Technical Information

Kollidon® CL-M

Crospovidone excipient for the pharmaceutical industry

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1. Introduction

Crospovidones, known for their unique swelling properties, are extensively used as excipients in solid oral dosage forms within the pharmaceutical industry, primarily serving as super-disintegrants. In most pharmacopeias, the differentiation between Type A and Type B crospovidone is based on particle size, measured by sieving particles suspended in water.

Kollidon® CL-M (M = micronized) a Type B crospovidone grade offered by BASF, stands out due to its unique properties and versatile applications in the pharmaceutical industry. This product not only enhances the disintegration of tablets for faster drug release but also improves tablet strength through its dry binding properties. Additionally, it prevents sedimentation in liquid formulations and provides a white appearance to tablets when used in tablet coating, being an alternative to white pigments, such as titanium dioxide.

This document provides detailed technical information on Kollidon® CL-M, including its chemical and physical properties, functionality, and various applications in the pharmaceutical industry.

Kollidon® CL-M complies with various pharmacopeial standards. Further details are available in RegXcellence®.

Supplied as a very fine white or nearly white powder, Kollidon® CL-M has weak flowability, a slight characteristic odor, and is practically tasteless. It is insoluble in all common solvents.

Additional crospovidone super-disintegrants from BASF include the following Kollidon® CL grades:

Kollidon® CL (crospovidone, Type A)
Kollidon® CL-F (F = fine, crospovidone, Type A)
Kollidon® CL-SF (SF = super fine, crospovidone, Type B)

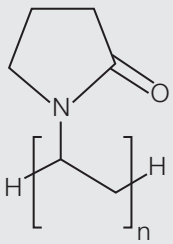
For more detailed information on Kollidon® CL-M and BASF Kollidon® CL grades, refer to the separate Technical Product Information and the books “Kollidon®, Polyvinylpyrrolidone for the Pharmaceutical Industry” published by BASF, or “Polyvinylpyrrolidone-Excipients for Pharmaceuticals” published by Springer-Verlag (ISBN 3-540-23412-8).

2. Chemical & Physical Properties

Name

Compendial name: Crospovidone
Other names: crospovidonum, insoluble polyvinylpyrrolidone, crosslinked PVP

Chemical Structure



CAS number

9003-39-8

Raw material and production information

Insoluble Kollidon® CL crospovidone grades are manufactured through a unique polymerization process known as “popcorn” polymerization.

This process starts with the monomer N-vinyl-pyrrolidone in an aqueous system, resulting in crosslinked insoluble polyvinylpyrrolidone particles. The crosslinking is both chemical and physical, with physical crosslinking - mainly achieved through polymer chain entanglement - dominating the product properties. Therefore, when analyzed with IR spectroscopy, insoluble crospovidone cannot be distinguished from soluble povidone (linear PVP).

Kollidon® CL-M is the only grade of Kollidon® CL where the final particles are obtained through a milling step. The particles have an irregular shape and surface, which can be observed using Scanning Electron Microscopy (Fig. 1).

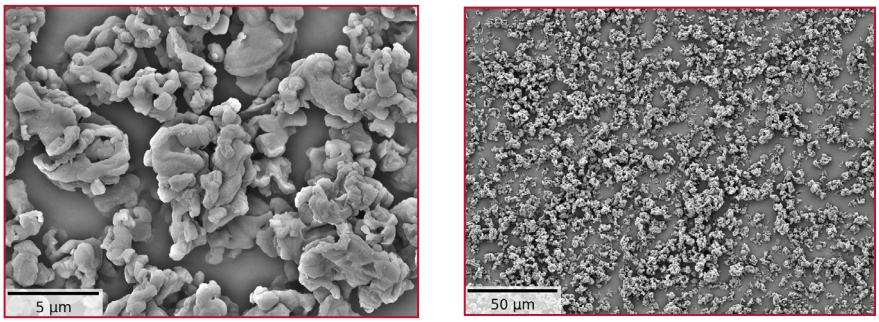


Fig. 1: Scanning Electron Microscopy Pictures

Particle Size Distribution

The particle size distribution is a crucial characteristic for Kollidon® CL-M and its various applications.

