Technical Information

June 2008
Supersedes issue dated October 2007

EMP 050602e-05/Page 1 of 16

Kollidon® VA 64
Kollidon VA 64 Fine

Copovidone Ph.Eur., USP, Copolyvidone JPE

® = Registered trademark of BASF SE

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 granulating agents, as retarding and as a film-forming agents.

BASF
The Chemical Company

Pharma Ingredients & Services

Contents

		Page
1.	**Introduction**	4
1.1	General	4
1.2	Synonyms	4
2.	**Specification, properties**	5
2.1	Description	5
2.2	Specification	5
2.3	Regulatory status	5
2.4	Infrared spectrum	5
2.5	Molecular weight	5
2.6	Solubility	6
2.7	Viscosity	6
2.8	Bulk density	6
2.9	Particle size distribution	6
2.10	Hygroscopicity	6
3.	**Applications**	7
3.1	General	7
3.2	Binder for tablets and granules	7
3.3	Application in roller-compaction	12
3.4	Film-coating	14
3.5	Sub-coating	15
3.6	Sugar-coating	15
3.7	Sprays	15
3.8	Controlled-release preparations	16
4.	**Toxicological studies**	16
5.	**PBG-Nos.**	16
6.	**PRD-Nos.**	16
7.	**Article-Nos. & contents**	16
8.	**Stability and storage**	16
9.	**Safety Data Sheet**	16
10.	**Note**	16

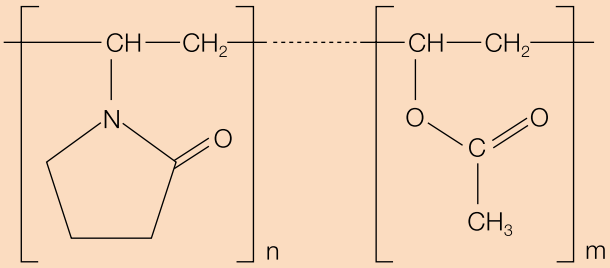
1. Introduction

1.1 General

Kollidon VA 64 and Kollidon VA 64 Fine are vinylpyrrolidone-vinyl acetate copolymers which are soluble both in water and in alcohols. They are used in the pharmaceutical industry as binder in tablets, as granulating agents, as retarding and as film-former.

For further details that are beyond the scope of this leaflet, please consult the book, “Kollidon – Polyvinylpyrrolidone excipients for the Pharmaceutical Industry” (MEP070802e-00).

1.2 Synonyms



$(C_6H_9NO)_n \times (C_4H_6O_2)_m$

$M_r = (111.1)_n \times (86.1)_m$

$n \approx 1.2\ m$

2. Properties and specification

2.1 Description

Kollidon VA 64 is a white or slightly yellowish, free-flowing powder with a faint characteristic odour and practically no taste.

2.2 Specification

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

The analytical methods can be found in the EP monograph “Copovidone”. The methods for the determination of the monomers by HPLC are available on request.

The microbial status is determined according to methods 2.6.12 and 2.6.13 in EP., latest edition. The limits for Kollidon VA 64 and Kollidon VA 64 Fine are those given in Table 1.

Table 1: Microbial purity requirements (EP. latest edition, method 5.1.4, categories 2 + 3 A).

- Max. 10^2 aerobic bacteria + fungi/g
- No Escherichia coli/g
- Max. 10^1 other Enterobacteriaceae/g
- No Pseudomonas aeruginosa/g
- No Staphylococcus aureus/g

2.3 Regulatory status

Kollidon VA 64 and Kollidon VA 64 Fine meet current Ph.Eur., USP monograph “Copovidone“ and the JPE monograph “Copolyvidone”.

A US-DMF with the number 6745 has been submitted in the United States.

2.4 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.

