Technical Information

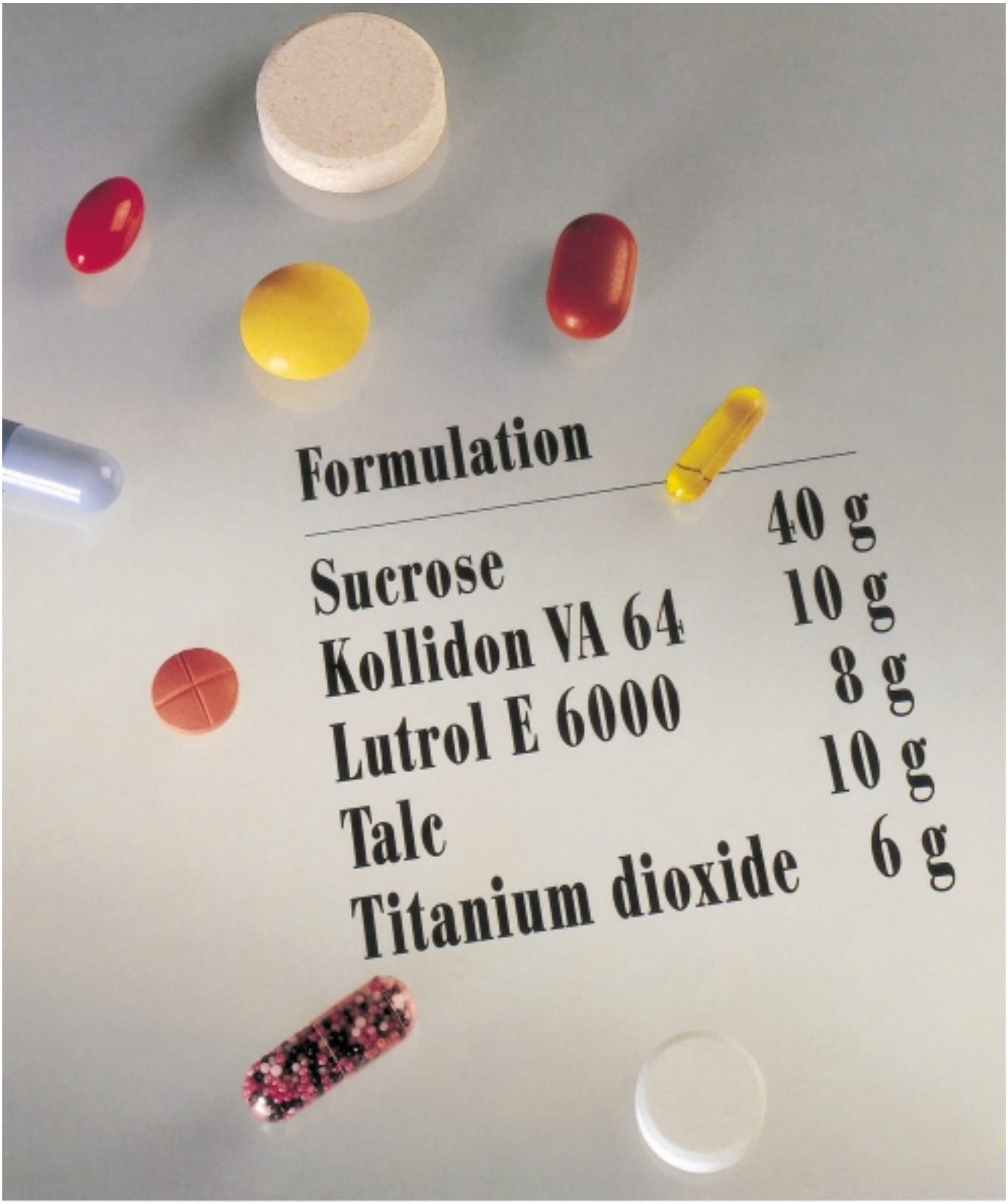
ME 080 e
(939) March 2000 (MPM)

Register 2

Kollidon® VA 64

Copovidone Ph. Eur.

Kollidon VA 64 is a vinylpyrrolidone-vinyl acetate copolymer that is soluble both in water and in alcohol. It is used as a dry binder in tabletting, as a granulating auxiliary and as a film-forming agent in the pharmaceutical industry.



