Technical Information

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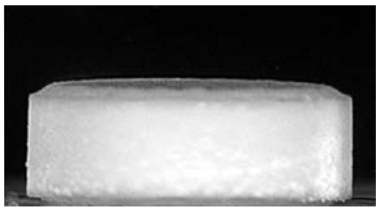
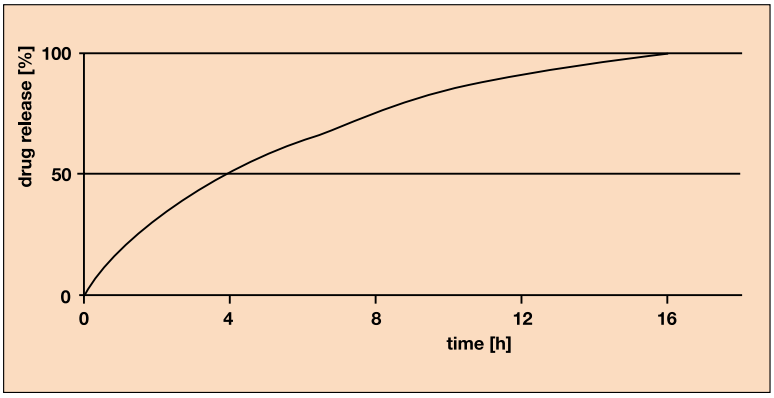
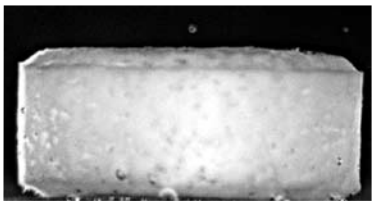
Kollidon® SR

Polyvinyl acetate and povidone based matrix sustained release excipient







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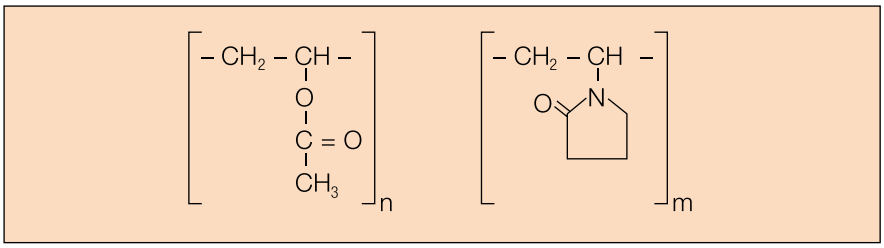
1. Introduction

1.1 General

Kollidon SR is a polyvinyl acetate and povidone based matrix retarding agent. It is particularly suitable for the manufacture of pH-independent sustained-release matrix tablets by direct compression. Polyvinyl acetate is a very plastic material that produces a coherent matrix even under low compression forces. When the tablets are introduced into gastric or intestinal fluid, the water soluble povidone is leached out to form pores through which the active ingredient slowly diffuses outwards. Kollidon SR contains no ionic groups and is therefore inert to drug substances. The sustained-release properties are unaffected by ions or salts.

1.2 Chemical structure



1.3 Trivial name

Polyvinyl acetate/polyvinylpyrrolidone

2. Compositions

Kollidon SR consists of 80% polyvinyl acetate and 19% povidone Ph.Eur./USP (Kollidon 30) in a physical mixture.

Approx. 0.8% of sodium laury sulfate and about 0.2% of silica are used as stabilizers.

3. Specifications and methods

3.1 Specification

See separate document “Standard Specification” (not for regulatory purposes), available via the BASF WorldAccount platform.

3.2 IR-spectra

The IR-spectra is measured in potassium bromide and a typical spectra is given in the following figure 1.

