Technical Information

Kollidon® VA 64
Kollidon® VA 64 Fine

Copovidone Ph. Eur., USP, Copolyvidone JPE.

Kollidon® VA 64 and Kollidon® VA 64 Fine are vinylpyrrolidone-vinyl acetate copolymers. They are used in the pharmaceutical industry as dry binder in tablets, as matrix formers for amorphous solid dispersions, as retarding and as film-forming agents.

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1. Introduction

Kollidon® VA 64 and Kollidon® VA 64 Fine are vinylpyrrolidone-vinyl acetate copolymers which are soluble both in water and in alcohols. They are well-known by their monographic name "Copovidone" or "Copolyvidone". In the pharmaceutical industry they are widely used as dry and wet binder in tablets, as film forming agent or in retard formulations. A major application of Kollidon® VA 64 is as matrix in amorphous solid dispersions.

For further details that are beyond the scope of this leaflet, please consult the book, “Kollidon® – Polyvinylpyrrolidone excipients for the Pharmaceutical Industry” (03_030743e).

2. Technical properties

Description

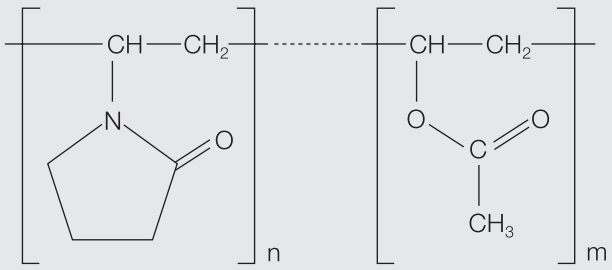
Kollidon® VA 64 and Kollidon® VA 64 Fine are spray dried polymer powders of a copolymer derived from the monomers N-vinylpyrrolidone (NVP) and vinyl acetate (VAc) with a weight ratio of approx. 6:4.

The powders are white or slightly yellowish, have a faint characteristic odor and practically no taste.

CAS-number

25086-89-9

Structural formula



$(C_6H_9NO)_n \times (C_4H_6O_2)_m$
$Mr = (111.1)_n \times (86.1)_m$
$n \approx 1.2\ m$

Infrared spectrum

The infrared spectrum shown in Fig. 1 was obtained with a tablet of Kollidon® VA 64 in potassium bromide. Arrows indicate where the spectrum differs from that of povidone.

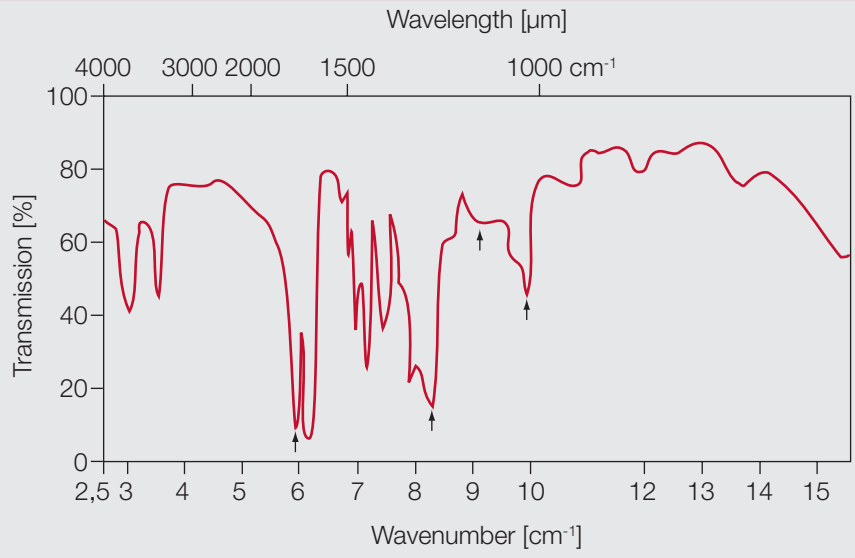


Fig. 1: Infrared spectrum of Kollidon® VA 64.

Molecular weight

The average molecular weight is usually expressed as a K value. The exact weight-average molecular weight, Mw of the product is best determined by measuring the light scatter of a solution. Values in the range of 45,000 – 70,000 have been determined for Kollidon® VA 64 and Kollidon® VA 64 Fine.

Solubility

Kollidon® VA 64 and Kollidon® VA 64 Fine readily dissolve in all hydrophilic solvents.

