Technical Information

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Insoluble Kollidon® grades

Crospovidone Ph. Eur., USP/NF, JPE

Crospovidone as excipient for the pharmaceutical industry

BASF
The Chemical Company

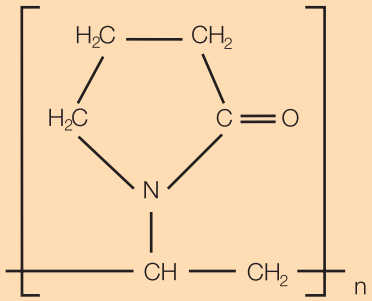
Pharma Ingredients & Services

Contents

1. Introduction

1.1 General

The insoluble grades of Kollidon (Crospovidone) are manufactured by a polymerization process that yields crosslinked insoluble polyvinylpyrrolidone in the form of a “popcorn” polymer. The polymerisation is performed using an aqueous system. Neither organic solvents nor radical starters are involved at any stage.



The crosslinking is of chemical and physical nature. The latter one, mainly achieved by entanglement of the polymer chains, dominates the product properties. This is supported by comparisons of the infrared spectra of the soluble and insoluble grades of polyvinylpyrrolidone which do not reveal any differences. In contrast, the infrared spectrum of chemically crosslinked insoluble vinylpyrrolidone polymer prepared in the laboratory is quite different.

The insoluble grades of Kollidon are widely used in the pharmaceuticals industry because of their swelling properties. They are thus predominantly used as disintegrants in tablets. Furthermore their application as pharmaceutical excipients is triggered by their ability to hydrophilize insoluble drugs, to stabilize suspensions and to form complexes, as well as by their adsorptive properties.

Details that are beyond the scope of this brochure can be found in the books, “Kollidon, Polyvinylpyrrolidone for the pharmaceutical industry”, published by BASF or “Polyvinylpyrrolidone-Excipients for Pharmaceuticals”, published by Springer-Verlag, ISBN 3-540 23412-8.

1.2 Synonyms

Crospovidone, crospovidonum, insoluble polyvinylpyrrolidone, crosslinked PVP.

1.3 Product range

Due to the fact that Crospovidone is completely insoluble in solvents the corresponding products cannot be named according to a K-value or a molecular weight. The product differentiation is done mainly by the particle size distribution. The following products are available:

Kollidon CL
Kollidon CL-F
Kollidon CL-SF
Kollidon CL-M

[1] M = micronized

The products differ not only in their particle size distributions but in other physical properties, too, such as in their bulk density and their swelling behaviour.

2. Specifications and stability

2.1 Specifications

Table 1: Specifications for the insoluble Kollidon grades

	Kollidon CL	Kollidon CL-F	Kollidon CL-SF	Kollidon CL-M
Identity	Passes test	Passes test	Passes test	Passes test
EP Identity Test D	Type A	Type A	Type B	Type B
Nitrogen, %	12.0 – 12.8	12.0 – 12.8	12.0 – 12.8	12.0 – 12.8
Water (K. Fischer), %	≤ 5.0	≤ 5.0	≤ 5.0	≤ 5.0
pH value (1% in water)	5.0 – 7.5	5.0 – 7.5	5.0 – 7.5	5.0 – 7.5
Vinylpyrrolidone (iodometric), %	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1
Vinylpyrrolidone (HPLC), ppm	≤ 10	≤ 10	≤ 10	≤ 10
Sulfated ash, %	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1
Heavy metals, ppm	≤ 10	≤ 10	≤ 10	≤ 10
Water-soluble substances, %	≤ 1.0	≤ 1.0	≤ 1.0	≤ 1.0
Peroxides, ppm H_2O_2	≤ 400	≤ 1000	≤ 1000	≤ 1000
Microbial status (see Table 2)	Passes test	Passes test	Passes test	Passes test
Residual solvents (Ph.Eur. 5.4)	Not present	Not present	Not present	Not present

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

The water-soluble substances are determined after centrifugation and filtration through a 0.4 µm membrane filter.

All the above data are determined by the methods in USP/NF and EP. The methods for determining the microbial status are given below in Section 2.3.

2.2 Regulatory status

Products meet current Crospovidone Ph. Eur., USP/NF and JPE monographs.

