.3 Viscosity

Fig. 1 shows the relationship between the viscosity of aqueous solutions of the different grades of Kollidon® and their concentration.

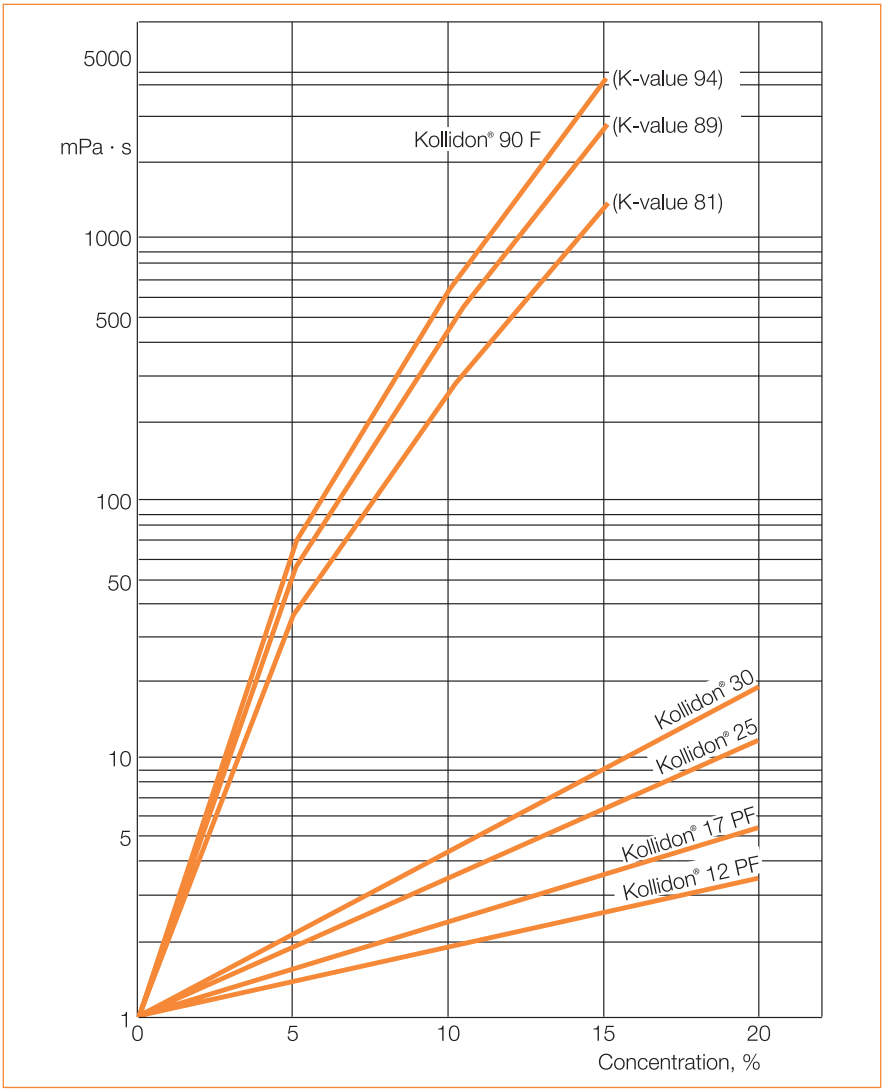


Fig. 1: Viscosity of Kollidon® solutions (Ubbelohde viscometer, 25 °C)

3.4 Solubility

The solubility of Kollidon® varies considerably from one solvent to another. In Table 2 below, “soluble” signifies that a solution of at least 10% can be prepared, and “insoluble” signifies that the solubility is less than 1%.

Table 2: Solubility of Kollidon® Grades

Soluble in:	
chloroform	n-butanol
cyclohexanol	n-propanol
ethanol abs.	polyethylene glycol 400
glycerine	(= Lutrol® E 400)
isopropanol	propylene glycol
methanol	triethanolamine
methylene chloride	water
Insoluble in:	
cyclohexane	pentane
diethyl ether	carbon tetrachloride
ethyl acetate	toluene
liquid paraffin	xylene

3.5 Hygroscopicity

The hygroscopic nature of Kollidon® is important in many applications. There is hardly any difference between the individual grades so that the same curve applies to all (Fig. 2).