Health and Nutrition

BASF

Contents

1 Introduction

1.1 General

Kollidon VA 64 is a vinylpyrrolidone-vinyl acetate copolymer that is soluble both in water and in alcohols. It is used in the pharmaceutical industry as a binder in tablets, as a granulating agent, as a retarding agent and as a film-forming agent.

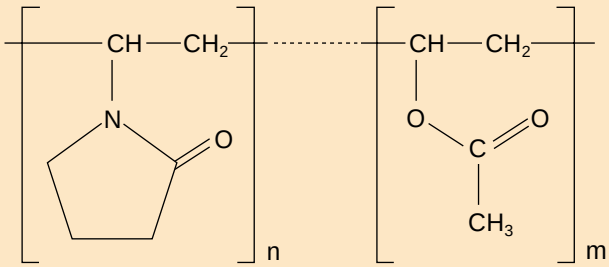
It is available from BASF as Product No. 95405-2-43.

For further details that are beyond the scope of this leaflet, please consult the book, “Kollidon – Polyvinylpyrrolidone for the Pharmaceutical Industry” 4th edition 1999 (BASF No. B 390 e).

1.2 Synonyms

Copolyvidone; Copovidone; VP/VAc copolymer 60/40; copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate in a ratio of 6 : 4 by mass.

1.3 Chemical formula



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

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

$n \approx 1.2\ m$

2 Specification, properties

2.1 Description

White or slightly yellowish, free-flowing powder with a faint characteristic odour and practically no taste.

2.2 Specification

Table 1: Specification of Kollidon VA 64

Identity (IR spectrum, see Fig. 1)	Conforms
Clarity of the solution (10 % in water)	No more opalescent than reference suspension III
Colour of the solution (10% in water)	No darker than B5, BY5 or R7
K-value (nominally 28)	25.2 – 30.8
Relative viscosity (1% in water)	1.178 –1.255
Nitrogen	7.0 – 8.0 %
Loss on drying	≤ 5.0 %
Vinylpyrrolidone (by HPLC)	≤ 10 ppm
Vinyl acetate (by HPLC)	≤ 10 ppm
Monomers VP + VAc (by titration)	≤ 0.4 %
Saponification value	230 – 270
Sulfated ash	≤ 0.1 %
Heavy metals	≤ 10 ppm
pH value (10 % in water)	3 – 7
Peroxides	≤ 400 ppm
Hydrazine	≤ 1 ppm
Vinyl acetate, polymerized	35.3 – 41.4 %
Acetaldehyde (enzymatic determination)	≤ 500 ppm
Microbial status	Conforms with Table 2
Residual solvents (Ph. Eur. 2000, 5.4)	Only Class 3: less than 0.5 %

The methods of determination are to be found in the Ph. Eur. monograph “Copovidone”. The methods for determining the monomers by HPLC and for determining acetaldehyde are given in the book, “Kollidon – Polyvinylpyrrolidone for the Pharmaceutical Industry” (BASF No. B 390 e).

The microbial status is determined according to methods 2.6.12 and 2.6.13 in Ph. Eur. 3. The limits for Kollidon VA 64 are those given in Table 2.

Table 2: Microbial purity requirements
(Ph. Eur. 3, 5.1.4, categories 2 + 3A)

- 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 Pharmacopoeias

Kollidon VA 64 fulfils the requirements of the current Ph. Eur. monograph, "Copovidone" and the JPE monograph, "Copolyvidone". A DMF with the number 6745 has been drawn up in the USA. It also meets the requirements of the USP-NF draft monograph „Copovidone" published in 1998.

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.