2.3 Microbiological status

The microbial status is determined according to Ph. Eur., method 2.6.12, latest edition.

The acceptance criteria for microbiological quality of non-sterile substances for pharmceutical use are published in EP 5.1.4.2 and are limited for the Kollidon grades as follows:

TAMC $<10^2$ CFU/g
TYMC <10 CFU/g

The acceptance criteria for microbiological quality are interpretated as described in EP 2.6.12, section 5.3.

3. Physical and chemical properties

3.1 Description, solubility

The insoluble Kollidon grades are supplied as fine white or almost white powders. They have a slight characteristic odor and are practically tasteless. They are insoluble in all of the usual solvents.

3.2 Hygroscopicity

The hygroscopic properties of the Kollidon grades are important in many applications. There is hardly any difference between the individual grades so that they can all be represented by a single curve (Fig. 1). The curve shows the amount of water absorbed after seven days' exposure to different conditions of relative humidity.

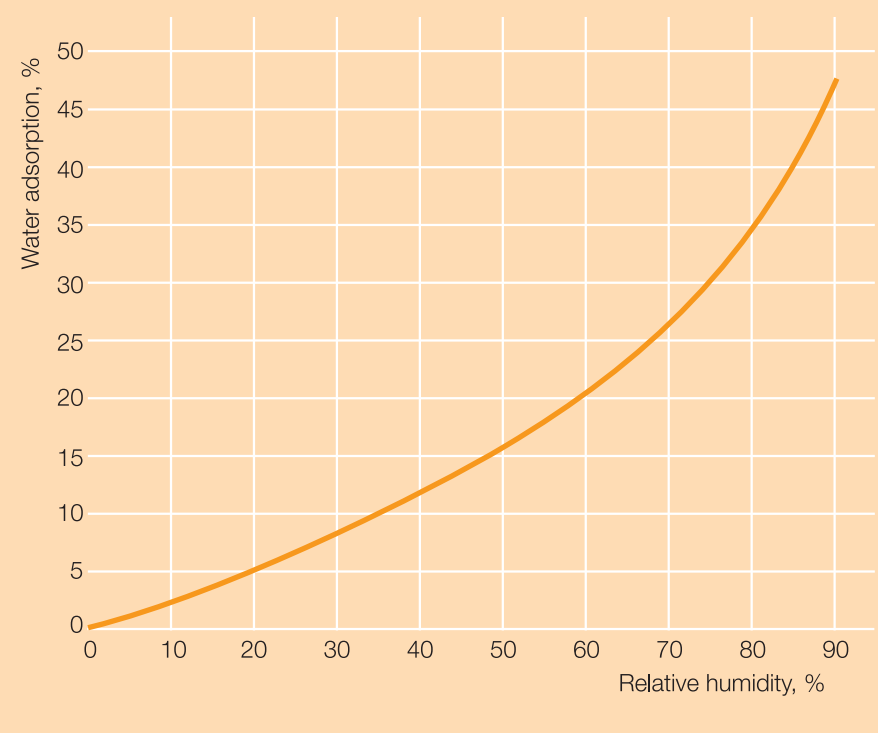


Fig. 1: Hygroscopicity of the Kollidon grades

3.3 Swelling and hydration properties

One of the most important properties of the insoluble Kollidon-CL grades used as tablet disintegrants is their property to swell very fast and predictably without forming a gel. A number of methods are described in the literature for measuring swelling properties in aqueous media.

The swelling pressure of poured and slightly compacted Kollidon CL powder in water is much higher than that one of Kollidon CL-M, Kollidon CL-SF and Kollidon CL-F. The pressure increase per time depends on the particle size distribution and is highest for Kollidon CL, followed by Kollidon CL-F and Kollidon CL-SF. The relative high swelling pressure of Kollidon CL-M is achieved after a comparably long swelling time.

