

# ExAct

No. 6, May 2001

Excipients & Actives for Pharma

## Calendar

### 11<sup>th</sup> to 13<sup>th</sup> June, 2001

INTERPHEX Asia (Internat. Exhibition for the Pharmaceutical Industry)  
Singapore, Singapore

### 23<sup>rd</sup> to 27<sup>th</sup> June, 2001

28<sup>th</sup> International Symposium on Controlled Release of Bioactive Materials  
San Diego\*, USA

### 10<sup>th</sup> to 12<sup>th</sup> July, 2001

CPhI, Pharmaceutical Ingredients China  
Shanghai, China

### 24<sup>th</sup> to 26<sup>th</sup> July, 2001

FCE Pharma International Exhibition For the Pharma Industry  
São Paulo, Brasil

### 8<sup>th</sup> to 10<sup>th</sup> October, 2001

CPhI, Pharmaceutical Ingredients Worldwide  
London\*, United Kingdom

### 21<sup>st</sup> to 25<sup>th</sup> October, 2001

AAPS (American Association of Pharmaceutical Scientists) Annual Meeting  
Denver\*, USA

### 9<sup>th</sup> to 12<sup>th</sup> November, 2001

PHARMA INDIA (Internat. Congress and Exposition for the Pharmaceutical Industry)  
Mumbai, India

### 8<sup>th</sup> to 11<sup>th</sup> April, 2002

4<sup>th</sup> World meeting on Pharmaceutics, Biopharmaceutics  
Pharmaceutical Technology  
Florence\*, Italy

\* BASF will be represented.

## Dear reader,

In the 5<sup>th</sup> edition of ExAct we reported on the reorganised pharma active ingredients business within the BASF. BASF now provides a whole range of active ingredients and excipients from one source.

At the beginning of this year BASF's and Takeda's vitamin businesses were combined under BASF's responsibility. This substantially strengthens our vitamin product portfolio for the pharmaceutical and nutritional supplement industries.

Detailed information on this widened vitamin product range, product grades and applications is given in a separate article within this ExAct edition.

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Dr. Volker Bühler, Valérie Filiatreau,  
Dr. Hubertus Foltmann, Klaus Kalter,  
Dr. Karl Kolter

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printec GmbH, Kaiserslautern

Yours sincerely,

BASF Aktiengesellschaft  
Global Marketing  
Pharma Solutions

Dr. Jens-Uwe Bliesener



# BASF

# Kollocoat® MAE 30 DP

## Aqueous Enteric Coating of Aspirin with Kollocoat® MAE 30 DP

K. Kolter, H.-B. Reich, C. Dangel, G. Schepky

### Introduction

Aqueous enteric coatings are gaining significant importance and are substituting manufacturing processes with organic solvents for ecological and economical reasons. Among the aqueous enteric coatings, methacrylic acid copolymers type C (Kollocoat® MAE 30 DP) offers advantages in acid resistance and manufacturing time compared to enteric cellulose derivatives [1]. Acid resistance was as strong as with coatings applied from organic solvents. The expectations are that the large amount of water in aqueous dispersions would interfere with the core and would lead to degradation in the core when humidity sensitive drugs are used. Aspirin and pancreatine are examples for such sensitive drugs.

### Objective

The objective of this study was to show whether Aspirin dosage forms can be coated using an aqueous dispersion of a methacrylic acid-ethyl acrylate copolymer (Kollocoat® MAE 30 DP) without degradation of this humidity sensitive drug. Two different dosage forms should be used, a bolus form (tablet) and a multiple unit form (crystals), which differ in excipients, porosity and water sorption.

### Materials and Methods

#### Materials

Kollocoat® MAE 30 DP (methacrylic acid-ethyl acrylate copolymer 1:1), BASF AG; Aspirin crystalline, E. Merck; Aspirin crystals 0.5-0.8 mm, Chemische Fabrik Aubing GmbH.

#### Apparatus

Accela Cota 24", Manesty Machines Ltd.; Aeromatic Strea 1, Aeromatic AG

### Composition and preparation of Aspirin cores

All ingredients were blended in a Diosna mixer and compressed with 10 kN compression force into cores of 9 mm diameter, 12 mm radius of curvature and 300 mg weight.

Tablet formulation	mg per tablet
Aspirin	100.0
Ludipress® (BASF AG)	148.5
Avicel PH 102	50.0
Magnesium stearate	1.5
<b>Total mass</b>	<b>300.0</b>

### Composition and preparation of the spray suspension

Spray formulation	%	%	
<b>Polymer dispersion</b>		<b>Pigment dispersion</b>	
Kollocoat® MAE 30 DP	50.00	Sicovit® Red 30 (BASF AG)	0.5
Propylene glycol	2.25	Titanium dioxide	0.5
Water	32.25	Talc	4.0
		Water	10.5

### Coating process

According to technical brochure Kollocoat® MAE 30 DP.

Coating parameters	Aspirin tablets Accela Cota 24"	Aspirin crystals Aeromatic Strea 1 Top spray
Core mass	5 kg	0.5 kg
Prewarming	30° C	30° C
Nozzle diameter	1.0 mm	1.0 mm
Atomizing pressure	2.0 bar	2.0 bar
Inlet air	52° C	60° C
Outlet air	32-35° C	35° C

### Determination of the uptake of gastric fluid into enteric coated tablets during the resistance test

Six film-coated tablets were agitated in 0.1 N HCl in a disintegration tester for 1 and 2 hours. The increase in tablet weight is given as a percentage of the initial weight.

