Soluble Kollidon® grades

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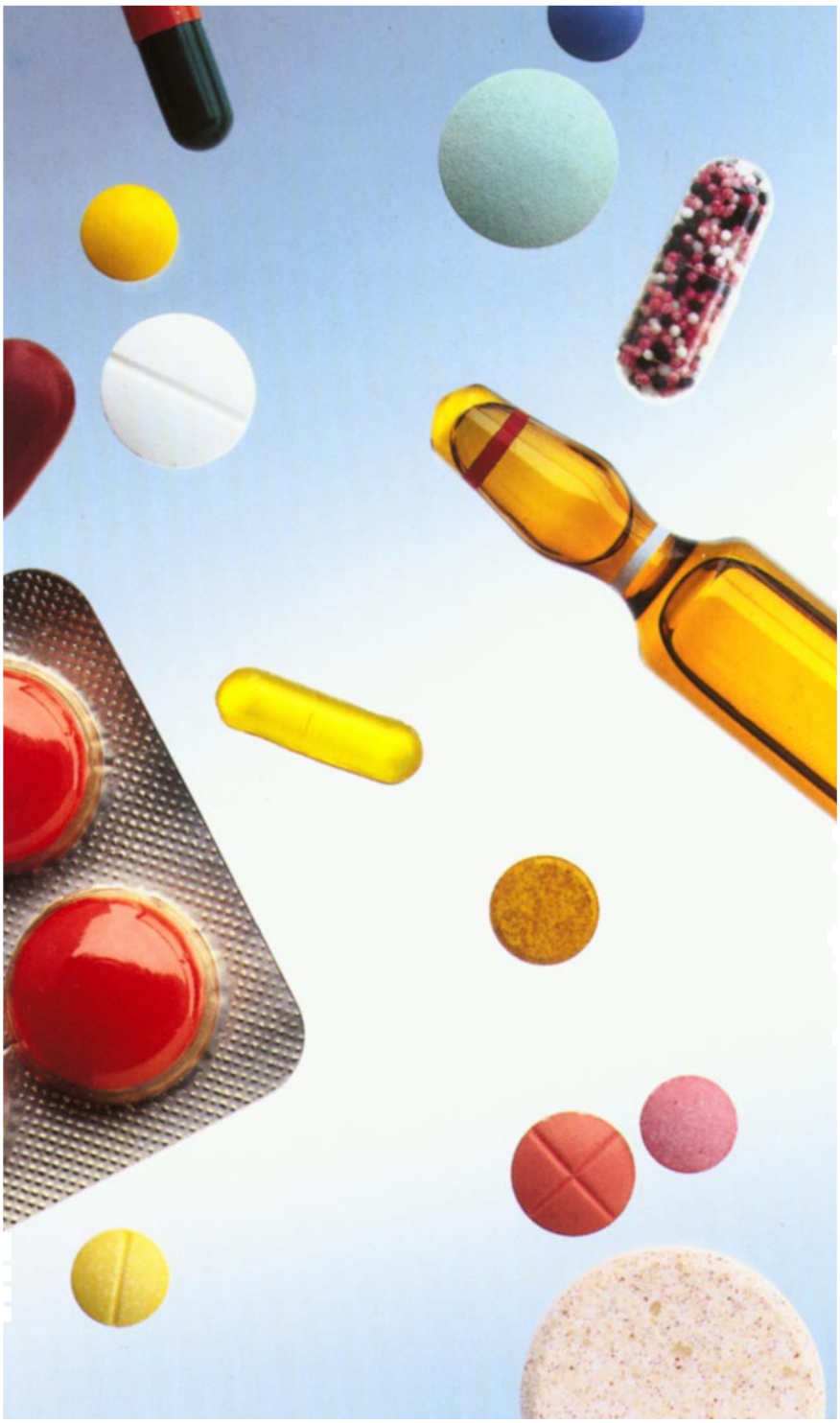
Register 2