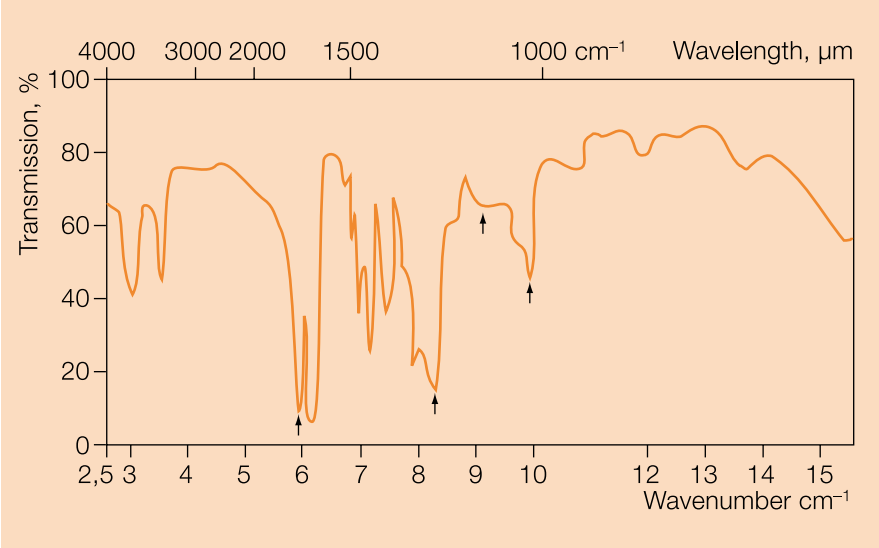


Fig. 1 Infrared spectrum of Kollidon VA 64

2.5 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.

2.6 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

2.7 Viscosity

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

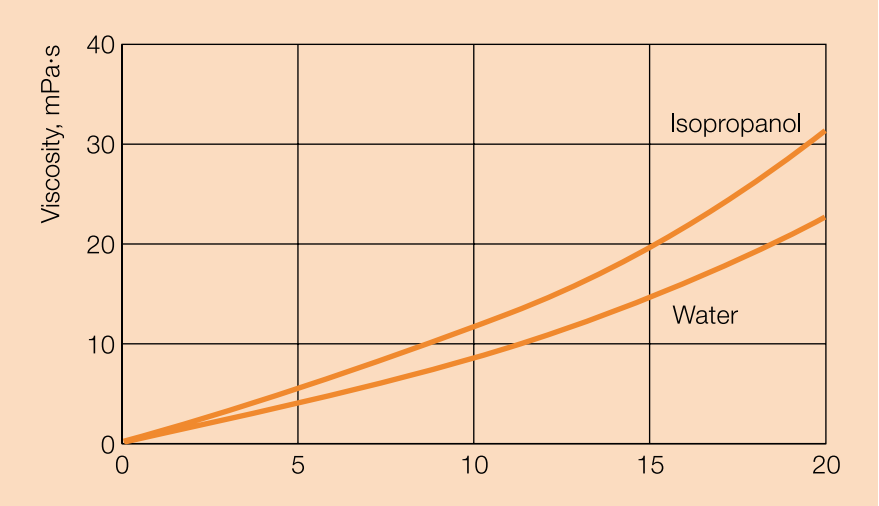


Fig. 2 Viscosity of Kollidon VA 64 in water and isopropanol

2.8 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 - 0.3 g/ml.

2.9 Particle size distribution

Typical values for the particle size of Kollidon VA64 and Kollidon VA64 Fine are as follows:

	Kollidon VA 64	Kollidon VA 64 Fine
> 250 µm [%]	max. 2	0
< 50 µm [%]	~15 ± 8	> 90

2.10 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).