Table 1 illustrates the exemplary range for particle size distribution, determined by means of laser diffraction of the material dispersed in water (wet dispersion). The test method applied by BASF (PM02331QC) is available in RegXcellence®.

A comparison of the particles size in their dry state and after dispersion in water is shown in Fig. 3.

Table 1: Particle Size	d (0.1) [µm]	d (0.5) [µm]	d (0.9) [µm]
	< 3	2 - 8	8 - 18

Hygroscopicity

All Kollidon® CL grades exhibit hygroscopic properties, which are essential for their primary application as disintegrants. There is hardly any difference between the individual grades so that they can all be represented by a single curve (Fig. 2). The curve shows the amount of water absorbed after seven days' exposure to different conditions of relative humidity.

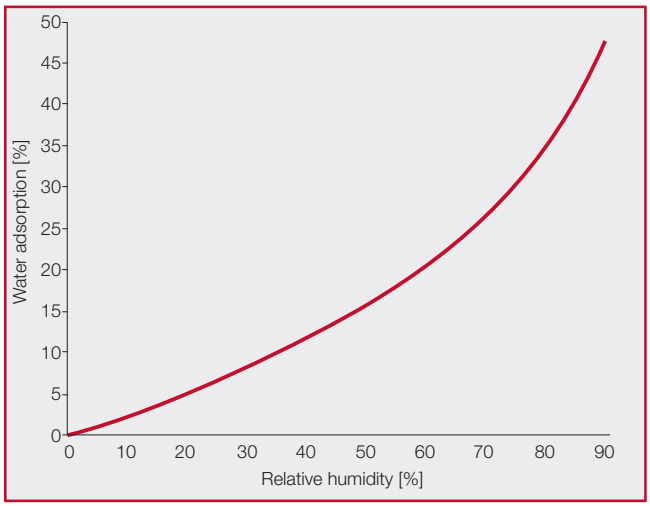


Fig. 2: Hygroscopicity of the Kollidon® CL-M

Bulk and Tap Density, Flowability

The fine particles correspond to relatively low bulk and tap density for Kollidon® CL-M, which is not free flowing.

Table 2:	Bulk Density [g/l]	Tap Density [g/l]
	0.15 - 0.27	0.25 - 0.35

3. Functionality related Characteristics

Swelling and Hydration Properties

The swelling behavior of crospovidone is crucial and can be described by its water adsorption or hydration capacity, as shown in Table 3. Kollidon® CL-M swells without forming a gel, although its absolute swelling is less pronounced compared to other crospovidone grades.

The sedimentation of Kollidon® CL-M suspended in water is very slow, as indicated by the settling volume test.

Table 3:	Hydration capacity [g water/g polymer]	Settling volume [ml]
	3.0 - 4.5	> 60

Test for Hydration Capacity and Settling Volume are conducted according to Ph.Eur. Monograph Crospovidone

The swelling of the material can be tested by comparing the particles size in their dry state and after dispersion in water. Figure 3 shows the increase of the particle size corresponding to the water uptake with one example batch of Kollidon® CL-M, measured by laser diffraction.