Solutions of more than 10% concentration can be prepared in:
water, ethanol, isopropanol, methylene chloride, glycerol and propylene glycol

It is less soluble in:
ether, cyclic, aliphatic and alicyclic hydrocarbons

Viscosity

The values shown in Fig. 2 were determined at 25 °C in a capillary viscometer. They represent typical values.

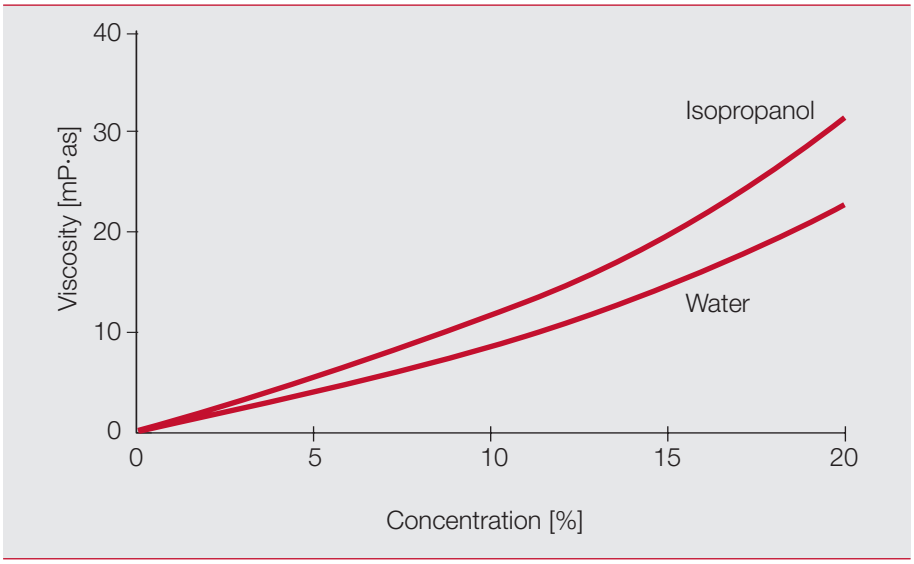


Fig. 2: Viscosity of Kollidon® VA 64 in water and isopropanol.

Bulk density

The bulk density of Kollidon® VA 64 Fine usually lies in the range of 0.08 – 0.15 g/ml.

The bulk density of Kollidon® VA 64 is above that one of Kollidon® VA 64 Fine and is in the range of about 0.2 – 0.4 g/ml.

Particle size distribution

Typical values for the particle size of Kollidon® VA 64 and Kollidon® VA 64 Fine are as follows:

	Kollidon® VA 64	Kollidon® VA 64 Fine
>250 µm [%]	max. 7%	max. 2%
<50 µm [%]	max. 35%	min. 35%

Hygroscopicity

Kollidon® VA 64 and Kollidon® VA 64 Fine absorb only about one third of the quantity of water absorbed by povidone, e.g. Kollidon® 30 (Fig. 3).

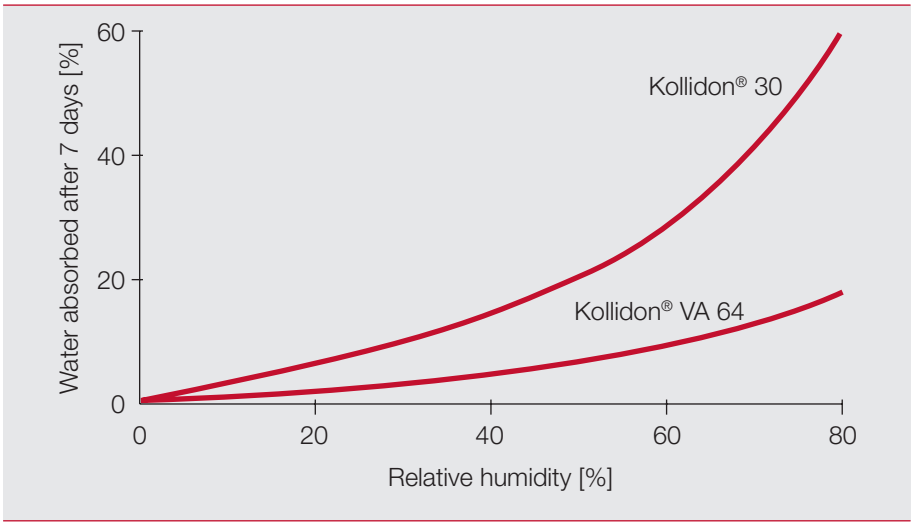


Fig. 3: Hygroscopicity of Kollidon® VA 64 and Kollidon® 30.