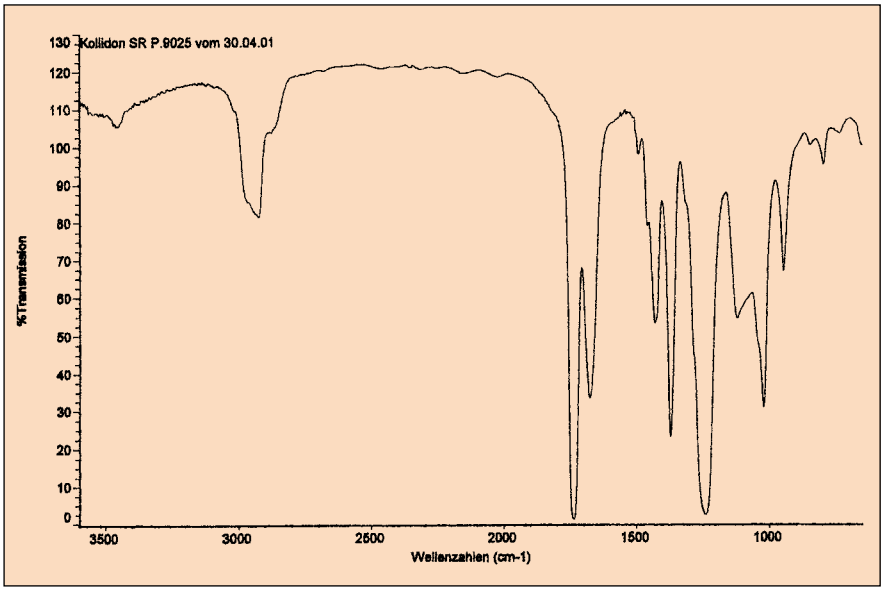


Fig. 1: IR-spectra of Kollidon SR

3.3 Content of polyvinyl acetate

Determine the saponification value (Ph.Eur. 2.5.6) in 1.5 g of Kollidon SR and calculate the content of polyvinyl acetate as follows:

Polyvinyl acetate in Kollidon SR (%) = Saponification value x 0.1534

3.4 Content of povidone

Determine the nitrogen content in 1.0 g of Kollidon SR according to the Ph.Eur. monograph “Povidone” and calculate the content of povidone as follows:

$$\text{Povidone in Kollidon SR (\%)} = \frac{\text{Nitrogen content (\%)}}{0.126}$$

3.5 Vinyl acetate

The monomer vinyl acetate is determined by the following HPLC method:

Principle:The sample is dissolved and separated by liquid reversed phase chromatography. The interfering polymeric components of the matrix are removed by column switching. A UV detector operating at 205 nm and a calibration with an external standard are used to determine the level of vinyl acetate (detection limit 20 ppm).

Sample preparation:
Weigh approx. 150 mg of Kollidon SR accurate to 0.01 mg, into a 25 ml volumetric flask, dissolve in 10 ml of acetonitrile. Then make up the mark with the same solvent and shake for 30 minutes. Use aliquots of this solution for the HPLC analysis.

Preparation of the calibration solutions:
Weigh 40-50 mg of vinyl acetate, accurate to 0.01 mg, into a 50 ml volumetric flask and dissolve in about 20 ml of eluent. Then make up to the mark with eluent. Prepare a series of dilutions from this stock solution to cover the expected range of vinyl acetate content in the sample of Kollidon SR.

Chromatographic conditions

Guard column:	25 x 4 mm cartridge packed with LiChrospher® 60 RP select B, 5 µm (Merck)
Separation column:	250 x 4 mm steel column packed with LiChrospher 60 RP select B, 5 µm (Merck)
Eluent (mobile phase):	Water/acetonitrile 92 + 8 (% w/w)
Flow rate:	About 1.2 ml/min
Sample volume	About 30 µl
Detection wavelength:	205 nm
Pressure	About 200 bar
Column temperature:	40°C
Retention time:	12-14 min

Column switching:
The analysis is started with the guard column and separation column in series. After about 1.2 minutes, the valves, controlled by the detector programme, switch over such that the eluent flows past the guard column, direct to the separation column. The columns are switched when the components to be determined, but not the interfering matrix, have already reached the separation column. Simultaneously, the guard column is washed out in the reverse direction by a second pump to remove the unwanted matrix components.
After about 18 minutes, the valves are reset to the starting position for the next analysis.

Figure 2 shows a typical chromatogramm obtained under these conditions.