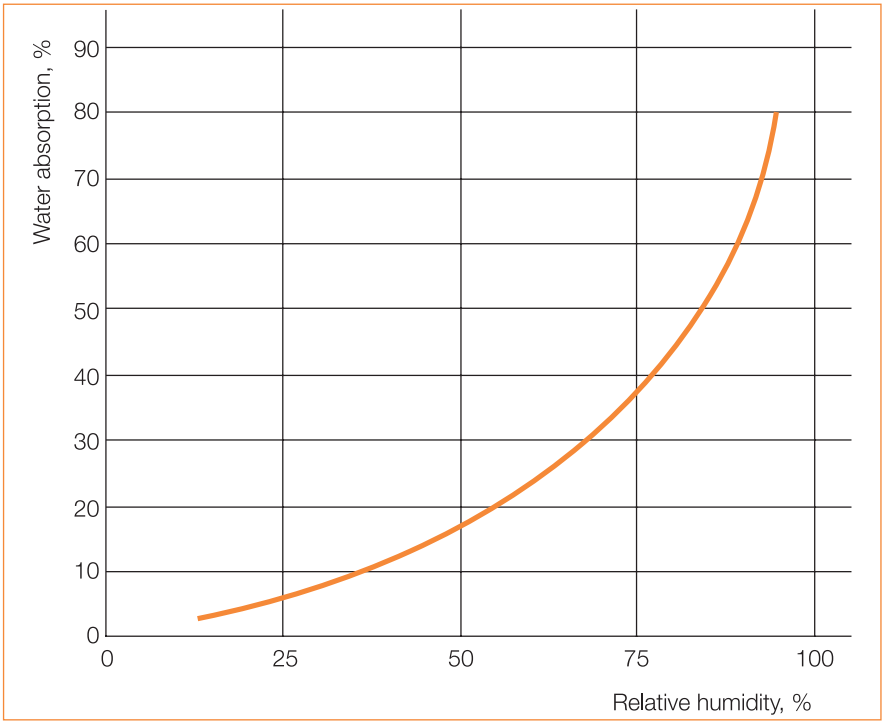


Fig. 2: Hygroscopicity of soluble Kollidon®

3.6 Particle-size distribution

In the pharmaceutical technology of solid dosage forms, particularly in the direct compression of tablets, the particle-size distribution of the solid ingredients used is a factor of some significance.

The following table gives some typical particle-size distribution values (determined in an air-jet sieve; 5 min, 20 mbar):

Table 3: Particle-size distribution, %

	<50 µm	>250 µm
Kollidon® 25/30	approx. 10	max. 5
Kollidon® 90 F	max. 10	max. 20

3.7 Bulk density

The bulk density of Kollidon® is determined according to Ph. Eur. 5, Section 2.9.16.

Table 4: Bulk density of the Kollidon® grades

Kollidon® 12	400 – 600 g/l
Kollidon® 12 PF	400 – 600 g/l
Kollidon® 17 PF	400 – 600 g/l
Kollidon® 25/30	400 – 600 g/l
Kollidon® 90 F	400 – 550 g/l

Particle size distribution and bulk density are considered characteristic values. They are not part of any specifications.

3.8 Stability in solution, sterilization

Aqueous solutions of povidone have no buffering action. If left to stand, and particularly if heated, they take on a slight yellowish colour. The yellowing can be diminished by adding a reducing agent, e. g. sodium metabisulfite or cysteine. Local legislation on the use of sodium metabisulfite in parenterals must be observed.

For sterilization purposes, 0.01 – 0.1% sodium metabisulfite or 0.05 – 0.1% cystein, as a proportion of the Kollidon®, is added to the solution which is then heated in the absence of air.

3.9 Complexation, chemical interactions

Povidone can form fairly stable association compounds or complexes with a number of active substances. The best known example is PVP-iodine which is the subject of a separate leaflet.

The ability of Kollidon® to form a water-soluble complex with insoluble active substances can be used in pharmaceuticals to improve the release rate and solubility of drugs (see Sections 4.3 and 4.4).

There are a few substances such as the polyphenols that form stronger complexes that can precipitate in neutral or acidic media.

It must be noted that if povidone is combined with strongly alkaline substances such as lithium carbonate or sodium hydroxide it can crosslink and become insoluble, particularly at elevated temperatures. In extreme cases, this can increase the viscosity of liquid presentation forms and delay bioavailability in solid presentation forms.

4. Applications

4.1 General

The main applications of the soluble Kollidon® grades are summarised in Table 5.