Table 3: Swelling pressure [kpa] and time to reach 90% of the maximum swelling pressure [s] of the insoluble Kollidon grades (typical values)

	Kollidon CL	Kollidon CL-F	Kollidon CL-SF	Kollidon CL-M
Swelling pressure, kPa	Ca. 170	Ca. 30	Ca. 25	Ca. 70
time to reach 90% of the maximum swelling pressure, s	< 10	< 15	< 35	> 100

Swelling can also be measured in terms of the adsorption of water, or hydration. It is determined as follows:

Weigh 2.0 g of Kollidon CL into a 100 ml centrifuge tube, add 40 ml of water and shake vigorously until the powder is suspended. Re-suspend after 5 and again after 10 minutes. Then centrifuge for 15 minutes at 2000 rpm. Decant the supernatant liquid, then weigh again.

The hydration capacity is calculated as the quotient of the weight after hydration and the initial weight. The hydration capacity is shown in Table 4.

Table 4: Hydration capacity of the insoluble Kollidon grades (typical values)

	Kollidon CL	Kollidon CL-F	Kollidon CL-SF	Kollidon CL-M
g water/g polymer	3.5 – 5.5	5.0 – 6.6	7.0 – 8.5	3.0 – 4.5

3.4 Particle size distribution

The particle size distribution of the solid ingredients must be taken into account when formulating tablets, particularly if they are to be made by direct compression. The following table gives some typical values for particle size distributions, determined in an air jet sieve after 5 min at 20 mbar:

Table 5: Particle sizes of the insoluble Kollidon grades (typical values)

	Kollidon CL	Kollidon CL-F	Kollidon CL-SF	Kollidon CL-M
< 15 µm	–	–	≥ 25%	≥ 90%
< 50 µm	≤ 60%	> 50%		–
< 250 µm	≥ 95%	≥ 95%	≥ 99%	–

3.5 Bulk density, tap density

Table 6 gives typical values for the bulk and tap densities after 500 taps of the insoluble Kollidon grades. One of the major differences between Kollidon CL and Kollidon CL-M lies in their bulk densities, and this affects their applications.

Table 6 Bulk and tap densities of the insoluble Kollidon grades (typical values)

	Bulk density	Tap density (500 taps)
Kollidon CL	0.30 – 0.40 g/ml	0.40 – 0.50 g/ml
Kollidon CL-F	0.18 – 0.28 g/ml	0.25 – 0.35 g/ml
Kollidon CL-SF	0.10 – 0.16 g/ml	0.18 – 0.25 g/ml
Kollidon CL-M	0.15 – 0.25 g/ml	0.25 – 0.35 g/ml

3.6 Specific surface area

The insoluble grades of Kollidon have different specific surface areas, as can be seen from Table 7.

Table 7: Specific surface areas of the insoluble Kollidon grades determined according to DIN 66131-132 (typical values)

Product	Specific surface area (N2-BET)
Kollidon CL	< 1 m^2/g
Kollidon CL-F	ca. 1.5 m^2/g
Kollidon CL-SF	ca. 3 m^2/g
Kollidon CL-M	> 6 m^2/g

3.7 Complex formation

Like the soluble grades of Kollidon, the insoluble Kollidon CL-grades form chemical complexes or associates with a large number of drugs and other substances. The formation of the complexes is reversible and no complex formation occurs in alkaline medium. Whether Crospovidone in general forms a complex with a drug depends very much on its chemical structure.

Systematic investigations have shown that complexes are formed much more readily with aromatic compounds that contain phenyl and/or carboxyl groups.

For most of the drugs that form complexes with Kollidon CL-grades, the degree of complex formation is usually such that the dissolution rate of the drug is accelerated.

The ability to form complexes has many uses in pharmaceuticals:
– to improve the dissolution and bioavailability of drugs,
– to adsorb and remove polyphenols and tannins from tinctures and herbal extracts and
– to improve the taste of azithromycin, paracetamol and vitamins.

3.8 Infrared spectrum

The insoluble Kollidon polymers are mainly physically crosslinked. No difference can be seen between the infrared spectra of Kollidon CL (Fig. 2 a) and that of povidone (Kollidon 90F, Fig. 2 b).