Calibration factor:

$$F = \frac{A_{St}}{W_{St}}$$

A_{St} = calibration substance peak area [mV s]
W_{St} = weight of calibration substance per 100 ml [mg/100 ml]

Calculation of vinyl acetate in the sample:
The content of the sample is calculated with the aid of an external standard:

$$\text{vinyl acetate (ppm)} = \frac{A}{F \cdot W_{Sa}} \; 10^6$$

A = peak area of vinyl acetate in the sample [mV s]
W_{Sa} = sample weight [mg/100 ml]

Linearity:The calibration curves were plotted from 5 points covering a concentration range of 0-1.0 µg/ml to check their linearity. A linear calibration curve was obtained.

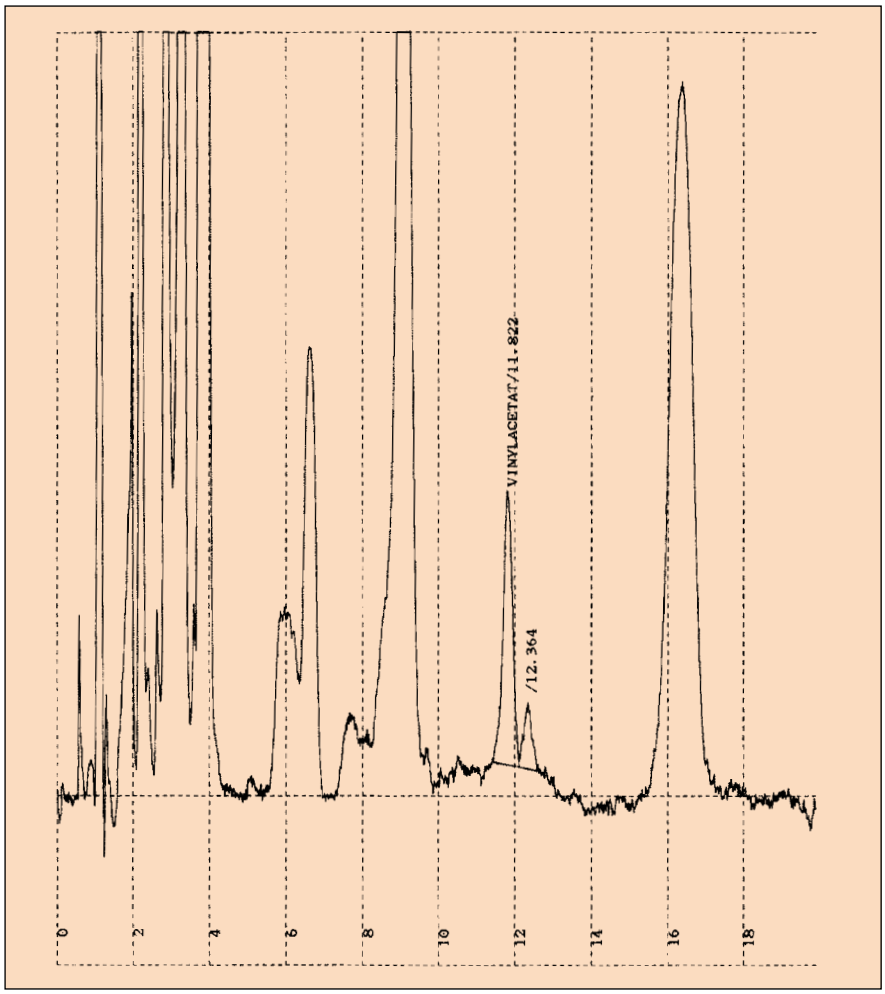


Fig. 2: Typical chromatogram

4. Properties

Description	White or slightly yellowish, free-flowing powder.
Solubility	Insoluble in water (The povidone part is soluble but the polyvinyl acetate part is insoluble). It is very soluble in N-methylpyrrolidone.
Molecular weight, K-value	The average molecular weights Mw of the polyvinyl acetate part is about 450,000. That one of the povidone K 30 part it is about 50,000. The average molecular weight of Kollidon SR as mixture is expressed as K-value according to the method described in the monographs “Povidone” and measured in a 1% solution in tetrahydrofurane. The typical K-value is 60-65.
Particle size distribution	The average particle size is about 100 µm.
Glas transition temperature	The glass transiition temperature Tg of the anhydrous material is about 35°C.
Bulk density	About 0.45 g/ml.
Flowability	Kollidon SR has outstanding flow properties with a angle of repose well below 30°. It can enhance the flowability of other components added for a tablet formulation.
Hygroscopicity	The water uptake is much less than that of povidone or copovidone. Figure 3 shows the water sorption and desorption isotherms at room temperature.