Soluble polyvinylpyrrolidone (Povidone Ph. Eur, USP, JP) for the pharmaceutical industry



Fine Chemicals

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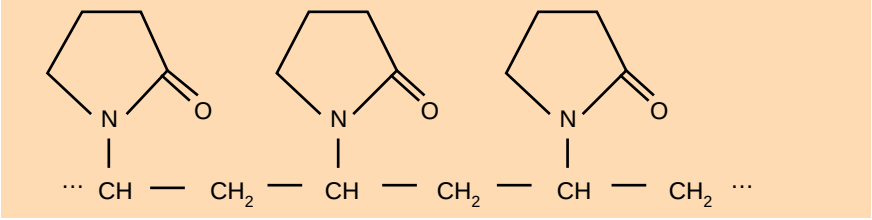
Contents

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 ability to form complexes, soluble polyvinylpyrrolidone occupies a special position among the synthetic colloids.

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 (copolyvidone).

More information on Kollidon than can be provided in this brochure may be found in the book, “Kollidon, Polyvinylpyrrolidone for the Pharmaceutical Industry”, 3rd edition 1996.

1.2 Synonyms

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

1.3 Range

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

The Kollidon range consists of the following products:

	Product number
Kollidon 12 PF	11265/1-99
Kollidon 17 PF	10750/1-75
Kollidon 25	00996/1-65
Kollidon 30	66831/1-87
Kollidon 90 F	96088/2-02

Kollidon 90 was available up to 1993 under Product No. 84341/1-05.

2 Specifications and stability

2.1 Specifications

All the soluble grades of Kollidon are of pharmaceutical purity and meet the following specifications:

Table 1 Specifications of the soluble grades of Kollidon

	Kollidon 12 PF	Kollidon 17 PF	Kollidon 25	Kollidon 30	Kollidon 90 F
Colour (10% in water)	lighter than B6/BG6/R6	lighter than B6/BG6/R6	lighter than B6/BG6/R6	lighter than B6/BG6/R6	lighter than B6/BG6/R6
Clarity (10% in water)	clear	clear	clear	clear	clear
K value	10.2–13.8	15.3–18.0	22.5–26.7	27.0–32.1	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 (HPLC), ppm	≤ 5	≤ 5	≤ 10	≤ 10	≤ 10
Sulfated ash, %	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1
Aldehyde (ppm)	≤ 500	≤ 500	≤ 500	≤ 500	≤ 500
Heavy metals, ppm	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10
Hydrazine, ppm	≤ 1	≤ 1	≤ 1	≤ 1	≤ 1
Peroxides (as H_2O_2), ppm	≤ 400	≤ 400	≤ 400	≤ 400	≤ 400
Microbial status (see Table 3)	passes test	passes test	passes test	passes test	passes test
Absence of pyrogens (Ph. Eur.)	passes test	passes test	not tested	not tested	not tested

All the physical and chemical properties are determined by the methods in the European Pharmacopoeia or the USP.

2.2 Pharmacopoeias

All the Kollidon grades meet the requirements of the current harmonized monographs for povidone in the following pharmacopoeias:

Table 2 Soluble Kollidon in the Pharmacopoeias

Product name	Ph. Eur.	USP/NF	JP
Kollidon 12 PF	+	+	n. a.
Kollidon 17 PF	+	+	n. a.
Kollidon 25	+	+	+
Kollidon 30	+	+	+
Kollidon 90 F	+	+	+

n. a. = monograph not available

2.3 Microbial status, absence of pyrogens

The microbial status is determined by Ph. Eur. methods 2.6.12 and 2.6.13. The limits given in the European Pharmacopoeia (Table 3) apply to all the soluble Kollidon grades.

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

- Max. 10^2 aerobic bacteria/g
- Max. 10^2 yeasts and fungi/g
- No Escherichia coli/g
- No Salmonellae/10 g
- Max. 10^2 other Enterobacteriaceae/g
- No Pseudomonas aeruginosa/g
- No Staphylococcus aureus/g

Kollidon 12 PF and Kollidon 17 PF are tested for absence of pyrogens by Method 2.6.8 in the 3rd edition of the European Pharmacopoeia. 10 ml of a 4% solution of Kollidon in isotonic pyrogen-free sodium chloride solution is administered per kg in rabbits.