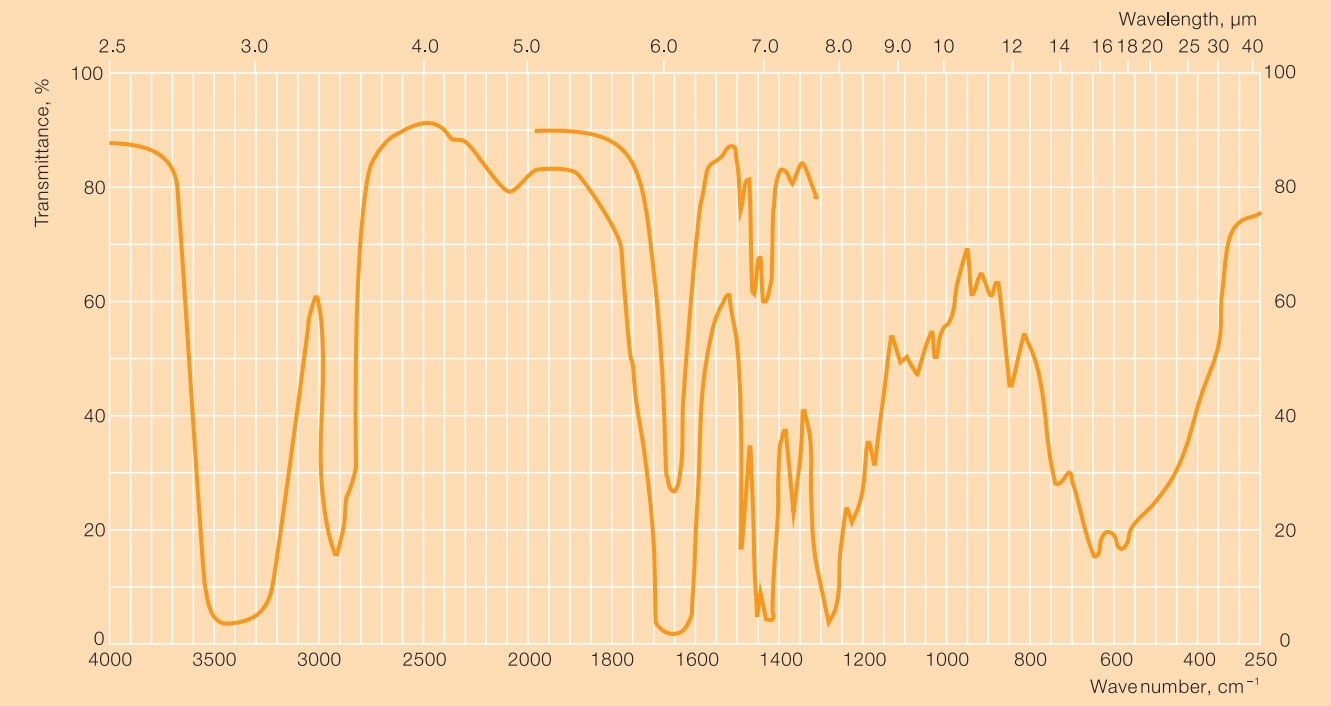


Fig. 2 a Infrared spectrum of Kollidon CL in KBr

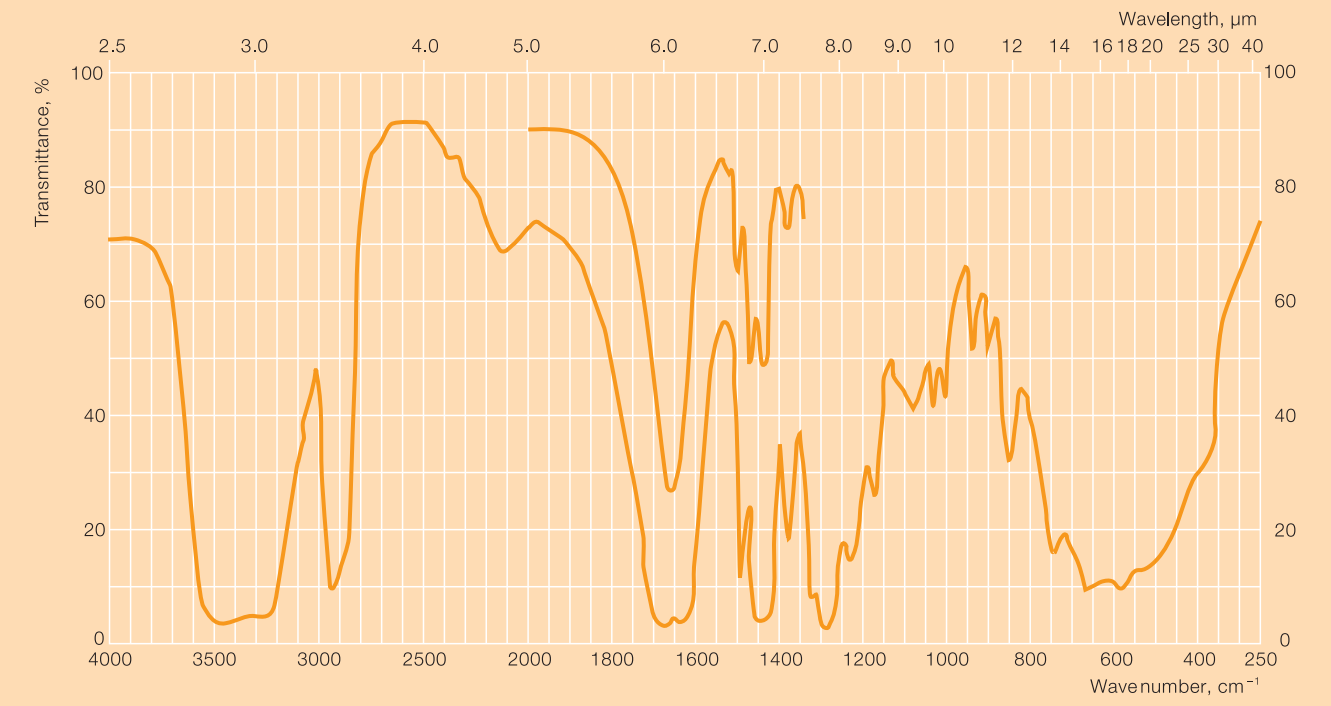


Fig. 2 b Infrared spectrum of Kollidon 90 F in KBr

4. Applications

4.1 General

The insoluble Kollidon CL-grades possess a number of useful properties for pharmaceutical products.

Table 8: Functionalities of Kollidon CL, Kollidon CL-F, Kollidon CL-SF and Kollidon CL-M in pharmaceuticals

- Improvement of tablet disintegration through predictable swelling without gel-formation
- Swelling properties paired with particle size distribution make the fine Kollidon CL-grades work efficiently in fast disintegrating formulations
- Narrow particle size distributions in conjunction with a high swelling pressure recommends Kollidon CL-SF as disintegrant for small tablets with low API-concentrations
- In contrast to other disintegrants the Kollidon grades improve the release and the bioavailability of drugs through complex formation
- Kollidon grades feature selective adsorption of polyphenols by complex formation
- Kollidon grades feature selective complex formation with some endotoxins
- As a hydrophilic polymer Kollidon CL-M stabilizes suspensions
- Due to its water adsorption properties Kollidon grades act as stabilizers of water sensitive compounds in sold dosage forms, e.g. in vitamin formulations