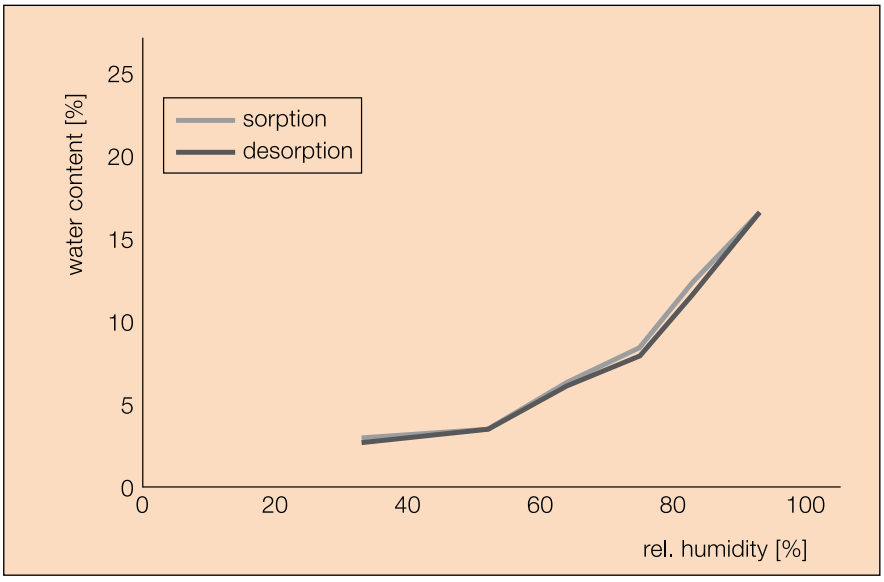


Fig. 3: Sorption isotherms of Kollidon SR

Compressibility

Kollidon SR has excellent compressibility and endows tablets with enormous hardness and low friability. This is due to the combination of the very plastic polyvinyl acetate and the also strongly binding povidone.

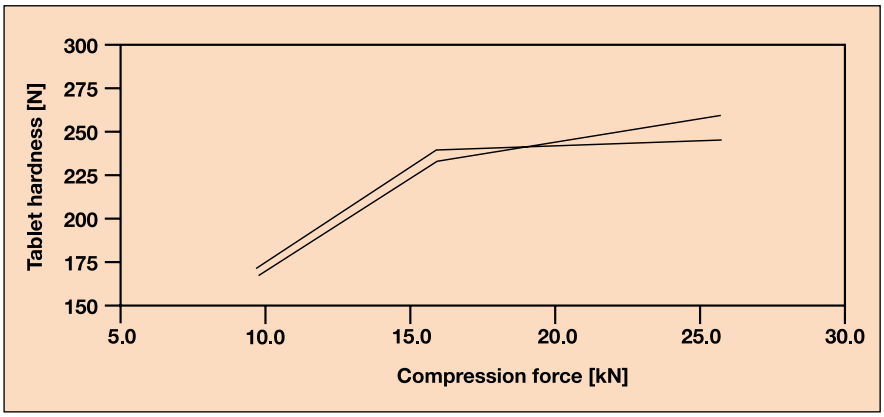


Fig. 4: Hardness-compression force profile of propranolol sustained release tablets containing 50% of Kollidon SR (2 Lots, Formulation see chapter 6.2)

5. Registration

5.1 Regulatory status

No monographs exist.

5.2 Drug Master File

For registration purposes a US-DMF was prepared.

