Technical Information

Insoluble Kollidon® grades

Crospovidone Ph. Eur., USP and JP

Crospovidone as excipient for the pharmaceutical industry

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1. Introduction

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 solid oral dosage forms such as tablets. Furthermore their application as pharmaceutical excipients is triggered by their ability to hydrophilize insoluble drugs, to stabilize suspensions and to form complexes.

2. Technical properties

Description

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.

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.

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

Synonyms

Crospovidone, crospovidonum, insoluble polyvinylpyrrolidone, crosslinked PVP.

Product range

Due to the fact that Crospovidone is completely insoluble 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

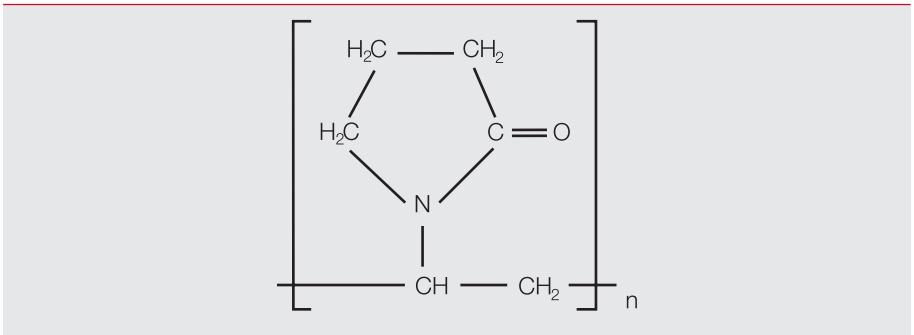
M = micronized

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 behavior.

CAS-number

9003-39-08

Structural formula



Picture 1: Crospovidone

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.

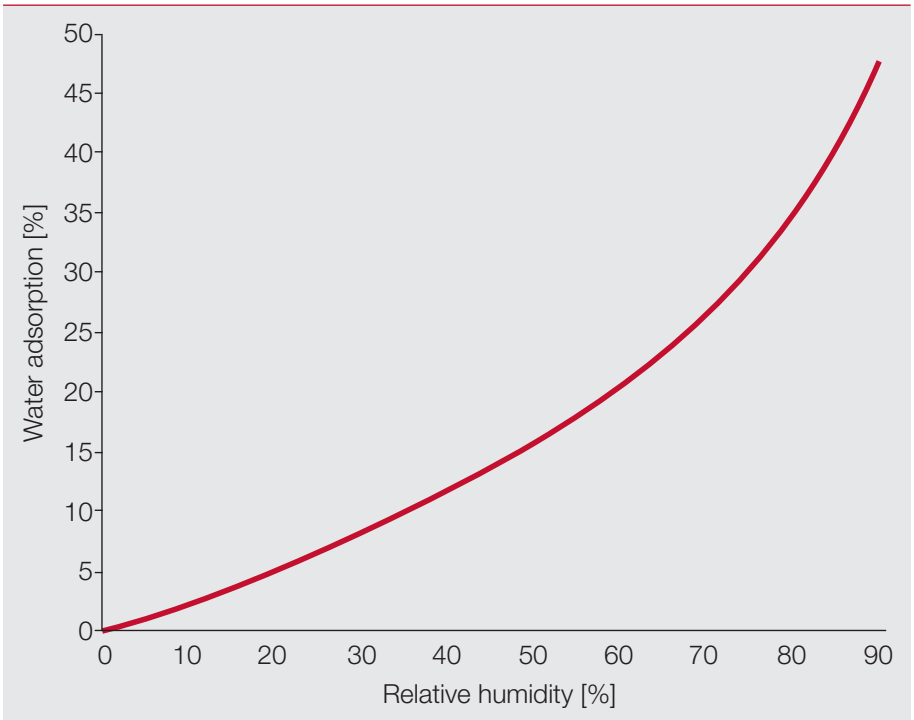


Fig. 1: Hygroscopicity of the Kollidon® CL-grades

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 data for the swelling pressure shown in table 1 were measured with a powder mass of 0.3 g and a punch diameter of 25 mm.

The swelling pressure of 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 1: 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	approx. 170	approx. 30	approx. 25	approx. 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 2.