Table 5: Main applications of the soluble Kollidon® grades

Binder	Tablets, capsules, granules
Bioavailability enhancement	Tablets, capsules, granules, pellets, suppositories, transdermal systems
Film formation	Opthalmic solutions, tablets, medical plastics
Solubilization	Oral, parenteral and topical solutions
Taste masking	Oral solutions
Lyophilising agent	Injection preparations, oral lyophilisates
Stabilisation of suspensions	Oral and parenteral suspensions, instant beverage powders and granules
Adhesives	Transdermal systems, adhesive gels
Drug stabilisation	Enzymes in diagnostics

The adhesive, film-forming, dispersing and thickening properties of the soluble Kollidon® grades are used in tablet production, sugar coating, film coating and in the preparation of other dosage forms. The improvement in the solubility of active ingredients brought about by complexation or association, and the thickening effect find use mainly in the manufacture of liquid presentation forms.

The grade of Kollidon® that is selected depends mainly on its molecular weight, as this dictates the viscosity, binding effect, the complexation capacity and how readily it is eliminated from the body.

A detailed description of the applications is to be found in the book, “Kollidon®, polyvinylpyrrolidone for the Pharmaceutical Industry”.

4.2 Tablet binding

Kollidon® 25, Kollidon® 30 and Kollidon® 90F

When applied for granulation in high shear mixers or fluid-bed granulators the resulting granules with Kollidon® 25, Kollidon® 30 and Kollidon® 90F are hard, free flowing with a low proportion of fines. Binding strength is excellent to achieve hard and stable tablets.

Kollidon® 25 and Kollidon® 30 require binder quantities of 2% and 5% related to the tablet weight. As Kollidon® 90F has a higher binding capacity the required quantities are 2% or even less. The high viscosity of binder solutions of Kollidon® 90F sometimes requires precautions to ensure the granules to be evenly wetted.

Kollidon® 25, 30 and 90 F are also suitable for the direct compression of tablets without granulation. This technique requires a certain relative humidity, as the powder mixture must have a certain moisture content to bind properly. If Kollidon® is used in addition to microcrystalline cellulose, it not only makes the tablets harder but also gives them stronger edges. For best results in direct compression, all the excipients should have a certain moisture content. This applies to starch, microcrystalline cellulose and lactose monohydrate as fillers.

It can be seen from Fig. 3 that there is hardly any difference in the hardness of lactose placebo tablets made with Kollidon® 25 and Kollidon® 30. However, the same quantity (3% of the tablet weight) of Kollidon® 90 F almost doubles the hardness, compared with Kollidon® 25.

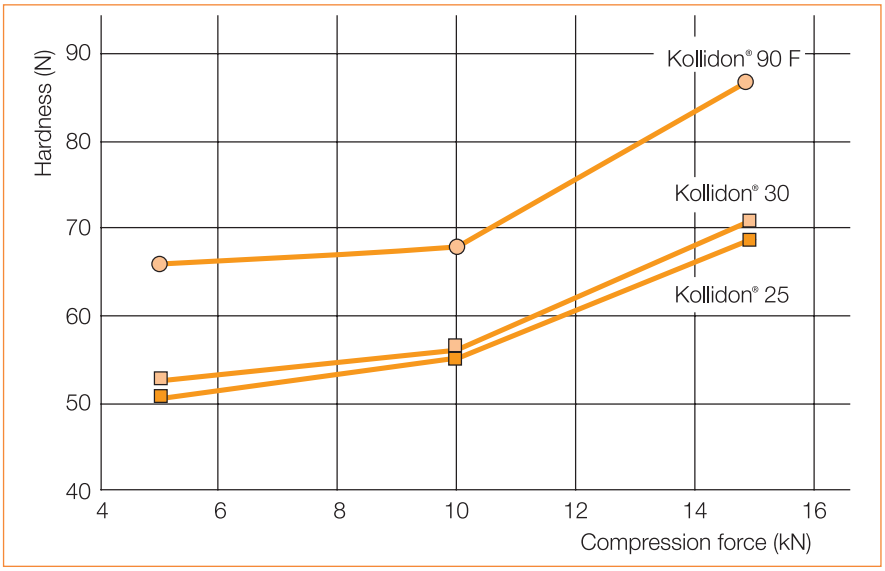


Fig. 3: Lactose monohydrate tablets with 3% Kollidon® (wet granulation)

Kollidon® is also suitable as a binder for modern processes such as fluidized-bed granulation. Thanks to their relatively low viscosity, solutions of Kollidon® 25 and Kollidon® 30 can be prepared relatively quickly, and sprayed easily, to quickly give hard dust-free uniform granules. If the spray includes pigments, Kollidon® improves their distribution.