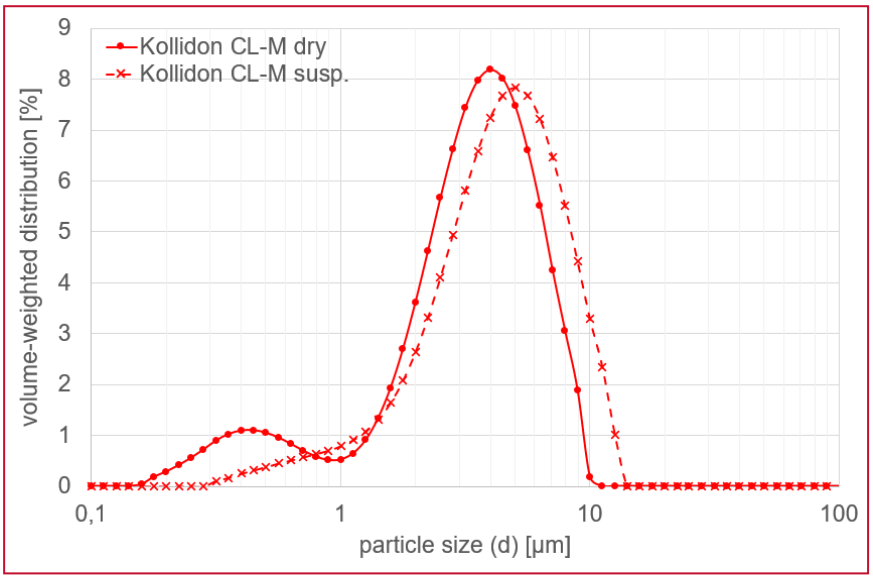


Fig. 3: Comparison of particle size distribution of Kollidon® CL-M: dry and wet, after dispersion in water (Qualitative example). The measurements have been carried out on Malvern Mastersizer 2000, 2.0 bar.

4. Example Application(s)

Kollidon® CL-M's unique properties make it a versatile excipient used in various and diverse pharmaceutical applications, as summarized in Table 4.

Table 4:	Main applications of Kollidon® CL-M
Disintegrant	Swelling without gel formation
Dry binder	Good dry binding properties combining very fine particles with good compactability
Coating	The micronized particles can be used in tablet coatings, offering an alternative to white pigments, such as titanium dioxide (TiO_2) or talcum.
Complex formation	Selective adsorption of substances like polyphenols and certain endotoxins through complex formation
Stabilizer	Acts as a stabilizer for water-sensitive compounds, such as in vitamin formulations, due to its hygroscopicity and ability to absorb water
Suspension stabilizers	Low settling tendency of dispersed hydrophilic micronized particles helps physically stabilize oral and topical suspensions

Disintegrant and Dry Binding Properties

While not a super disintegrant, Kollidon® CL-M's dual functionality as both a disintegrant and an effective dry binder makes it a unique bi-functional excipient, often termed a 'binding disintegrant'.

The example below demonstrates the bi-functionality of Kollidon® CL-M in placebo tablets (Table 5) obtained through direct compression of Ludipress® LCE, a co-processed excipient consisting of lactose monohydrate and Kollidon® 30 (Povidone).

Table 5: Tablets composition [g/100g]

	Kollidon® CL-M	No disintegrant
Kollidon® CL-M	5.0	-
Ludipress® LCE	94.5	99.5
Magnesium Stearate	0.5	0.5

Ludipress® LCE is mixed with Kollidon® CL-M in a turbula mixer, followed by the addition of the lubricant magnesium stearate

Round-shaped tablets are prepared applying compression forces of 5, 7.5, 10, 12.5, and 15 kN, respectively. For comparison, formulations with and without Kollidon® CL-M have been tested.

Tablets with Kollidon® CL-M clearly show faster disintegration than the corresponding tablets without disintegrant, especially when higher compression forces were applied (Table 6).

Table 6: Disintegration of tablets [min]

Compression force [kN]	Kollidon® CL-M	No disintegrant
5	~ 3.5	~ 3
7.5	~ 4	~ 5
10	~ 4	~ 6.5
12.5	~ 5	~ 8.5
15	~ 5	~ 9