2.4 Stability and storage

The soluble Kollidon grades retain the properties given in the specifications over a period of more than three years, if they are stored in the unopened original containers at room temperature (20 – 25 °C). Kollidon 90 F is an exception in that, under these conditions, its stability is guaranteed for one year, as its K value gradually decreases.

If Kollidon 90 F is kept refrigerated, its K value decreases more slowly.

Kollidon must be stored tightly closed and protected from light at max. 25 °C.

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 and are practically tasteless.

3.2 Solubility

The solubility of Kollidon in different solvents varies considerably. In Table 4 below, “soluble” signifies that a solution of at least 10% can be prepared, and “insoluble” signifies that the solubility is less than 1%.

Table 4 Solubility of Kollidon

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

3.3 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. 1).

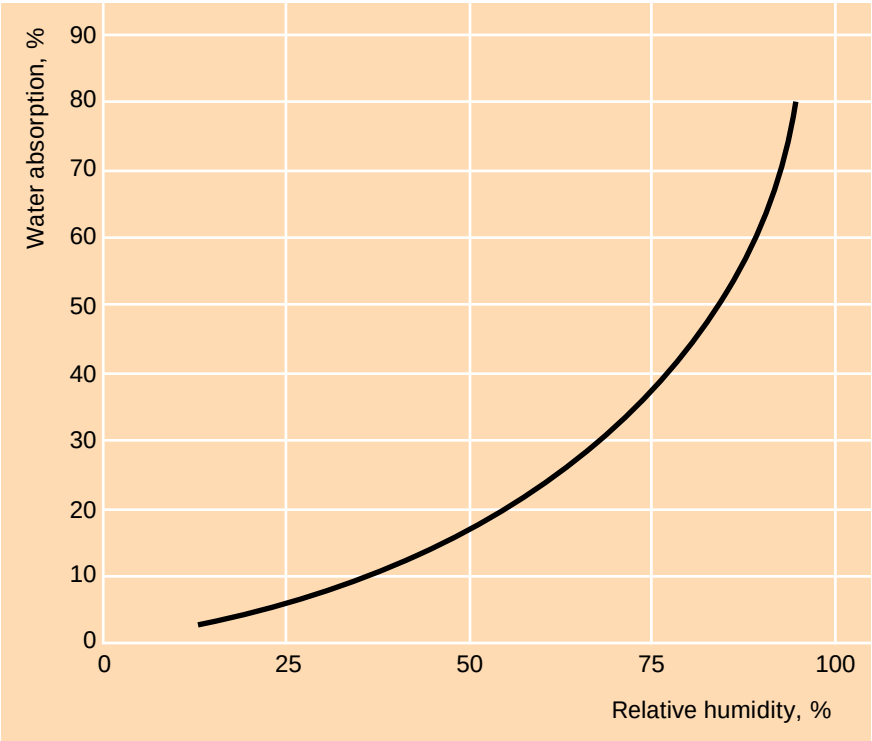


Fig. 1: Hygroscopicity of soluble Kollidon

3.4 Viscosity

Fig. 2 shows the relationship between the viscosity of aqueous solutions of the different grades of Kollidon and their concentration.