3. Example application

General

Copovidone has been used for decades in the pharmaceutical industry. Up to about 1975 it was marketed under the name of Luviskol® VA 64, which today is used only for the technical/cosmetic grade of this copolymer. This is why older publications often refer to the use of Luviskol® VA 64 in pharmaceuticals.

Binder for tablets and granules

Kollidon® VA 64 and Kollidon® VA 64 Fine are excellent binders for tablets and granules. Between 2% and 8%, as a proportion of the final weight of the preparation, is usually used.

An important property of Kollidon® VA 64 and Kollidon® VA 64 Fine in this application is the plasticity, which distinguishes the products from povidone (e.g. Kollidon® 30).

This property often gives granules and mixtures that are less susceptible to capping during tabletting, and tablets that are less brittle.

Dry Binder for direct compression

Kollidon® VA 64 and Kollidon® VA 64 Fine have been found to be excellent dry binders for direct compression. Especially the Kollidon® VA 64 Fine gives much better results than any of the Povidone grades or other dry-binders of the group of cellulose derivatives.

The hardness, friability, porosity and disintegration time of lactose and starch placebo tablets produced with Kollidon® VA 64 are directly related to the compression force used (see Table 1).

Table 1: Tablet properties related to the compression force

Compression force [kp]	Hardness [N]	Friability [%]	Porosity [%]	Disintegration time [s]
500	23.5	3.07	13.03	17
1000	55.8	0.98	6.87	58
1500	61.7	0.59	6.41	77
2000	65.7	0.49	5.33	90
2500	67.6	0.35	5.07	102

Kollidon® VA 64 and Kollidon® VA 64 Fine can be added to materials such as sorbitol, mannitol, starch, or direct compression aids, e.g. micro crystalline cellulose, whose own binding strength is inadequate, to give tablets with very good properties.

Table 2, for example, is suitable for direct compression. The literature contains a large number of vitamin formulations with Kollidon® VA 64 (see "Generic Drug Formulations" latest edition).

Table 2: Ascorbic acid chewable tablets 100 mg

Ascorbic acid powder	42.4%
Sucrose ground	13.0%
Sucrose crystalline	8.0%
Microcrystalline cellulose	28.3%
Kollidon® VA 64	2.4%
Polyethylene glycol 6000 powder	2.0%
Orange aroma + strawberry aroma (2 + 1)	1.2%
Cyclamate sodium	2.4%
Saccharin sodium	0.1%
Aerosil 200	0.2%

Equipment

Rotary press:	Korsch PH 100/6
Punch diameter:	8 mm, biplanar
Speed:	30 rpm

Tablet Properties:

Weight	250 mg
Hardness	157 N
Friability	<0.1%

The following examples show the properties of Kollidon® VA 64 Fine in formuations for direct compression.

Table 3: Acetyl salycilic acid tablets 500 mg formulated with Kollidon® VA 64 Fine

Acetylsalicylic acid	500.0 mg
Avicel PH 102	200.0 mg
Kollidon® VA 64 Fine	60.0 mg
Kollidon® CL	25.0 mg
Magnesium stearate	3.0 mg
Total	**788.0 mg**

The individual components were sieved through a 0.8 mm sieve. After a blending time of 10 minutes in a Turbula Blender the powder blend is compressed with compression forces of 6, 10, and 18 kN respectively.

Equipment

Rotary press: Korsch PH 100/6
Punch diameter: 12 mm beveled edge
Speed: 30 rpm

Tablet properties

Compression Force [kN]	Tablet weight [mg]	Hardness [N]	Disintegration [min:sec]	Friability [%]
6.8	772.3	81	04:13	0.4
10.7	777.5	140	08:25	0.2
16.5	768.0	187	15:03	<0.1

Table 4: Indomethacin Tablets 50 mg formulated with Kollidon® VA 64 Fine

Indomethacin	50.0 mg
Kollidon® VA 64 Fine	20.0 mg
Di-tab	212.0 mg
Kollidon® CL	15.0 mg
Magnesium stearate	3.0 mg
Total	**300.0 mg**

The individual components were sieved through 0.8 mm. After a blending time of 10 minutes in a Turbula Blender the powder blend is compressed with compression forces of 6, 10, and 18 kN, respectively.