Detailed descriptions of the applications can be found in the books, “Polyvinylpyrrolidone-Excipients for Pharmaceuticals”, published by Springer-Verlag, ISBN 3-540 23412-8 or “Kollidon, Polyvinylpyrrolidone for the pharmaceutical industry”, published by BASF.

4.2 Tablet disintegration and dissolution (Kollidon CL, Kollidon CL-F or Kollidon CL-SF)

Today Crospovidone is described in the literature as one of the three “superdisintegrants”. A large number of papers have been published that substantiate this in comparisons of the various disintegrants in placebo and active tablets. They come to the conclusion that there is no universal ideal disintegrant and that the best disintegrant must be determined individually for each application.

The usual quantity of Kollidon CL, Kollidon CL-F and Kollidon CL-SF used is a range of 2 – 8%, as a proportion of the tablet weight. The following formulation for an analgesic tablet has been selected for testing and comparing disintegrants, properties.

Table 9: Comparison of disintegrants in an analgesic tablet

1	Composition	
I	Paracetamol cryst.	250 mg
	Acetylsalicylic acid cryst.	250 mg
	Caffeine cryst.	50 mg
II	Kollidon 30 (dissolved in water)	27.5 mg
III	Magnesium stearate	5 mg
	Disintegrant	16 mg
	Total tablet weight	598.5 mg

Granulate I with II, dry sieve, mix with III and compress into tablets.