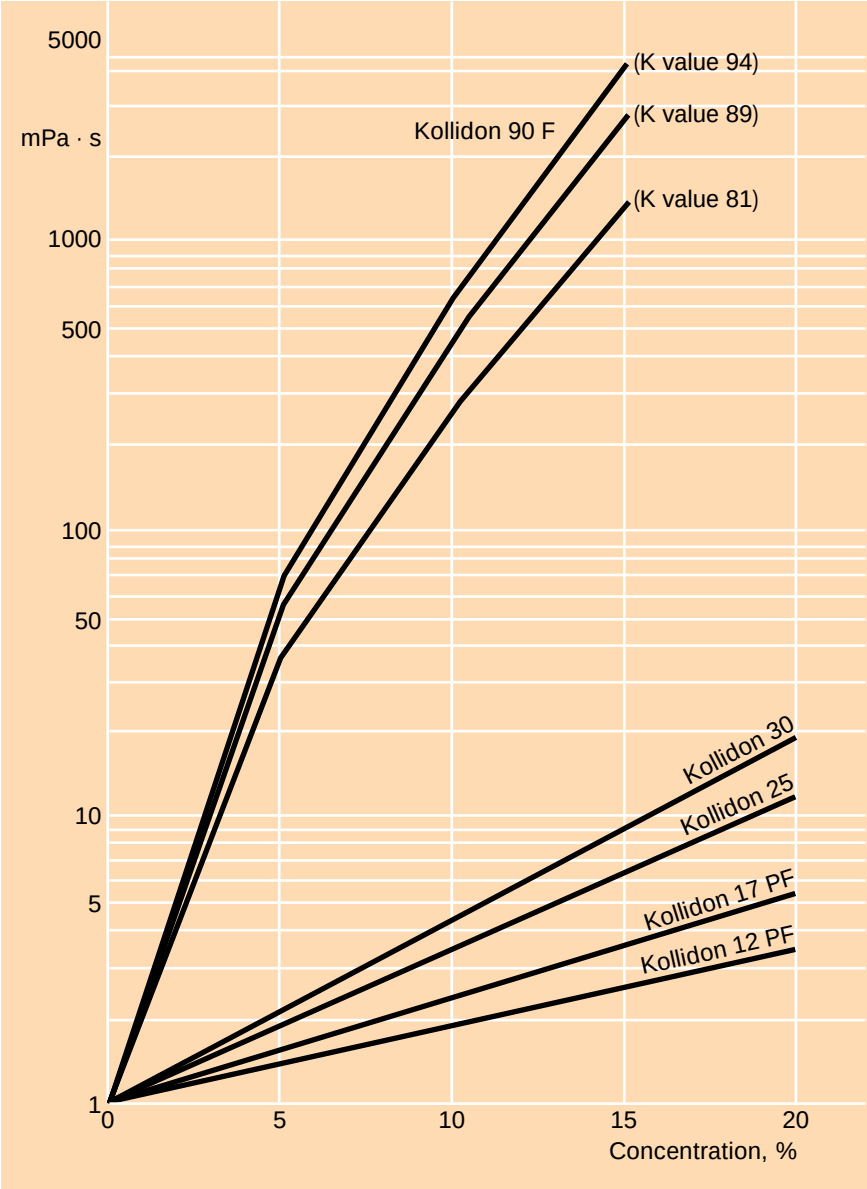


Fig. 2 Viscosity of Kollidon solutions (Ubbelohde viscometer, 25 °C)

3.5 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 5 Particle-size distribution, %

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

3.6 Bulk density

The bulk density of Kollidon is determined according to Ph. Eur. 3, Section 2.9.16.

Table 6 Bulk density of the insoluble Kollidon grades

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

3.7 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 cystein. 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% cysteine, as a proportion of the Kollidon, is added to the solution which is then heated in the absence of air.

3.8 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. This effect can be used in the removal of polyphenols and anthocyanogens from solutions or beverages. However, crospovidone (Kollidon CL) is most suitable for this purpose.

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.

3.9 Molecular weight

With polymers generally, the average molecular weight can be expressed in three forms: weight, numerical 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 ($\overline{M}_v$).

However, the weight average molecular weight ($\overline{M}_w$) 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 $\overline{M}_w$ values were determined for different grades of Kollidon in recent measurements.