Equipment

Rotary press: Korsch PH 100/6
Punch diameter: 8 mm, beveled edge
Speed: 30 rpm

Tablet properties

Compression Force [kN]	Tablet weight [mg]	Hardness [N]	Disintegration [min:sec]	Friability [%]
5.6	301.9	62	00:22	0.16
9.7	304.5	101	00:36	<0.1
15.9	304.0	158	01:12	<0.1

Table 5: Atenolol Tablets 50 mg formulated with Kollidon® VA 64 Fine

Atenolol	50.0 mg
Ludipress®	135.7 mg
Kollidon® VA 64 Fine	15.0 mg
Kollidon® CL	25.0 mg
Aerosil 200	1.3 mg
Magnesium stearate	3.0 mg
Total	**230.0 mg**

The individual components were sieved through 0.8 mm. After a blending time of 10 minutes in a Turbula Blender the powder blend is compressed with compression forces of 6, 10, and 18 kN, respectively.

Equipment

Rotary press: Korsch PH 100/6
Punch diameter: 8 mm, beveled edge
Speed: 30 rpm

Tablet properties

Compression Force [kN]	Tablet weight [mg]	Hardness [N]	Disintegration [min:sec]	Friability [%]
5.8	230.8	94	03:54	< 0.1
9.6	221.4	132	04:14	< 0.1
15.8	218.6	147	05:03	< 0.1

Wet granulation

Kollidon® VA 64 and Kollidon® VA 64 Fine can also be used as a binder in wet granulation for the production of tablets and granules, since it is readily soluble in all the usual solvents. It can then be added either as a solution during granulation, or dry to the other ingredients, in which case the solvent is added alone during granulation. Trials so far conducted with both methods, using equal quantities of liquid, produced tablets of much the same hardness. A combination of the two methods, i.e. mixing some of the Kollidon® VA 64 with the active ingredient, and dissolving the rest in the solvent, sometimes gives the best results. This is particularly recommended if the active ingredient does not readily absorb the solvent. Since it is less hygroscopic than povidone (e.g. Kollidon® 25 or 30), Kollidon® VA 64 gives granules that have less tendency to stick to the punches of the tabletting machine, when operating under humid conditions. The binding power of Kollidon® VA 64 is comparable to that of Kollidon® 25 and Kollidon® 30.

The formulations in Table 3 are typical of those used for producing tablets by wet granulation (see “Generic Drug Formulations”, latest edition).

Table 6: 500 mg ampicillin tablets and 400 mg cimetidine tablets formulated with Kollidon® VA 64

I	Ampicillin trihydrate	500 g	–
	Cimetidine	–	400 g
	Corn starch	242 g	170 g
II	Kollidon® VA 64	25 g	20 g
	Isopropanol or water	q.s.	q.s.
III	Kollidon® CL	15 g	–
	Magnesium stearate	10 g	3 g
	Aerosil 200	8 g	–

Mixture I is granulated with solution II, dried and sieved. The granules are then mixed with III and pressed into tablets at low to medium pressure. Tablets obtained in the laboratory had the following properties:

	Weight	798 mg	601 mg
	Diameter	16 mm	12 mm
	Hardness	170 N	91 N
	Disintegration in gastric juice	5 min	91 min
	Friability	0.35%	0.5%
	Dissolution (USP)		
	10 min:	not tested	62%
	20 min:		91%
	30 min:		100%

Apart from its use in tablets, Kollidon® VA 64 can also be used to produce very stable granules, e.g. for instant multivitamin drinks.

Roller compaction

Kollidon® VA 64 Fine was specifically suitable for the application in roller-compaction and is the material of choice in terms of particle size distribution and particle shape for this application. Due to the particle size it is able to cover a bit surface area and to form numerous bridges in the tablet structure that lead to hard tablets with a reduced friability.

The formulations in tables 4 and 5 are typical examples for Kollidon® VA 64 Formulation using this technique.