5.3 Analytical monograph

For registration purposes a Pharmacopoeia like monograph of Kollidon SR was prepared including all analytical methods and limits. It is available on request.

5.4 Description of synthesis

For registration purposes a short description of the production of Kollidon SR is available on request.

5.5 Use of polyvinyl acetate in drugs and food

Polyvinyl acetate is used in a variety of drugs for oral administration in numerous countries including Germany, France, Japan and USA.
Polyvinyl acetate also is allowed in the food industry in several countries like Germany, USA and Japan.

6. Applications

6.1 General Information

Kollidon SR can be used for the production of the following sustained release matrix dosage forms: Tablets, pellets and granules.

Different technologies to obtain such dosage forms can be applied:
Direct compression, roller compaction, wet granulation and extrusion.

The excellent flowability and compressibility of Kollidon SR makes this excepient particulary suitable for the manufacture of sustained release tablets obtained by **direct compression**.

The required content of Kollidon SR in the tablet depends on the solubility of the active ingredient. The following table gives an information about the usual amounts of Kollidon SR to obtain a sustained release during 12-24 hours.

Solubility of the active ingredient	Kollidon SR in the tablet
Very slightly soluble to practically insoluble	15 - 25%
Sparingly soluble to slightly soluble	25 - 40%
Soluble to freely soluble	40 - 55%

The sustained release characteristics can be modified by varying the Kollidon SR content in the formulation. Figure 5 shows the influence of the amount of Kollidon SR on the release of caffeine as a example of a soluble active ingredient.

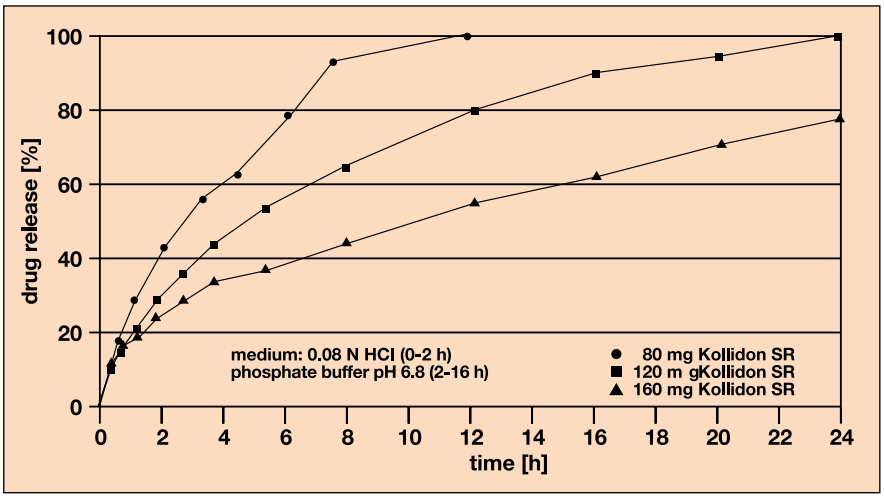


Fig. 5: Influence of the amount of Kollidon SR on the drug release in a caffeine sustained release tablet (160 mg Caffeine)

In the case of slightly soluble or practically insoluble drug substances the release can be accelerated not only by reducing the content of Kollidon SR but also by the addition of hydrophilic substances like lactose, Kollidon 30 or Kollidon CL-M which act as pore former.

Interesting and important properties of sustained release matrix tablets based on Kollidon SR are the following:

1. **The drug release is independent of the pH (see figure 6).**
2. **The drug release is independent of the ionic strength of the dissolution medium (see figure 6, addition of 2.5% of NaCl).**
3. **The drug release is independent of the usual compression force and tablet hardness (see figure 7).**