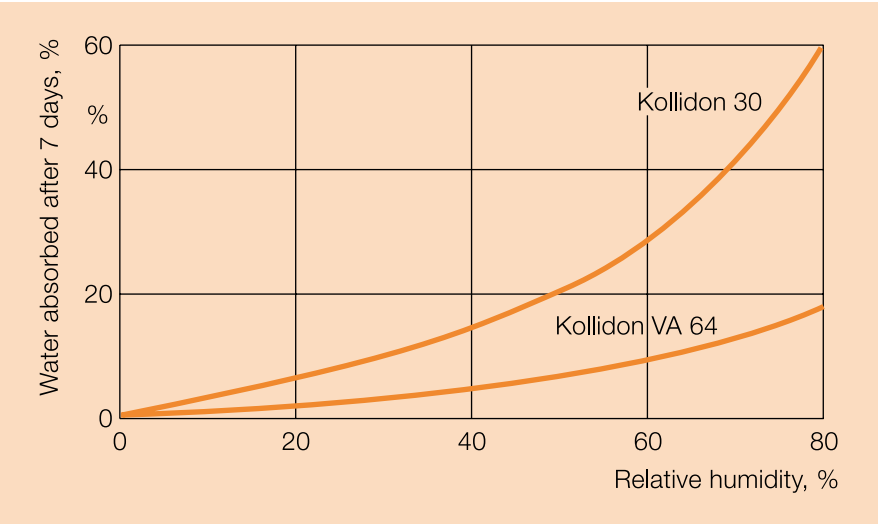


Fig. 3 Hygroscopicity of Kollidon VA 64 and Kollidon 30

3. Applications

3.1 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.

3.2 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.

3.2.1 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 2)

Table 2 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 3, 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 3: 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 VA64 Fine in formuations for direct compression

Table 4: 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 5 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 0.8mm. 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 6 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

3.2.2 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 4 are typical of those used for producing tablets by wet granulation (see “Generic Drug Formulations”, latest edition).

Table 7 500 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.

3.3 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 5 and 6 are typical examples for Kollidon VA 64 formulation using this technique.

Table 8 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 9 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	

3.4 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 5 and 6 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 10: Sugar film coating (Accela Cota 24")

Suspension:	
Sucrose	200 g
Kollidon VA 64	50 g
Macrogol 4000	40 g
Sicovit® colour 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 11: 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

3.5 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.

3.6 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.

3.7 Sprays

Because of its good film-forming properties, Kollidon VA 64 can also be used in topical sprays. The formulation in Table 7 provides a typical example of a spray bandage.

Table 12: 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.

3.8 Controlled-release preparations

Kollidon VA 64 is frequently cited in the literature as a matrix material for instant release and for sustained release dosage forms. Formulations with cellulose derivatives, polyacrylic acid, stearyl alcohol or polyhydroxyethyl methacrylate have been described for sustaining or controlling release. The formulations can be treated in various ways, e.g. freeze-dried or extruded, to produce a granulate, or melted and extruded, to produce pellets. Any relevant patents must be respected.

4. Toxicological studies

Toxicological studies are available on request. For detailed information and reports a secrecy agreement has to be signed in advance.

5. PBG-Nos.

Kollidon VA 64	10095405
Kollidon VA 64 Fine	10585104

6. PRD-Nos.

Kollidon VA 64	30034977
Kollidon VA 64 Fine	30239644

7. Article-Nos. & Contents

Kollidon VA 64	50000781	35 kg
Kollidon VA 64 Fine	57071976	15 kg

8. Stability and storage

When stored in unopened original containers at room temperature (max. 25°C) the retest periodes for both Kollidon VA 64 and Kollidon VA 64 Fine are 3 years.

9. Safety Data Sheet

Safety Data Sheets for Kollidon VA 64 and Kollidon VA 64 Fine are available on request.

10. Note

This document, or any answers or information provided herein by BASF, does not constitute a legally binding obligation of BASF. While the descriptions, designs, data and information contained herein are presented in good faith and believed to be accurate, it is provided for your guidance only. Because many factors may affect processing or application/use, we recommend that you make tests to determine the suitability of a product for your particular purpose prior to use. It does not relieve our customers from the obligation to perform a full inspection of the products upon delivery or any other obligation. NO WARRANTIES OF ANY KIND, EITHER EXPRESS OR IMPLIED, INCLUDING WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, ARE MADE REGARDING PRODUCTS DESCRIBED OR DESIGNS, DATA OR INFORMATION SET FORTH, OR THAT THE PRODUCTS, DESIGNS, DATA OR INFORMATION MAY BE USED WITHOUT INFRINGING THE INTELLECTUAL PROPERTY RIGHTS OF OTHERS. IN NO CASE SHALL THE DESCRIPTIONS, INFORMATION, DATA OR DESIGNS PROVIDED BE CONSIDERED A PART OF OUR TERMS AND CONDITIONS OF SALE.

June 2008