Table 7: Allopurinol Tablets 300 mg formulated with Kollidon® VA 64 Fine

1.	Allopurinol	100.0 mg
2.	Ludipress®	50.0 mg
3.	Kollidon® VA 64 Fine	10.0 mg
4.	Kollidon® CL	6.0 mg
5.	Magnesium stearate	1.0 mg

The compounds were compacted using a Gerteis compactor under the following conditions

Roller compactor:	Gerteis Type Mini-Pactor M1114
Roll width:	25 mm
Compression force:	2 kN/cm
Gap width:	3 mm
Tamping/feeding ratio:	120%
Roll speed:	2 rpm
Mesh sizes	1.25 mm

After compaction the material was blended for 10 minutes in a Turbula blender with the remaining Ludipress® and the magnesium stearate and tableted as follows.

Allopurinol compacted formulation	167.0 mg
Ludipress®	133.0 mg
Magnesium stearate	1.0 mg
Total weight	**301.0 mg**

Equipment

Tablet press:	Korsch PH 100/6
Compression force:	18kN
Punch diameter:	8 mm, beveled edge
Compression speed:	30 rpm

Tablet properties:

Compression force [kN]	Tablet weight [mg]	Hardness [N]	Disintegration time [min:sec]	Friability [%]
16.4	280.8	246	09:29	< 0.1

Table 8: Paracetamol Tablets 300 mg formulated with Kollidon® VA 64 Fine

1.	Paracetamol Powder	500.0 mg
2.	Avicel PH 102	131.0 mg
3.	Kollidon® VA 64 Fine	45.0 mg
4.	Kollidon® CL	21.0 mg
5.	Aerosil 200	5.0 mg
6.	Magnesium stearate	3.0 mg

The compounds 1 to 6 were compacted using a Gerteis compactor under the following conditions.

Roller compactor:	Gerteis Type Mini-Pactor M1114
Roll width:	25 mm
Compression force:	2 kN/cm
Gap width:	3 mm
Tamping/feeding ratio:	120%
Roll speed:	2 rpm
Mesh size:	1.25 mm

After compaction the material was blended for 10 minutes in a Turbula blender with the remaining Kollidon® CL and the magnesium stearate and tableted as follows.

Paracetamol compacted formulation	695.0 mg
Kollidon® CL	7.0 mg
Magnesium stearate	3.0 mg
Total weight	**705.0 mg**

Equipment

Tablet press:	Korsch PH 100/6
Compression force:	18 kN
Punch diameter:	12 mm, beveled edge
Compression speed:	30 rpm

Tablet properties:

Compression force [kN]	Tablet weight [mg]	Hardness [N]	Disintegration [min:sec]	Friability [%]
17.6	683.8	66	00:18	

Film-coating

Kollidon® VA 64 forms films that are soluble at all pH values. They are less hygroscopic and more elastic than those formed by povidone (e.g. Kollidon® 30). Nevertheless, Kollidon® VA 64 usually still absorbs too much water, so that it can seldom be used as the sole film-forming agent in a formulation. It is therefore recommended to combine it with less hygroscopic substances such as cellulose derivatives, shellac or polyethylene glycol. Plasticizers are normally not required. The formulations in Tables 4 and 5 are typical formulations for tablet coatings. They were tested on 9 mm diameter, 3.4 mm thick, 200 mg placebo tablet cores in the laboratory. Kollidon® VA 64 significantly improves their brittleness and solubility when it is combined with cellulose derivatives. When it is used in film coatings based on shellac, the properties of the film are more consistent.

Table 9: Sugar film coating (Accela Cota 24")

Suspension:	
Sucrose	200 g
Kollidon® VA 64	50 g
Macrogol 4000	40 g
Sicovit® color lake	15 g
Sicovit titanium dioxide	30 g
Talc	50 g
Water	ad 1,200 g

Continuously spray 1,200 g of this suspension onto 5 kg of tablet cores.

The spray conditions are as follows:

Inlet air temperature	45 °C
Outlet air temperature	36 °C
Nozzle diameter	0.8 mm
Spraying pressure	2.0 bar
Coating pan speed	15 rpm
Spraying time	50 min
Quantity of film former applied	4 mg/cm^2

Table 10: Film coating with Hypromellose (Accela Cota 24“)

I	Kollidon® VA 64	53 g
	PEG 6000	12 g
	HPMC 6 mPa·s	79 g
	Water	732 g
II	Sicovit® Titanium Dioxide	36 g
	Sicovit® Iron Oxide Red 30	18 g
	Talc	54 g
	Water	216 g
	Total	**1200 g**

Mix Solution I with Suspension II, pass through a disc mill.
The spray dispersion is calculated to be suitable for 5 kg of cores. The quantity of film former applied is about 3 mg/cm^2. The cores size was 9 mm, biconvex.