2 Disintegration times of the tablets (in synthetic gastric juice)

Disintegrant	Minutes
None	> 70
Kollidon CL	9
Kollidon CL-F	11
Kollidon CL-SF	9
Croscarmelose	24
Sodium carboxy methyl.starch	34

Although the disintegration time of a tablet is important, the dissolution rate of the active ingredient is just as important in assessing and comparing disintegrants.

To demonstrate this effect, Table 10 below shows the formulation and physical properties of an acetylsalicylic acid tablet that has a very poor dissolution rate without a disintegrant (Fig. 3).

Table 10: Acetylsalicylic acid tablets with different disintegrants (direct compression)

1 Composition

Acetylsalicylic acid cryst.	400 g
Ludipress®	99 g
Stearic acid	1 g
Disintegrant	15 g

2 Properties (Laboratory rotary tablet press, compression force 8 kN)

	Without disintegrant	Kollidon CL	Croscarmelose	Sodium carboxymethyl starch
Weight	503 mg	516 mg	522 mg	540 mg
Hardness	95 N	90 N	84 N	89 N
Disintegration time (gastric juice)	22 min	30 s	48 s	50 s
Friability	0.4%	0.4%	0.3%	0.3%
Dissolution (USP)	see Fig. 3			

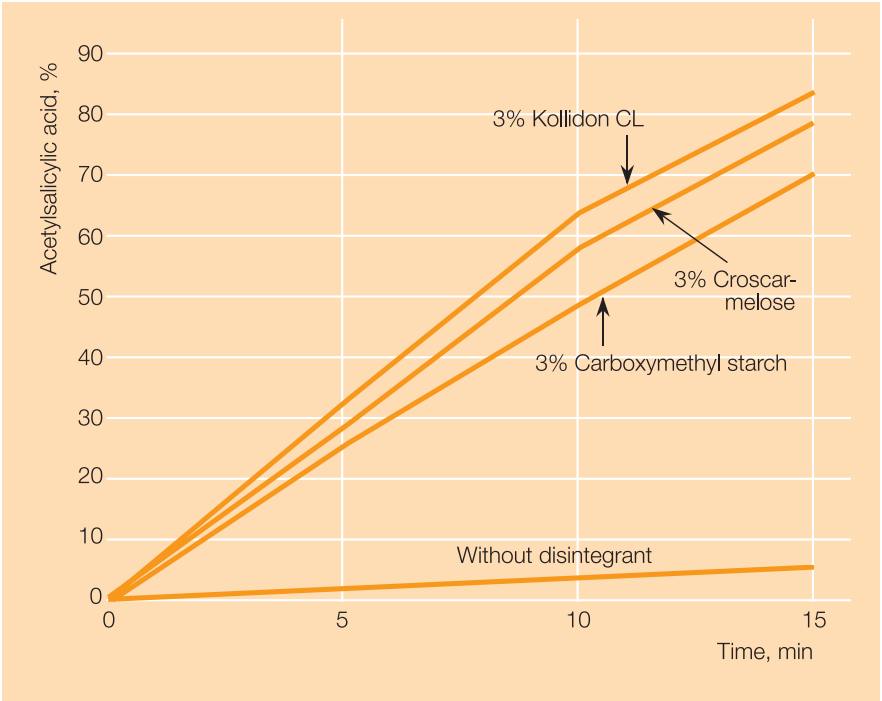


Fig. 3 Dissolution of the acetylsalicylic acid tablets described in Table 10 (USP method):

Rating
1 Smooth
2 small unevenness on the tablet surface
3 small unevenness, rough tablet surface
4 remarkable unevenness, formation of “pimples” begins
5 slight formation of “pimples”
6 medium formation of “pimples”
7 strong formation of “pimples”
8 strong formation of “pimples”/ tablet fragile and swollen

Storage conditions 23 °C, 65% r.h.

Disintegrant	65% rel. humididy after 1 day	65% rel. humididy after 3 days	65% rel. humididy after 7 days
Kollidon CL	5	5	5
Kollidon CL-SF	2	2	2
Kollidon CL-F	3	4 – 5	4 – 5
Kollidon CL-M	1	1	1
Croscarmelose	3*[1]	3*[1]	3*[1]
Carboxymethyl starch sodium	3*[1]	3*[1]	3*[1]

Storage conditions 23 °C, 75% r.h.