A typical formulation for wet granulation with Kollidon® 30 is given below in Table 6 for alpha-methyldopa tablets. The formulation was tried out on a laboratory scale.

Table 6: Alpha-methyldopa tablets and cores (275 mg)

I	Alpha-methyldopa	275 g
	Lactose monohydrate	55 g
II	Kollidon® 30	15 g
	Isopropanol	80 ml
III	Kollidon® CL	8 g
	Magnesium stearate	2 g

Granulate mixture I with solution II, dry, sieve, mix with the ingredients in III and compress into tablets on a rotary tablet press with medium force (approx. 15 kN).

The tablets produced in the laboratory had the following properties:

Weight (measured)	361 mg
Diameter:	12 mm
Hardness:	118 N
Disintegration time (gastric juice):	5 min
Friability:	0%
Dissolution acc. to USP in 0.1 N hydrochloric acid:	15 min: 77% 30 min: 98%

4.3 Solubilization

Some examples are given as in Table 7 of typical drugs that can be solubilized with soluble Kollidon®.

Table 7: Some of the active ingredients that can be solubilized with soluble Kollidon®

Acetaminophen (paracetamol)	Oxytetracycline
Allopurinol	Reserpine
Amoxicillin	Rifampicin
Chloramphenicol	Sulfadimethoxine
Clonazepam	Sulfamethazine
Coumarin	Sulfamoxole
Diclofenac-Na	Sulfathiazole
Doxycycline	Tranilast
Furaltadone	Trimethoprim
Hydroflumethiazide Nitrofural	Tyrothricin

Kollidon® 12, 12 PF, 17 PF

The low-molecular grades, Kollidon® 12 PF and Kollidon® 17 PF are intended for use as solubilizing agents, dispersants and crystallization inhibitors particularly for injectables. These properties are of particular interest for antibiotics in solution or lyophylisate form.

Kollidon® 25, 30

In the same way as Kollidon® 12 PF and Kollidon® 17 PF are used in injectables, Kollidon® 25 and 30 can be used in preparations for oral or external application as solubilizers for the same active ingredients. One typical example is the formulation for a paracetamol syrup, in which Kollidon® 25 increases the solubility of the active substance and also reduces its bitter taste.

4.4 Co-precipitation, co-milling

Kollidon® 25, 30

The dissolution rate and therefore the absorption rate of drugs that do not dissolve readily in water can be greatly improved by comilling or coprecipitation with Kollidon® 25 or Kollidon® 30, as the complex formed is, in effect, a solid solution of the drug in the Kollidon®. This requires an excess of Kollidon® to maintain the (partially) amorphous form of the active substance. Suitable processes include mixing, comilling or melt extrusion of the Kollidon®-drug mixture, or coprecipitation, granulation onto a carrier, or spray-drying a solution containing the drug and Kollidon®.

The literature contains hundreds of publications on this application. The most frequently tested active substance mentioned is probably nifedipine.

4.5 Stabilizers of suspensions

Kollidon® 25, 30, 90 F

Kollidon® 25, 30 and 90 F can be used to stabilize oral and topical suspensions with a wide range of active ingredients, e. g. acyclovir, ibuprofen, magaldrate, nystatin, phenytoin, trimethoprim, sulfonamides and antibiotics, as well as sugar-coating suspensions. Combinations of Kollidon® 90 F with Kollidon® CL-M have often given very good results.

Kollidon® 12 PF and Kollidon® 17PF

The low-molecular weight endotoxin tested grades of Kollidon® can be used to stabilize parenteral suspensions. This applies particularly for antibiotics.

4.6 Thickener

Kollidon® 90 F

Because of its good solubility in water and alcohol, Kollidon® 90 F can be used as a thickener for aqueous-alcoholic solutions for oral application (viscosity curve, see Section 3.4).

4.7 Use in ophthalmic preparations

Soluble Kollidon® can also be used in eye preparations, because of its solubilising, film-forming and viscosity modifying properties. This allows certain APIs to be solubilised, ensures the eye to be wetted and encreases the residence time of formulations on the cornea.