The coating process is performed using the following conditions:

Pan speed	12	rpm
Spraying rate [1 nozzle]	50	g/min
Spraying time	34	min
Quantity of applied film former	3.1	mg/cm^2
Final drying at 60 °C	5	min

Subcoating

If it is intended to coat tablet cores with aqueous solutions or suspensions, it is recommended to provide them with a barrier if they contain a watersensitive active ingredient or a highly effective disintegrant (e.g. Kollidon® CL) that is activated by water. This also applies if the cores are too soft or if their adhesive properties are inadequate for aqueous coatings. The cores are warmed to about 35 °C and sprayed with a 10% solution of Kollidon® VA 64 dissolved in an organic solvent, e.g. isopropanol, ethanol, ethyl acetate or acetone. As soon as a barrier film of adequate thickness has been built up, the aqueous coating can be applied. It has been found that 0.4 mg Kollidon® VA 64/cm^2 is adequate.

Sugar-coating

Kollidon® VA 64 is used in sugar-coating to improve the adhesion of the coating to the surface of the tablet core and to increase the capacity of the coating solution for pigments and improve their dispersibility. However, Kollidon® VA 64 helps not only in the application of sugar coatings but also in the automation of the sugar-coating process.

Sprays

Because of its good film-forming properties, Kollidon® VA 64 can also be used in topical sprays. The formulation in Table 6 provides a typical example of a spray bandage.

Table 11: Polidocanol wound spray

Polidocanol	5 g
Lutrol® E 400	20 g
Kollidon® VA 64	50 g
Ethocel 20 (Dow)	50 g
Ethyl acetate	675 g
Isopropanol	200 g

Fill this solution into spray cans together with the necessary quantity of propellant.

Amorphous Solid Dispersions

Poorly water-soluble drugs are a constant and growing challenge within the pharmaceutical industry. One proven and viable technology to overcome this challenge is the production of amorphous solid dispersions or ASDs. ASDs are prepared by dissolving the poorly soluble drug within a polymeric matrix, which then releases the drug upon contact with aqueous media, and results in an overall increase of drug solubility and dissolution rate. ASDs may be prepared using well proven methods such as hot melt extrusion, or for temperature sensitive drugs, spray drying.

For both technologies, Kollidon® VA 64 has proven its suitability to generate thermodynamically and kinetically stable forms of solid API dispersions in a polymer matrix.

Amorphous Solid Dispersions by melt extrusion

The formulation of stable amorphous solid dispersion by melt extrusion based on Kollidon® VA 64 has been established for more than two decades. This polymer has proved its suitability for this application because of its low glass transition temperature (101 °C), high temperature resistance (up to 220 °C) and optimum thermorheological properties.

A number of product parameters have been optimized to minimize degradation of the API during melt extrusion and to ease powder handling.

First, the LOD/water content of Kollidon® VA 64 was adjusted to a level below the compendial upper limit to reduce the concentration of API degradation products during processing. Secondly, the particle size and morphology were optimized to reduce dust formation during powder dispensing, mixing operations and extruder feeding.

The resulting intermediate extrusion products can be processed downstream by either filling them directly into hard gelatin capsules or by subsequently milling the extrudates and processing tablet cores or coated tablets.

Amorphous Solid Dispersions by spray drying

For the manufacturing of solid dispersions using spray drying, it is essential that both API and matrix polymer are soluble in a suitable volatile organic solvent. Kollidon® VA 64 is soluble in a number of organic solvents (see section 2.5) at levels greatly exceeding 10 % [w/w] while simultaneously retaining a low viscosity, which is crucial for successful spray drying. An example of spray dried Kollidon® VA 64 from methanol as a model solvent is shown in Figure 4.