Disintegrant	75% rel. humididy after 1 day	75% rel. humididy after 3 days	75% rel. humididy after 7 days
Kollidon CL	6	6	6
Kollidon CL-M	1	1	1
Kollidon CL-F	4	5	5
Kollidon CL-SF	2	3	4
Croscarmelose	3*[1]	3*[1]	3*[1]
Carboxymethyl starch sodium	3 – 4*[1]	3 – 4*[1]	3*[1]

*[1] tablets show light brown discolouration as of day 1. The color intensifies throughout storage

Moisture-proof packaging is therefore always recommended for tablets and capsules that contain the coarse Kollidon CL-grades.

The disintegration effect of Kollidon CL-grades can be used to increase the bioavailability of the active constituent not only in tablets but also in suppositories. In a polyethylene glycol-based suppository, the addition of 1 – 10% of Kollidon CL-grades improve the dissolution rate of the active constituent.

4.3 Coating Kollidon CL-, Kollidon CL-F- or Kollidon CL-SF-containing tablet cores

When tablet cores that contain Kollidon CL as a disintegrant are sugar or film coated, it is necessary to exercise care in selecting a suitable coating pan. This is particularly important if the coating suspension is water-based.
In many cases, it is therefore recommended to subcoat the cores before applying the coating proper.

A 10% solution of Kollidon VA 64 in isopropanol, ethanol or ethyl acetate provides a good subcoating. It can be sprayed briefly onto the prewarmed tablet cores in the same coating pan before the final aqueous coating is applied (see Technical Information Sheet, “Kollidon VA 64”).

4.4 Stabilization of suspensions (Kollidon CL-M)

Kollidon CL-M is a hydrophilic polymer that can be used in concentrations of 5 – 12% to physically stabilize oral and topical suspensions. It achieves this effect by increasing the volume of the sediment and reducing its sedimentation rate, and by making it easy to redisperse the sediment by shaking (anticaking effect), practically without increasing the viscosity of the preparation.

These properties apply whether the final product is a ready-to-use suspension or an instant drink powder or granulate from which the patient prepares a suspension before use.

It has been found in practice that the increase in sediment volume achieved with Kollidon CL-M in such suspensions can be further enhanced by adding auxiliaries such as sodium citrate as an electrolyte, sugar, Lutrol® F 127 or one of the soluble grades of Kollidon, such as Kollidon 90 F.

Table 11 presents a formulation for an antibiotic dry syrup as an example of the use of Kollidon CL-M. The formulation has been developed in the laboratory for a number of different active ingredients and can therefore be regarded as a typical standard formulation. Citric acid has been included to give a pH value of 4.9, at which the two active ingredients, ampicillin and amoxicillin trihydrate are most stable in this administration form.

Table 11: Antibiotic dry syrup for children, with Kollidon CL-M

Formulation (sales product)	
Ampicillin or amoxicillin trihydrate	5.0 g
Sodium citrate	5.0 g
Citric acid	2.1 g
Sodium gluconate	5.0 g
Sorbitol	40.0 g
Kollidon CL-M	6.0 g
Orange flavouring	1.5 g
Lime flavouring	0.5 g
Saccharin sodium	0.4 g

Drink containing 250 mg of active substance per 5 ml:

Shake 66 g of the powder mixture with water to give a total volume of 100 ml.

Sedimentation is very slow and any sediment that does form can very readily be redispersed even after several weeks.

The main applications for Kollidon CL-M are in instant drink granules, ready-to-use suspensions or dry syrups that contain the following types of active ingredient:
– antibiotics
– antacids
– vitamins
– analgesics.

A notable property of Kollidon CL-M in suspensions is that, in concentrations of 5 – 10%, it hardly increases the viscosity of the suspension.

Kollidon CL-M has also been found to stabilize suspensions in lipophilic media such as liquid paraffin.

4.5 Stabilization of vitamins (Kollidon CL-grades)

As with the soluble grades of Kollidon, Kollidon CL-grades are also able to stabilize active ingredients in pharma-ceutical products. A typical example is provided by a multivitamin instant drink granulate. The stability of the vitamins in a formulation prepared in the laboratory was found to be almost ideal.