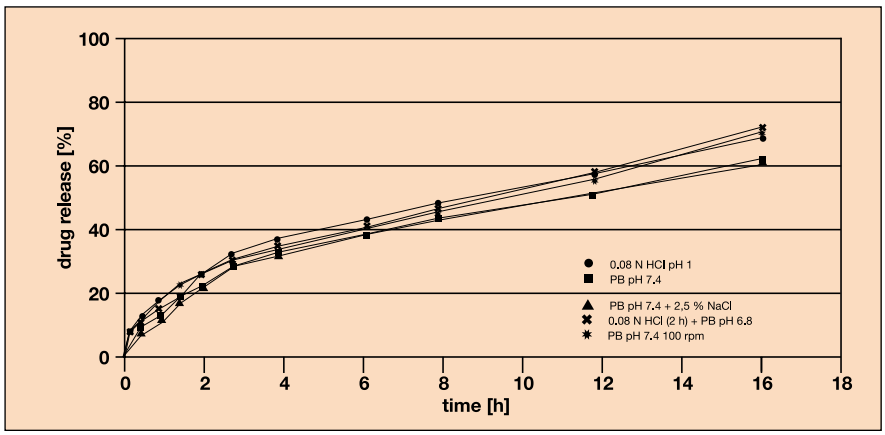


Fig. 6: Influence of the pH and the ionic strength of the dissolution medium on the release of caffeine tablets (Caffeine + Kollidon SR 1+1)

It is recommended to store the matrix tablets containing Kollidon SR at temperatures below 30°C and in tightly closed containers to avoid the uptake of humidity which could modify the release profile of formulations containing a higher percentage of Kollidon SR.

In the following chapters three typical examples of soluble and practically insoluble active ingredients are given in form of sustained release tablets.
Further formulations can be found in the current edition of BASF CD-ROM "Generig Drug Formulations".

6.2 Propranolol Sustained Release Matrix Tablets

Formulation

	Parts by weight [g]	Composition [%]
Propranolol-HCl	160.0	49.23
Kollidon SR	160.0	49.23
Silicon dioxide, colloidal	3.4	1.05
Magnesium stearate	1.6	0.49
Total	325.0	100.00

Manufacture

All ingredients were passed through a 0.8 mm sieve, blended for 10 min in a Turbula mixer and then pressed on a rotary press.

Tablet properties

Diameter	10 mm
Weight	330 mg
Compression force	10 kN / 18 kN / 25 kN
Hardness	170 N / 235 N / 250 N
Friability	0.1%
Drug release	See Figure 7

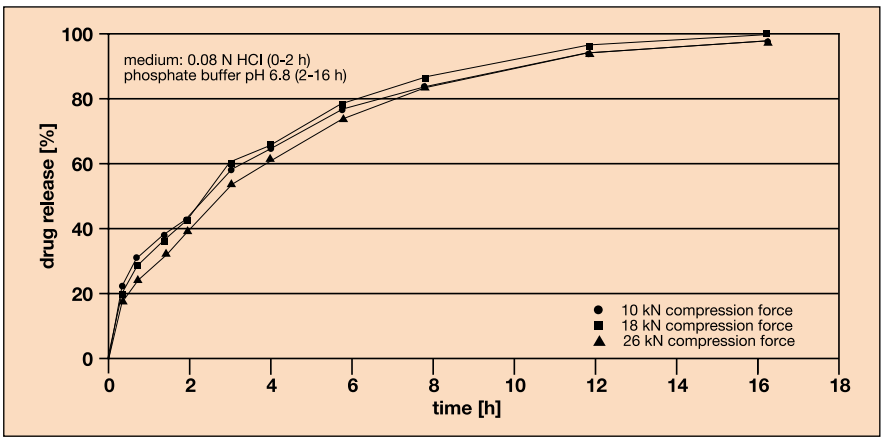


Fig. 7: Propranolol sustained release tablets: Influence of the compression force on the drug release

6.3 Diclofenac Sustained Release Matrix Tablets

Formulation

	Weight	Percent
Diclofenac sodium	100 g	48.4
Kollidon SR	100 g	48.4
Aerosil 200	3.4 g	1.6
Magnesium stearate	3.4 g	1.6

Manufacture

All ingredients are mixed, passed through a 0.8 mm sieve and pressed with a medium compression force on a rotary press.