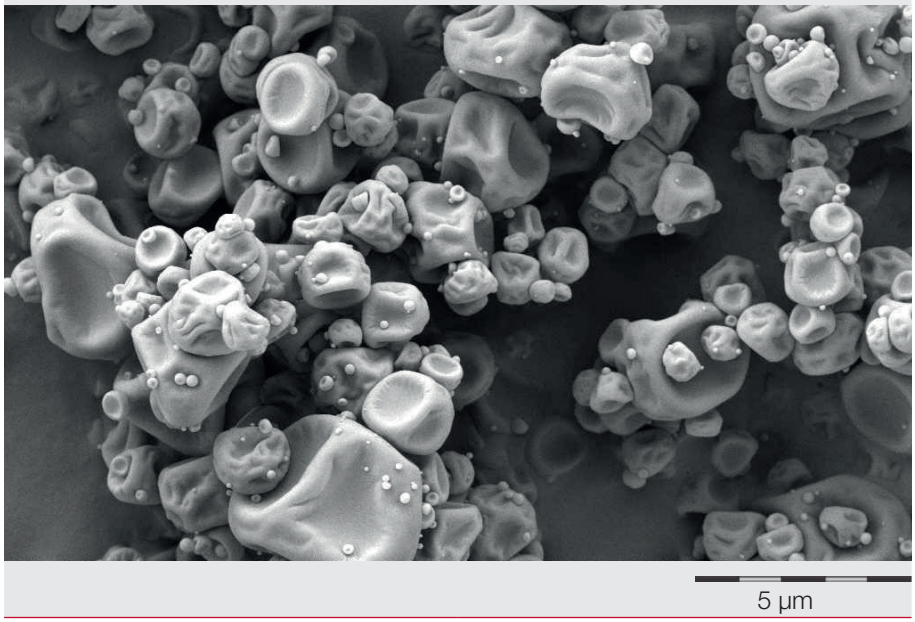


Figure 4: Spray dried Kollidon® VA 64 from methanol from a 10% solution.

The high solubility, when combined with the low viscosity of the achieved polymer/API-solutions, as well as the strong thermodynamic and kinetic interactions with poorly soluble drugs, make this polymer an outstanding matrix polymer for this application.

Inhibition of the crystallization of APIs in liquid soft gel formulations

Another aspect to the challenge of poorly water-soluble drugs is the ability to retain them in solution once dissolved, thereby maximizing absorption during the transit time of the gastrointestinal tract. Compounds that expand this absorption window are often called crystallization inhibitors as they retain drugs in a supersaturated state for a prolonged time through what is known as the “parachute effect”. This is in contrast with the “spring effect”, where drugs immediately recrystallize once in contact with gastrointestinal media. Kollidon® VA 64 exhibits these effects when utilized with poorly water-soluble compounds. In this case, the oral dose primarily includes a hard or softgel capsule where Kollidon® VA 64 is dissolved in hydrophilic fill formulations such as low molecular weight polyethylene glycols (PEGs), such as Kollisolv® PEG 400.

With Kollidon® VA 64, it is possible to prevent recrystallisation and to achieve a “Parachute Effect” in both low pH stomach conditions and high pH intestinal conditions. Under stomach conditions, this is shown in Figure 5 for the model poorly soluble drug Danazol with Kollidon® VA 64 used at 5% w/w in a PEG 400 liquid fill. The effect is compared with known crystallization inhibitor Kollidon® 12 PF and solubilizer Kolliphor RH 40, which exhibits a spring effect.

Drug dissolution was determined using a Pion Inform system with 50 ml buffer system of pH 2.0 and pH 6,8, respectively, and 0.5 ml of liquid formulation representing the filling volume of a soft gel capsule.