The effect of Kollidon CL-M on vitamin B1, calcium pantothenate and vitamin C was demonstrated in an accelerated storage test (Table 12).

Table 12: Vitamin degradation in multivitamin instant drink granules with and without Kollidon CL-M (30 °C/70% relative humidity)

	1 month	2 months	3 months	5 months
Vitamin B_1:				
Without Kollidon CL-M	4%	11%	16%	26%
With Kollidon CL-M	0%	1%	7%	10%
Vitamin C:				
Without Kollidon CL-M	17%	18%	40%	49%
With Kollidon CL-M	0%	2%	13%	19%
Ca-Pantothenate:				
Without Kollidon CL-M	–	8%	21%	50%
With Kollidon CL-M	–	10%	10%	15%

4.6 Improvement of dissolution/ bioavailability

As with the soluble Kollidon grades, Kollidon CL-grades are capable of forming complexes with active substances and increasing their dissolution rate and bioavailability. Different mixing methods can be used:
– physical mixture with the active ingredient
– comilling with the active ingredient
– coevaporation of a suspension of Kollidon CL in a solution of the active ingredient.

All published papers on investigations into the crystalline structure of preparations made by these methods have found that the active ingredient has a stable amorphous form and that the dissolution rate and/or the bioavailability is increased. For comilling, Kollidon CL-M or Kollidon CL-SF are preferable to Kollidon CL or Kollidon CL-F, which are coarser.

The quantity of Kollidon CL-grades required for this purpose is about 1- to 10-fold the quantity of the active ingredient. In principle, it can be assumed that all active substances whose dissolution rate can be improved with polyvidone (e.g. Kollidon 30) can benefit in the same way from the insoluble Kollidon CL-grades.

4.7 Filtration aid (Kollidon CL)

The ability of Crospovidone to form stable complexes with tannins and polyphenols can be used not only in the beverage technology for the stabilization of beer but also in the purification of aqueous or alcoholic herbal extracts and tinctures. Polyphenols are selectively bound by the Kollidon CL-grades which can therefore be used to improve the stability of such phytopharmaceuticals.

The Kollidon CL-grades can either be suspended in the extract then filtered off after a certain time, or the extract can be slowly percolated through a bed of Kollidon CL-grades.

5. Registration

5.1 Pharmaceuticals

Crospovidone is registered and approved throughout the world in oral pharmaceuticals.

In France, it is also approved as an active ingredient in two specialities.

5.2 Foods application

The European authorities have issued an E number for crospovidone – E 1202 – for its use in dietetic tablets (vitamins, fibre products, vegetable extracts etc.), and for its use in tabletop sweeteners.

It is also approved almost worldwide for stabilizing beer and wine. These products are marketed by BASF under the brand names of Divergan®.

6. Toxicological data

Polyvinylpyrrolidone has been used for decades in a wide variety of pharmaceutical products. A large number of publications report that it is well tolerated. The JECFA, a joint FAO and WHO body, set a revised ADI value of 0 – 50 mg/kg per day for soluble polyvinylpyrrolidone in 1987. In 1983, the same body determined that it was unnecessary to specify a maximum ADI value for Crospovidone.

A summary of the toxicological findings is available. If necessary we will share under Secrecy Agreement – summaries or complete copies of the original toxicological reports of the studies conducted by our toxicology department.

7. PRD-Nos.

Kollidon CL	30034964
Kollidon CL-F	30274401
Kollidon CL-SF	30274400
Kollidon CL-M	30034966 30444355 (Origin Germany)

8. Packaging

Kollidon CL is supplied in 40 kg plastics drums with welded, gastight Aluminium/PE inliners.

Kollidon CL-F is supplied in 30 kg plastics drums with welded, gastight Aluminium/PE inliners.

Kollidon CL-SF is supplied in 30 kg plastics drums with welded, gastight Aluminium/PE inliners

Kollidon CL-M is supplied in PE-drums of 30 kg with a PE inliner.

9. Stability and storage

Retest date, if stored in the unopened original containers at max. 25 °C, is 36 months.

Products must be kept tightly sealed and protected from light at max. 25 °C.

10. Safety Data Sheets

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

11. Note

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