Kollidon 12 PF	2,000 – 3,000
Kollidon 17 PF	7,000 – 11,000
Kollidon 25	28,000 – 34,000
Kollidon 30	44,000 – 54,000
Kollidon 90 F	1,000,000 – 1,500,000

Earlier measurements of $\overline{M}_w$ that were not quite so accurate gave values of 40,000 for Kollidon 30 and 700,000 for Kollidon 90, for example.

3.10 Safety Data Sheets

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

4 Applications

4.1 General

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” (BASF, B 390 e, 3rd edition 1996).

4.2 Tablet binders

Kollidon 25, 30 and 90 F

Kollidon 25, 30 and 90 F give hard, free-flowing granules with a low proportion of fines and high binding strength when compressed into tablets. For Kollidon 25 and 30, the quantity required lies between 2% and 5% of the tablet weight. For Kollidon 90 F, less than 2% is generally required, because of its great binding capacity. The high viscosity of binder solutions made with Kollidon 90 F sometimes requires certain precautions to ensure that the granules are evenly wetted. Granulators or spraying machines that have a strong mixing action are helpful.

The addition of polyethylene glycol 400 (Lutrol E 400) as a plasticizer is recommended if the granules are very brittle. Alternatively, Kollidon VA 64 can be used instead of povidone.

Kollidon 25, 30 and 90 F are also suitable for the direct compression of tablets without granulation (prior to 1993, Kollidon 90 was unsuitable for this purpose because of its particle size). 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, 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 by wet granulation. However, the same quantity (3% of the tablet weight) of Kollidon 90 F almost doubles the hardness, compared with Kollidon 25.

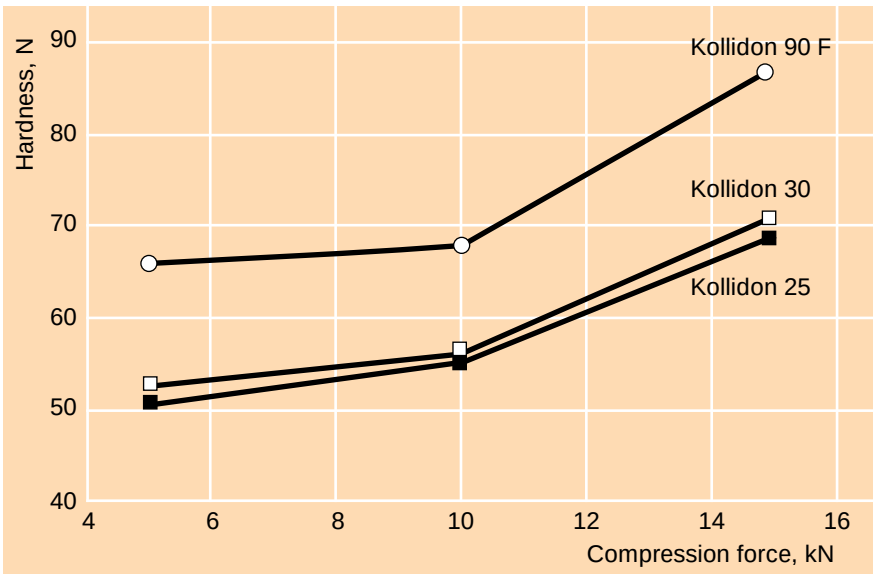


Fig. 3 Lactose monohydrate tablets with 3% Kollidon (wet granulation)

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 7 for alpha-methyldopa tablets. The formulation was tried out on a laboratory scale.

Table 7 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

Table 8 lists some typical drugs that can be solubilized with the aid of soluble Kollidon.

Table 8 Some of the active ingredients that can be solubilized with soluble Kollidon

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

Kollidon 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 e.g. antibiotics.

Kollidon 25, 30

In the same way as Kollidon 12 PF and Kollidon 17 PF are used in injectibles, 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. The chloramphenicol solution in Table 9 for application to the eye or the ear is another example.