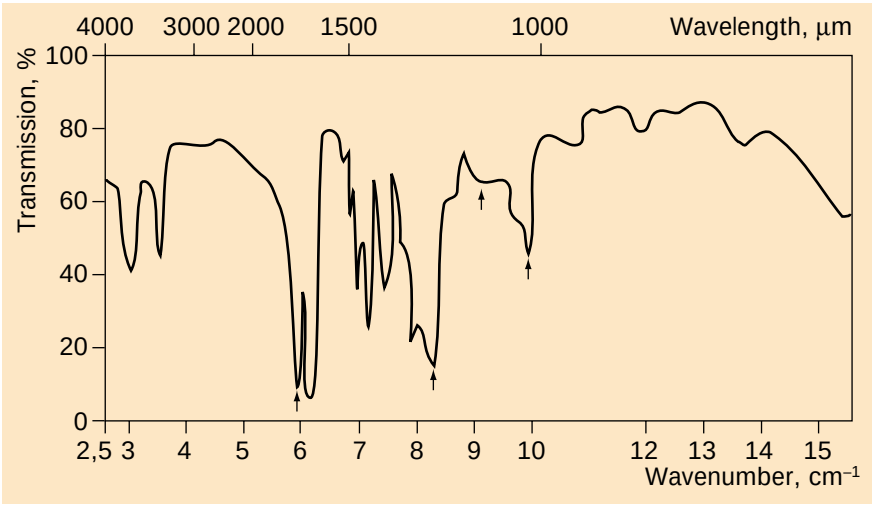


Fig. 1 Infrared spectrum of Kollidon VA 64

2.5 Solubility

Kollidon VA 64 readily dissolves in all hydrophilic solvents.

Solutions of more than 10% concentration can be prepared in:

water
ethanol
isopropanol
methylene chloride
glycerol
propylene glycol

It is less soluble in:

ether
cyclic, aliphatic and alicyclic hydrocarbons.

2.6 Viscosity

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

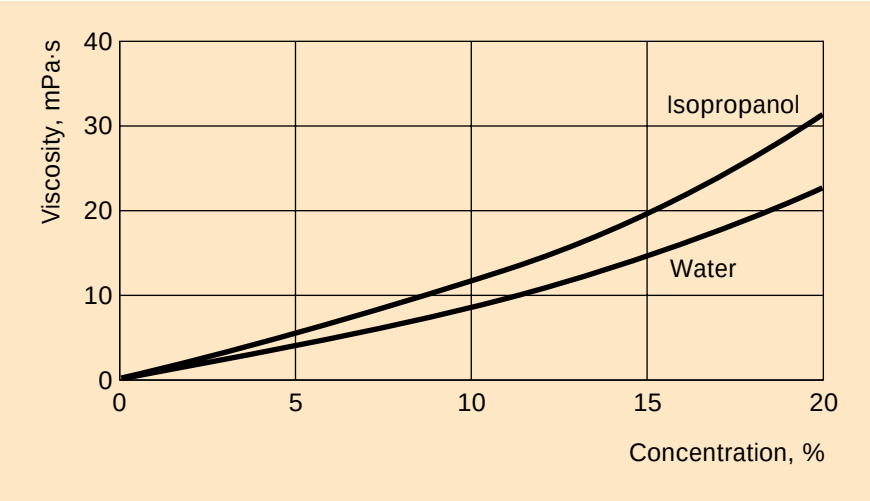


Fig. 2 Viscosity of Kollidon VA 64 in water and isopropanol

2.7 Particle size distribution

The following values were determined with an air-jet sieve and should be regarded as typical values.

Finer than 50 µm	approx. 15 %
Coarser than 250 µm	approx. 1 – 2 %

2.8 Bulk density

The bulk density of Kollidon VA 64 usually lies in the 0.2 – 0.3 g/ml range.