Table 2: 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

Particle size distribution (PSD)

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 using an air jet sieve after 5 min at 20 mbar:

Table 3: Particle sizes of the insoluble Kollidon® grades (typical values)

	Kollidon® CL	Kollidon® CL-F	Kollidon® CL-SF	Kollidon® CL-M
<15 µm	–	–	–	≥ 90%
>50 µm	max. 80%	max. 60%	max. 30%	–
>100 µm	max. 60%	max. 20%	max. 10%	–

For the determination of the PSD of Kollidon® CL-M laser diffraction is applied.

Bulk density, tap density

Table 4 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 4: 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

Specific surface area

The insoluble grades of Kollidon® have different specific surface areas, as can be seen from Table 5.

Table 5: 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 m²/g
Kollidon® CL-F	approx. 1.5 m²/g
Kollidon® CL-SF	approx. 3 m²/g
Kollidon® CL-M	>6 m²/g

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.

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® 90 F, Fig. 2 b).

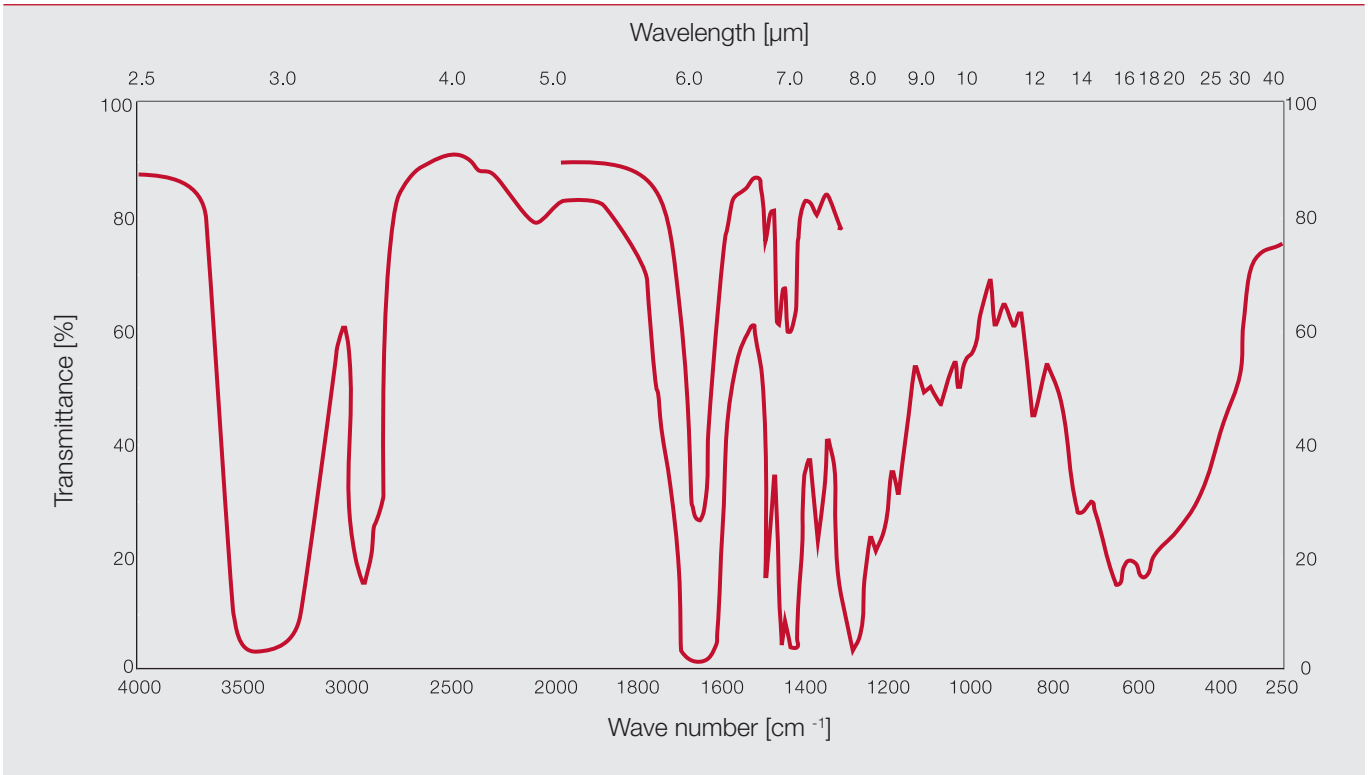


Fig. 2 a: Infrared spectrum of Kollidon® CL in KBr

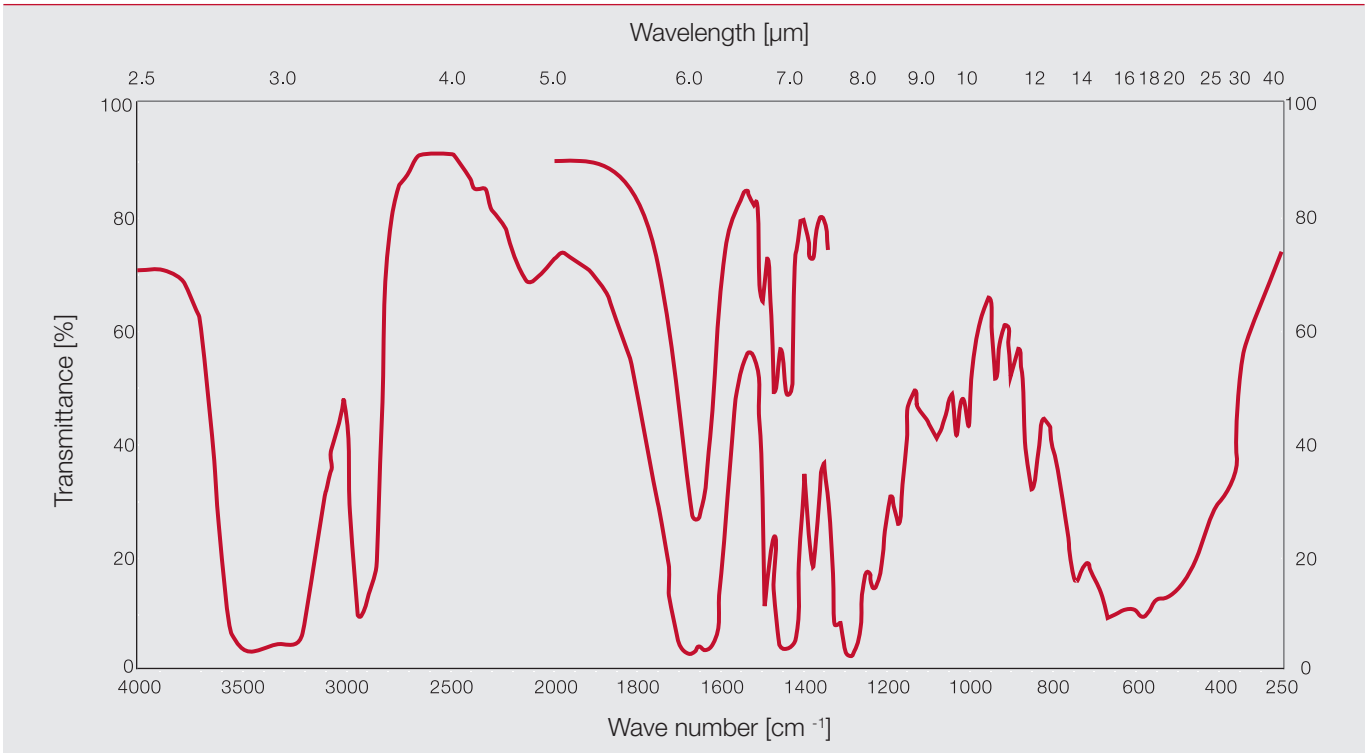


Fig. 2 b: Infrared spectrum of Kollidon® 90 F in KBr

3. Handling

Please refer to the individual Material Safety Data Sheet (MSDS) for instructions on safe and proper handling and disposal.

4. Example application

General

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

Table 6: 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.