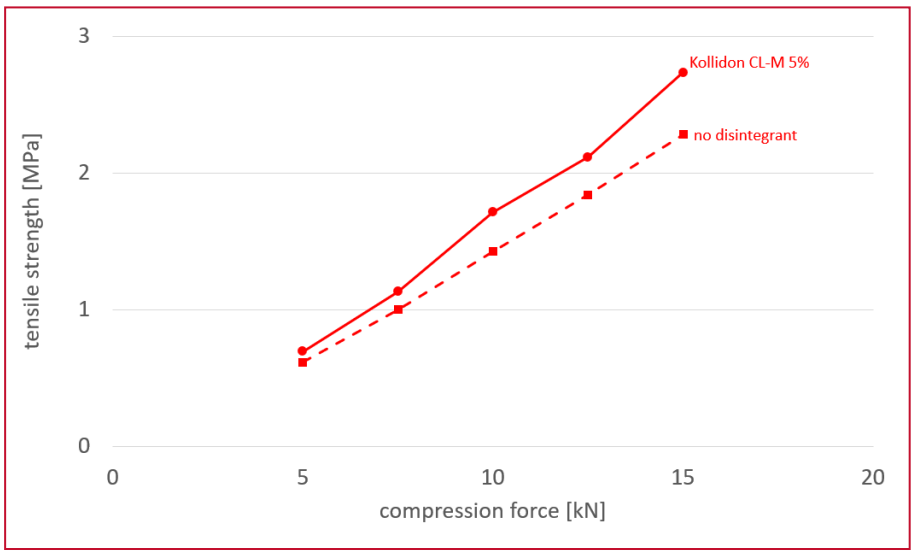


Fig. 4: Tensile strength of tablets as function of compression pressure: comparison with and without Kollidon® CL-M (Korsch XP1 single punch press; round shape tablets: 12 mm diameter 300mg weight)

The tensile strength plot demonstrates the dry binding effect that is observed when Kollidon® CL-M is used in the formulations of the tablets (Fig. 4).
Beside direct compression, Kollidon® CL-M contributes as dry-binder in roll compaction applications, too.

Coating tablet cores containing Kollidon® CL-M

When tablet cores containing a high amount of Kollidon® CL-M are sugar or film coated, it is important to carefully select suitable coating parameters and equipment due to crospovidone's tendency to absorb water and swell. This is particularly crucial if water is used as the solvent for the coating process.

In such cases, it is recommended to increase the drying efficiency during the process or use a polymer dissolved in an organic solvent as a sub-coating layer. A 10% solution of Kollidon® VA 64 in isopropanol, ethanol, or ethyl acetate provides an effective sub-coating. This solution can be sprayed onto the prewarmed tablet cores in the same coating pan before applying the aqueous coating (see Technical Information, “Kollidon® VA 64”).

Complex Formation

Like soluble Kollidon® grades and other Kollidon® CL grades, Kollidon® CL-M forms chemical complexes or associates with a wide range of drugs and other substances. The formation of these complexes is reversible and no complex formation occurs in alkaline medium. Whether crospovidone in general forms a complex with an API depends significantly on the API´s chemical structure. Systematic investigations have shown that complexes are more readily formed with aromatic compounds that contain phenyl and/or carboxyl groups. For several APIs that form complexes with Kollidon® CL-M, accelerated dissolution rates have been observed. The ability to form complexes has many uses in pharmaceuticals, such as:

- improving the dissolution and bioavailability of drugs
- adsorbing and removing polyphenols and tannins from tinctures and herbal extracts
- improving the taste of azithromycin, paracetamol and vitamins

Stabilization of Vitamins

The stabilizing effect of Kollidon® CL-M is demonstrated using a multivitamin liquid suspension as example. As shown in Table 7, the accelerated storage test of the vitamins (vitamin B1, calcium pantothenate and vitamin C) in the formulation prepared with Kollidon® CL-M presented better results than the one without it, highlighting the stabilizing property of this crospovidone grade.

Table 7: Vitamin degradation in multivitamin instant drink with and without Kollidon® CL-M (30°C / 79% relative humidity)

Storage Time [months]	1	2	3	5
Vitamin B1:				
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%

Stabilization of suspensions

Kollidon® CL-M hydrophilic particles can be used in concentrations of 5 – 12% to physically stabilize oral and topical suspensions.