2.9 Hygroscopicity

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

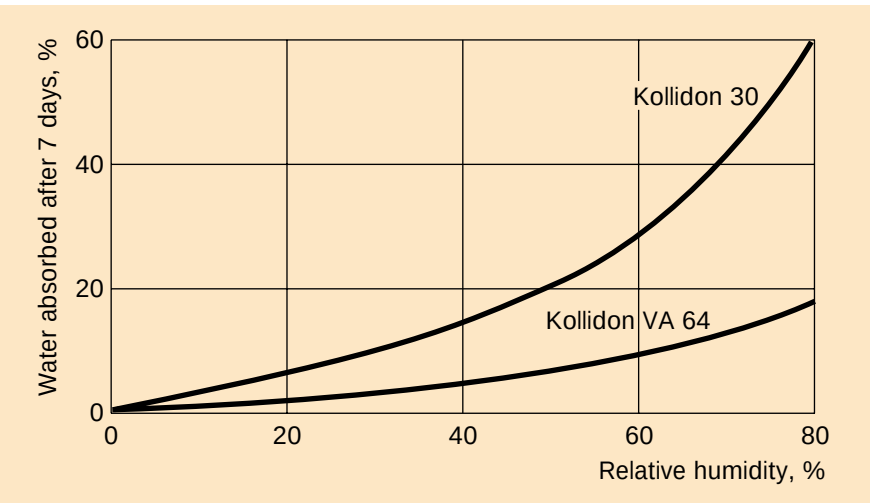


Fig. 3 Hygroscopicity of Kollidon VA 64 and Kollidon 30

2.10 Molecular weight

The average molecular weight is usually expressed as a K value. The exact weight-average molecular weight, $\overline{M}w$ 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.

2.11 Stability, storage

Kollidon VA 64 can be stored at room temperature (max. 25 °C) in the unopened original containers for at least 3 years.

The storage temperature should be kept below 25 °C.

3 Applications

3.1 General

Copovidone has been used for decades in the pharmaceutical industry in Europe. 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 is an excellent binder for tablets and granules. Between 2% and 5%, as a proportion of the final weight of the preparation, is usually used.

An important property of Kollidon VA 64 in this application is its plasticity, which distinguishes it 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 has been found to be the best dry binder for direct compression that gives much better results than any of the povidone grades. 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:

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 can be added to materials such as sorbitol, mannitol, starch, or direct compression aids, e.g. microcrystalline 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” 1999).

Table 3: Ascorbic acid chewable tablets 100 mg

Ascorbic acid powder	42.2	%
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 (Degussa)	0.2	%
Weight	250	mg
Diameter	8	mm
Hardness	157	N
Disintegration in water	15	min
Friability	less than 0.1	%

3.2.2 Wet granulation

Kollidon VA 64 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” 1999).

Table 4: 500-mg ampicillin tablets and 400-mg cimetidine tablets

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	4 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 good granules, e.g. for instant multivitamin drinks.

3.3 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 (e.g. Lutrol® E 6000). 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 5: Sugar film coating (Accela Cota)

Suspension:		
Sucrose	40	g
Kollidon VA 64	10	g
Lutrol E 6000	8	g
Sicovit® colour lake	3	g
Sicovit titanium dioxide	6	g
Talc	10	g
Water	ad 240	g

Continuously spray 1,200 g of this suspension onto 5 kg of tablet cores that contain 5% Kollidon CL as a disintegrant, under the following conditions:

Coating pan speed	15	r.p.m.
Spray jet	0.8	mm
Spraying pressure	2	bar
Air temperature, in	45	°C
Air temperature, out	36	°C
Spraying time	50	min
Quantity applied	approx. 4	mg film-forming agent/cm^2

Table 6: Film coating with hydroxypropyl methylcellulose (Accela Cota 24″)

Suspension:		
I. Kollidon VA 64	53	g
Lutrol E6000	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

Mix Solution I with Suspension II, pass through a disc mill, and spray at 2 bar onto 5 kg of cores. The quantity of film former applied is about 3 mg/cm^2.

Air temperatures in/out	60 °C/40 °C
Spraying time	50 g/min
Spraying time (continuous)	34 min
Drying after spraying	5 min at 60 °C

3.4 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 water-sensitive 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.

3.5 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.

3.6 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 7: 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.

3.7 Controlled-release preparations

Kollidon VA 64 is frequently cited in the literature as a matrix material for rapid 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

The following toxicological studies are available in the form of reports:

– Acute oral toxicity (rat, mouse, dog)
– Acute intraperitoneal toxicity (mouse)
– Skin irritation (rabbit)
– Eye irritation (rabbit)
– 4 weeks oral toxicity (dog)
– 13 weeks oral toxicity (dog)
– 3 months oral toxicity (rat)
– Prenatal toxicity after oral administration (rat)
– Intraduodenal absorption and excretion (rat)

Note

The data submitted in this publication are based on our current knowledge and experience. They do not constitute a guarantee in the legal sense of the term and, in view of the manifold factors that may affect processing and application, do not relieve processors from the responsibility of carrying out their own tests and experiments. Any relevant patent rights and existing legislation and regulations must be observed.

BASF Aktiengesellschaft
Unternehmensbereich Feinchemie
67056 Ludwigshafen, Germany

BASF

Printed in Germany