4.8 Sugar coating

Kollidon® 25, 30

The good film-forming properties, great adhesive strength and very good dispersing action of Kollidon® are very useful in both traditional and automatic sugar-coating processes. Kollidon® 25 and 30 can be added to sugar-coating suspensions to prevent crazing of the sugar coating, and it also ensures that any pigments in the coating are evenly distributed and that the suspension remains stable. The sugar coating often develops crazing if the tablets are dried very quickly, resulting in a moisture gradient between the outside and the inside of the tablet, which can also happen if the suspension contains large quantities of pigment. Kollidon® prevents the pigment particles from aggregating again and promotes the homogeneity of the sugar layer. Kollidon® can also be used to prevent the migration of soluble dyes.

4.9 Film coatings

Kollidon® 25, 30

Kollidon® 25 and Kollidon® 30 are applicable in film coatings. They are used as pore-forming agents. They also improve the water solubility of the coating.

However, it must be noted that soluble Kollidon® can never be used as the sole film-forming agent as it is very hygroscopic and the coatings it gives are too tacky.

Kollidon® can be combined with all the usual film-forming agents such as cellulose derivatives or methacrylates. Alcoholic pigment suspensions can be prepared with a mixture of shellac and soluble Kollidon®, and these give homogeneous coatings particularly in modern spray-coating and fluidized-bed machines. The addition of Kollidon® 25 or Kollidon® 30 improves the rate of disintegration in aqueous solution, as the film-forming agents usually used have poor solubility in water. In most cases, it is recommended to strongly dilute the suspension for spraying.

4.10 Miscellaneous applications

Apart from the applications described above, the soluble grades of Kollidon® can be used for the following purposes:

- adhesives in adhesive gels, e. g. for dentures
- stabilization of nitroglycerin in transdermal systems
- in controlled release preparations and transdermal systems to regulate the release of active substances
- hydrophilization and pore formation in plastics for medical applications, e. g. “hollow fibres”
- reduction of the toxicity of certain active substances
- cryoprotection, lyophilisation
- enzyme stabilization, e. g. in diagnostics
- vitamin stabilization

4.11 Food products

In 1995, soluble polyvinylpyrrolidone (povidone) with k-values of 25 and higher was assigned Europe number E 1201 for use in dietetic tablets, e. g. vitamin and dietary fibre tablets, and in sweeteners.

5. Toxicological data

Soluble polyvinylpyrrolidone has been used for decades in all kinds of pharmaceutical preparations, and there are many publications on its good tolerance. In 1987, its ADI value was set at 0 – 50 mg/kg body weight by the World Health Organization (WHO).

From this literature and the toxicity studies listed below, which were conducted with different grades of Kollidon®, there emerges the following profile of action:

The tolerance of soluble Kollidon® after oral absorption is very good on the acute time scale and after long-term administration. It is neither teratogenic, mutagenic nor carcinogenic.

It has good skin and mucous membrane tolerance.

The low-molecular grades are quickly eliminated from the system and have been used for parenteral formulations.

Toxicological and biochemical studies have been carried out with the individual Kollidon® grades. Abridged reports summarizing the toxicological results are available on request. The original reports can be provided when secrecy agreements are in place.

6. PRD-Nos.

Product	PRD-No.
Kollidon® 12	30553394
Kollidon® 12 PF	30034972
Kollidon® 17 PF	30034981
Kollidon® 25	30034967
Kolildon® 30 Origin Germany	30034974 30525451
Kollidon® 30 LP	30255812
Kollidon® 90 F	30034978

7. Packaging

Kollidon® 12	90 kg PE drum with PE inner liner
Kollidon® 12 PF and Kollidon® 17 PF	50 kg PE drum with PE inliner
Kollidon® 25	25 kg carton with welded EVOH-inliner
Kollidon® 30	25 kg carton with welded EVOH-inliner 50 kg PE drum with PE inliner
Kollidon® 30 LP	25 kg carton with welded EVOH-inliner
Kollidon® 90F	25 kg carton with welded EVOH-inliner

8. Stability and storage

For the soluble grades Kollidon® 25 and 30 the retest period could be prolonged to 48 months if stored in unopend original containers. The retest period for Kollidon® 12, Kollidon® 12 PF and Kollidon® 90 F, retain their properties as defined in the standard specificatlons over a period of at least 3 years if stored in unopeoed orignal containers. To achieve a retest period of 36 months Kollidon® 17 PF needs to be stored at temperatures of 2 – 8 °Celcius. In cases this can not been ensured it is recommended to consume the product within 24 months.

9. Safety Data Sheets

Safety Data Sheets for the individual grades of Kollidon® are available on request.

10. Note

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