Table 9 Chloramphenicol solution for ear drops

Chloramphenicol	3.0 g
Kollidon 25	15.0 g
Preservative	q.s.
Water	ad 100.0 g

4.4 Coprecipitation, comilling

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 Suspension stabilizer

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. nystatin, ibuprofen, 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, Kollidon 17 PF

The low-molecular pyrogen-free grades of Kollidon can be used to stabilize parenteral suspensions, e.g. of 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

Kollidon 17 PF, 25, 30, 90 F

Soluble Kollidon can also be used in eye preparations, because of its solubilizing, film-forming and thickening properties, for instance to ensure that the preparation remains in the eye for a certain time, to lubricate the eye, or to solubilize an active ingredient. This application requires between 2% and 10% Kollidon. It is added to some eye drops e.g. with pilocarpine, to prolong the therapeutic effect. The bioavailability of many active substances in ophthalmic preparations can also be improved or controlled by adding Kollidon.

Kollidon is also used in contact-lens cleaning fluids.

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 during processing.

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 and Kollidon 30 are also very useful in film coating. They are used as film-forming agents, adhesion promoters and pigment dispersers; they also improve the solubility of the coating in water.

However, it must be noted that soluble Kollidon can never be used as the sole film-forming agent as it is highly hygroscopic and makes the coatings 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.

10 % solutions of Kollidon 25 or Kollidon 30 in ethanol or isopropanol can be used for subcoating moisture-sensitive tablet cores.

4.10 Various 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 false teeth
- 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
- enzyme stabilization, e. g. in diagnostics
- vitamin stabilization

4.11 Food products

In 1995, soluble vinylpyrrolidone (povidone) was given the E number E 1201 for use in dietetic tablets, e. g. vitamin and ballast 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:

Orally administered soluble Kollidon has very good acute and long-term tolerance. It is neither teratogenic, mutagenic nor carcinogenic.

It has good skin and mucous membrane tolerance.

It also shows very good tolerance after parenteral administration. The low-molecular grades are quickly eliminated from the system.

The following toxicological and biochemical studies have been carried out with the individual soluble grades of Kollidon.

Kollidon 12 PF:

Acute toxicity, mouse i.v.: LD_{50} > 11 g/kg
4-week toxicity, rat i.v.
Prenatal toxicity, rabbit i.v.
Excretion of C^{14}-labelled Kollidon 12 by female rats after intravenous administration
Renal elimination of C^{14}-labelled Kollidon 12 after intravenous administration

Kollidon 17 PF:

Acute toxicity, mouse i.v.: LD_{50} > 15 g/kg
Acute toxicity, rat oral: LD_{50} > 10 g/kg
Excretion of C^{14}-labelled Kollidon 17 by female rats after intravenous administration
Renal elimination of C^{14}-labelled Kollidon 17 after intravenous administration
Mucous membrane tolerance in rabbit's eye

Kollidon 25:

Acute toxicity, mouse i.v.: LD_{50} > 15 g/kg
Acute toxicity, rat oral: LD_{50} > 10 g/kg
2-year toxicity, rat oral
Prenatal toxicity, rat oral
Mucous membrane tolerance in rabbit's eye

Kollidon 30

Acute toxicity, mouse i.v.: LD_{50} > 15 g/kg
Acute toxicity, rat oral: LD_{50} > 10 g/kg
Test for mutagenic effect of single intraperitoneal application in male mice
Mucous membrane tolerance in rabbit's eye
Cytogenetic studies in Chinese hamsters after two intraperitoneal applications

Kollidon 90

Acute toxicity, rat oral: LD_{50} > 8.25 g/kg
4-week toxicity, rat oral
4-week toxicity, dog oral
Prenatal toxicity, rat oral
2-year toxicity, rat oral

Summaries of all the studies carried out by our Toxicological Department or copies of the original reports will be forwarded on request.

6 Note

The data submitted in this publication are based on our current knowledge and experience. They do not constitute a guarantee in the legal sense of the term and, in view of the manifold factors that may affect processing and application, do not relieve processors from the responsibility of carrying out their own tests and experiments. Any relevant patent rights and existing legislation and regulations must be observed.

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