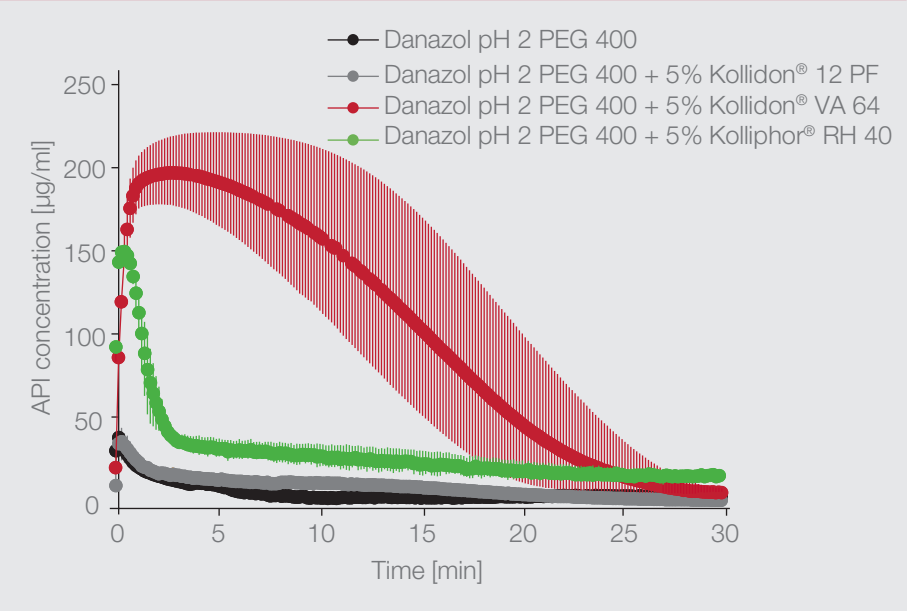


Figure 5: Parachute effect of Kollidon® VA 64 under stomach conditions (pH = 2).

Under gastric, acidic conditions, the effect is self-evident, showing Kollidon® VA 64 with a significantly improved absorption window. Under intestinal conditions, the same effect is achieved, as shown in Figure 6.

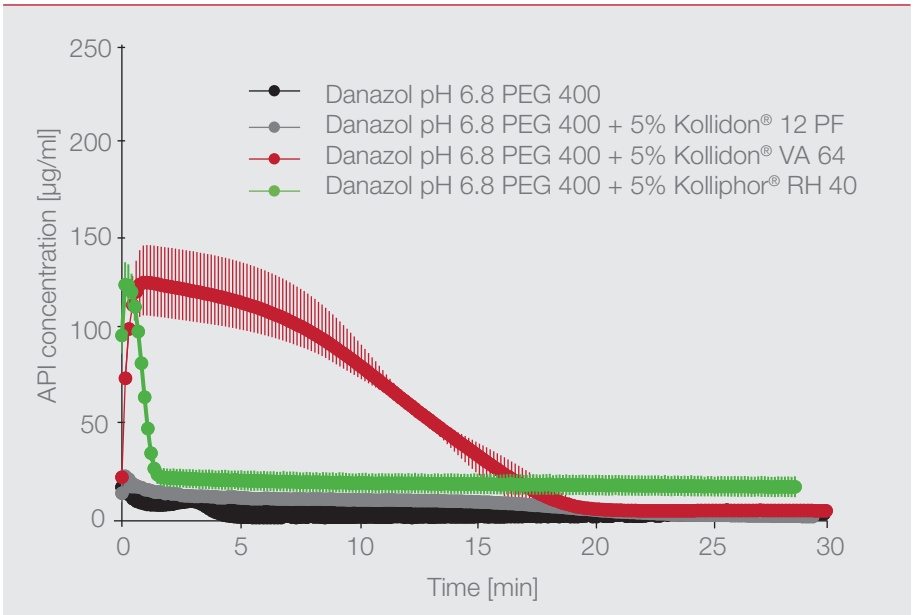


Figure 6: Parachute effect at pH 6.8 under intestinal conditions.

Under intestinal conditions, a classic spring model for Kolliphor® RH 40 is observed, while very little effect of Kollidon® 12 PF is noted. However, Kollidon® VA 64 shows a significantly improved absorption window.

4. Handling & Safety

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. In addition they are available on BASF RegXcellence®* or from your local BASF sales representative.

5. Product specification

The current version of the product specification is available on BASF RegXcellence® * or from your local BASF sales representative.

6. Regulatory & Quality

Please refer to the individual document quality & regulatory product information (QRPI) which is available on BASF WorldAccount, RegXcellence® *, and from your local sales representative **The QRPI covers all relevant information including retest dates, and storage conditions.**

7. Toxicology

The safety of the polymer in Kollidon® grades as pharmaceutical excipient in film coating of solid oral dosage forms is supported by a comprehensive non-clinical study. A summary of the study is available on BASF WorldAccount, RegXcellence® * or from your local sales representative. A detailed report can be shared as part of a non-disclosure agreement.

* https://worldaccount.basf.com, RegXcellence (https://mypharma.basf.com/)

8. PRD and Article numbers

PRD-No.*	Product name	Article numbers	Packaging
30499395	Kollidon® VA 64	50131775	35 kg PE drum with PE liner
30499398	Kollidon® VA 64	50131776	35 kg PE drum with PE liner
30239644	Kollidon® VA 64 Fine	57071976	15 kg Cardboard box with PE liner aluminium laminated

* BASF's commercial product number.

9. Publications

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

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