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 7: 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
	Croscarmellose	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 8 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 8: 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**	**Cros-carmellose**	**Sodium carboxy-methyl 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			

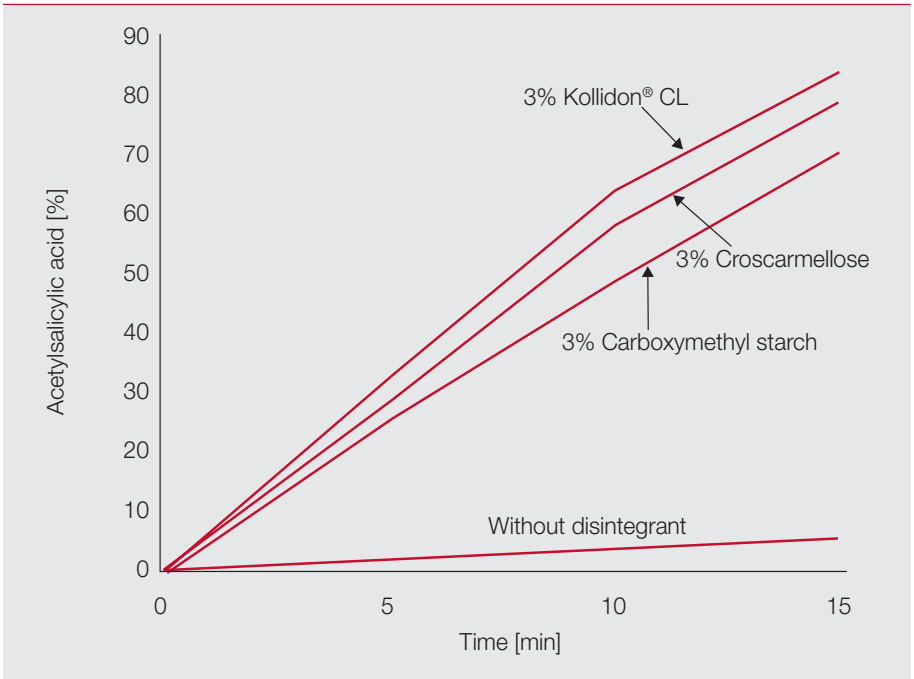


Fig. 3: Dissolution of the acetylsalicylic acid tablets described in Table 8 (USP method):

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. humidity after 1 day	65% rel. humidity after 3 days	65% rel. humidity 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
Croscarmellose	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. humidity after 1 day	75% rel. humidity after 3 days	75% rel. humidity 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
Croscarmellose	3*[1]	3*[1]	3*[1]
Carboxymethyl starch sodium	3 – 4*[1]	3 – 4*[1]	3*[1]

*[1] tablets show light brown discoloration 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.

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”).

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, Kolliphor® P407 or one of the soluble grades of Kollidon®, such as Kollidon® 90 F.

Table 9 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 9: 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.

Stabilization of vitamins (Kollidon® CL-grades)

As with the soluble grades of Kollidon®, Kollidon® CL-grades are also able to stabilize active ingredients in pharmaceutical 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 10).

Table 10: 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%

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 bio-availability. 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.

Absorptive polymer (Kollidon® CL)

The ability of Crospovidone to form stable complexes with various 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.

Under caustic conditions absorbed polyphenols can be released from the polymer and recovered if desired.

5. Safety data sheet

Safety data sheets are available on request and are sent with every consignment.

6. Retest date and storage conditions

Please refer to Quality & Regulatory Product Information (QRPI).

7. Specification

For current specification, please speak to your local BASF sales or technical representative.

8. Regulatory status

Please refer to Quality & Regulatory Product Information (QRPI).

9. Toxicological data

For information on toxicological issues please refer to the tox abstract which can be supplied on request.

More/detailed toxicological information for Kollidon® grades is available on request under Secrecy Agreement.

10. PRD and Article numbers

PRD-No.*	Product name	Article numbers	Packaging
30034964	Kollidon® CL	50000695	40 kg Plastic drum
		50347948	0.5 kg Plastic pail**
30274401	Kollidon® CL-F	53216545	30 kg Plastic drums
		50539226	0.25 kg Plastic pail**
30274400	Kollidon® CL-SF	52595650	30 kg Plastic drums
		50348145	0.25 kg Plastic pail**
30444355	Kollidon® CL-M Origin Germany	51928647	30 kg Plastic drums
		50348144	0.25 kg Plastic pail**

* BASF's commercial product number.

** Corresponding product sample

11. Publications

http://pharmaceutical.basf.com/en.html

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