Tablet properties

Diameter	8 mm
Weight	206 mg
Compression force	medium
Hardnes	195 N
Friability	<0.1%
Drug release	See Figure 8

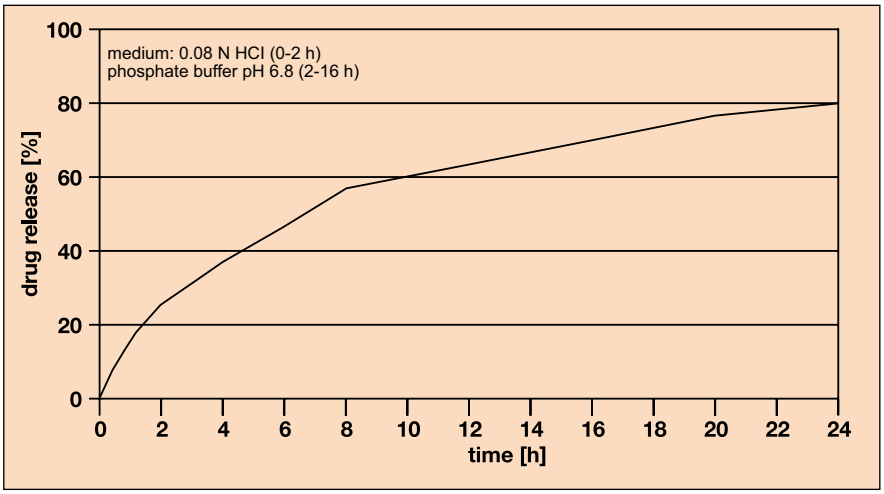


Fig. 8: Dissolution of Diclofenac sustained release tablets

6.4 Theophylline Sustained Release Matrix Tablets

Formulation

	Parts by weight [g]	Composition [%]
Theophylline gran.	500.0	53.9
Kollidon SR	200.0	21.6
Ludipress® LCE	225.0	24.2
Magnesium stearate	3.0	0.3
Total	928.0	100.00

Manufacture

All ingredients were passed through a 0.8 mm sieve, blended for 10 min in a Turbula mixer and then pressed on a rotary press.

Tablet properties

Diameter	19.0 x 8.5 mm (football shape)
Weight	928 mg
Compression force	11 kN
Hardness	172 N
Friability	<0.1%
Drug release	See Figure 9

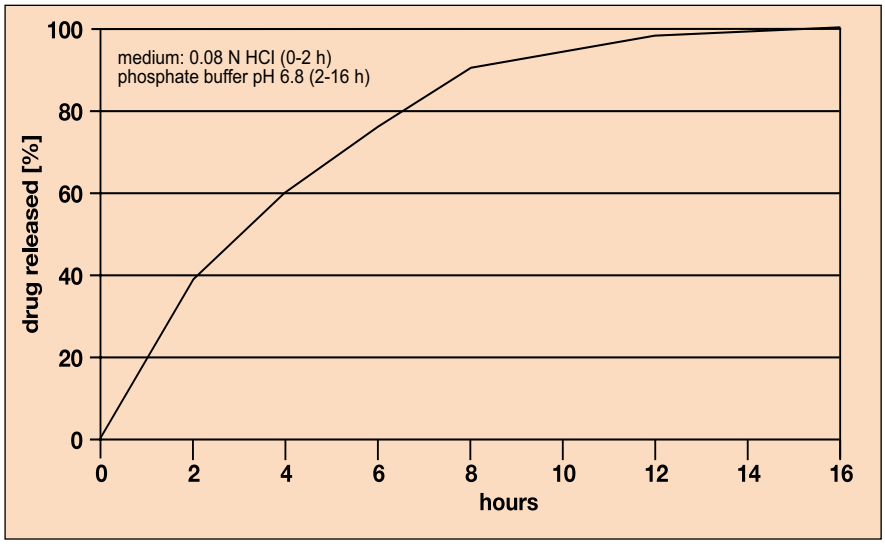


Fig. 9: Dissolution of theophylline sustained release tablets

7. Storage

Store below 30°C

8. Stability

At least 24 months in the unopened original container at room temperature.

9. PBG-No./PRD-No.

10235112 /30071321

10. Packaging

20 kg plastic container

Note

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