The stabilizing effect is achieved as the swollen particles increase the volume of the sediment, leading to a reduced sedimentation rate and an improved re-dispersion ability of the sediment upon shaking (anticaking effect). Importantly, Kollidon® CL-M does thereby not increase the viscosity of the preparation.

As suspension stabilizers, Kollidon® CL-M can be applied into readily formulated suspensions as well as into powder dosage forms for suspension preparation.

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), sugars, or one of the soluble grades of Kollidon® such as Kollidon® 90 Evo. Kollidon® CL-M can also stabilize suspensions in lipophilic media such as liquid paraffin.

Table 8 presents a standard antibiotic powder formulation for suspension preparation, including Kollidon® CL-M. Citric acid is included to ensure a pH value of 4.9, which is necessary for the stability of the active ingredients, ampicillin and amoxicillin trihydrate.

The sedimentation rate is very slow, and the suspension remains readily re-dispersible for several weeks.

Table 8: Example of a standard antibiotic powder for suspension formulation	Quantity [g]	Percentage [g/100g]
Ampicillin or amoxicillin trihydrate	5.0	7.6
Sodium citrate	5.0	7.6
Citric acid	2.1	3.2
Sodium gluconate	5.0	7.6
Sorbitol	40.0	61.1
Kollidon® CL-M	6.0	9.2
Orange flavouring	1.5	2.3
Lime flavouring	0.5	0.8
Saccharin sodium	0.4	0.6

Reconstitution procedure: dissolve 66 g of the final powder for suspension with purified water to obtain a final volume of 100 mL. Shake well. Final concentration: 250 mg of API per 5 mL of suspension.

White pigment for coating

Kollidon® CL-M can be used for tablets coating, substituting white pigments such as titanium dioxide (TiO_2) and/or talcum.

The major benefits of Kollidon® CL-M for such applications include its high opacity, low sedimentation rate, and low tendency to form aggregates. These properties make the polymer suitable for this application, offering a simple preparation procedure and high process reliability.

Additionally, Kollidon® CL-M can be combined with all pigments.

Table 9 describes an application example where Kollidon® CL-M is used as white pigment in coating formulation based on the immediate release coating polymer Kollicoat® IR. For the formulation, Kollidon® CL-M is poured in water while stirring (no high-shear mixer required). Kollicoat® IR is then slowly added for avoiding lump formation, and the mixture stirred for 30 minutes.

Table 9: Example formulation for white coating	Content [g/100g]
Kollidon® CL-M	10
Kollicoat® IR	10
Water	80

5. Handling & safety instructions

The primary packaging of Kollidon® CL-M is a PE/EVOH liner with excellent oxygen barrier properties and is heat-sealed for proper closure. The secondary packaging is a HDPE plastic drum.

Please refer to the individual material safety data sheet (MSDS) for instructions on safe and proper handling and disposal. Material safety data sheets are sent with every consignment.

6. Handling & safety instructions

The product is typically stable for 36 months after date of production provided storage under recommended conditions. The actual retest period and storage conditions can be found in RegXcellence®.

The actual version of the safety data sheet is accessible via MyProductWorld and sent with every consignment.

7. Articles and Packaging

PRD-No.*	Product name	Article numbers	Packaging Type and Size
30444355	Kollidon® CL-M	51928647	Plastic drum 30kg
		50348144	Plastic pail 0.25kg

* BASF's commercial product number.

8. Documents, Quality & Regulatory Information

Visit our BASF website to learn about the benefits of Kollidon® CL-M:

Access product documentation anytime via the BASF Virtual Pharma assistants:
Virtual Pharma Assistants

Meet your Virtual Pharma Assistants! MyProductWorld, RegXcellence® and ZoomLab™

www.virtualpharmaassistants.com

MyProductWorld: article numbers, sample order, safety data sheet, sustainability information

RegXcellence® specification, compliance documents, regulatory product summary

ZoomLab: formulation assistance to predict starting formulations and expedite drug development.

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