### Determination of dissolution

Aspirin tablets: According to USP 23 (75 rpm)  
Aspirin crystals: According to USP 23 (150 rpm)

### Determination of Aspirin and salicylic acid

Spectrophotometrically at 280 and 310 nm [2]

## › Results

### Aspirin film-coated tablets

To determine exactly the gastric resistance of a bolus form, the USP resistance test was completed by detecting the weight increase representing the acid uptake through the film. The Aspirin film-coated tablets with 4 mg/cm<sup>2</sup> coating showed no sign of disintegration and comparably low values of 3.15% weight increase after 1 hour and 4.78% after 2 hours in gastric fluid. It must be taken into consideration that a part of the acid uptake didn't penetrate into the core due to swelling of the coat (**figure 1**).

The results are confirmed by the dissolution testing where less than 0.04% Aspirin was delivered after 2 hours in gastric fluid. After changing the dissolution medium to intestinal fluid, a quick release of Aspirin occurred, which was nearly as fast as from the uncoated tablets (**figure 2**). Less than 1% salicylic acid was found in the tablets after film-coating, as well as after 2 hours treatment in gastric fluid, indicating that the rate of hydrolysis was very low. It is important to start the coating process initially with a low spraying rate and a high bed temperature, resulting in a "dry" process to minimize water uptake from the spray suspension into the tablet. A low water uptake of the core is important, particularly to achieve high stability during storage. The stability can be further increased by selecting a core with a low porosity and a smooth surface.

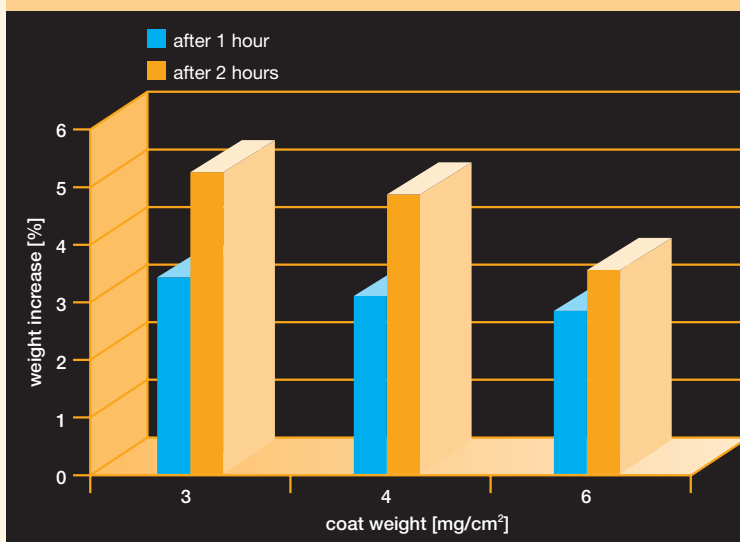
### Aspirin film-coated crystals

At equivalent coating levels a higher amount of drug was released into gastric fluid from the Aspirin crystals (1.82% at 4 mg/cm<sup>2</sup> coat weight) than from the tablets. This is due to the angular shape of the crystals with edges, where the coating is not sufficient to prevent drug release completely. Nevertheless the requirements of the USP were fulfilled (**figure 3**).

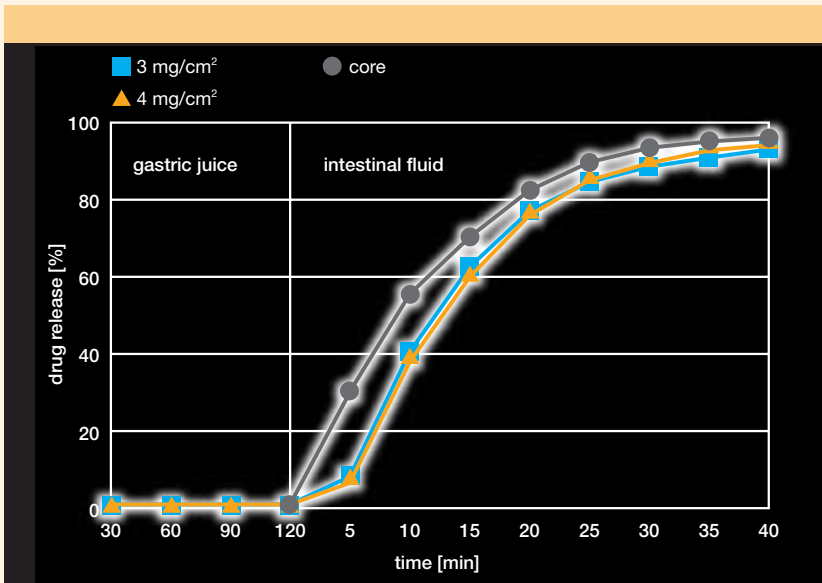
Dissolution rate in intestinal fluid was quick with a delay of about 5 min compared to the uncoated crystals. Compared to the tablets, the hydrolysis rate of the crystals was low, too.

The higher surface/volume ratio, which should result in a higher rate of hydrolysis, is offset by the lack of porosity and a low water sorption of the crystals. Film-coated Aspirin crystals with 4 mg/cm<sup>2</sup> coating level stored at 25°C/55% r.h. for 6 months, exhibited no sign of degradation. With a higher level of coating (6 mg/cm<sup>2</sup>) even 40°C/75% r.h. were tolerated. An increasing coating level resulted in a higher stability during storage.

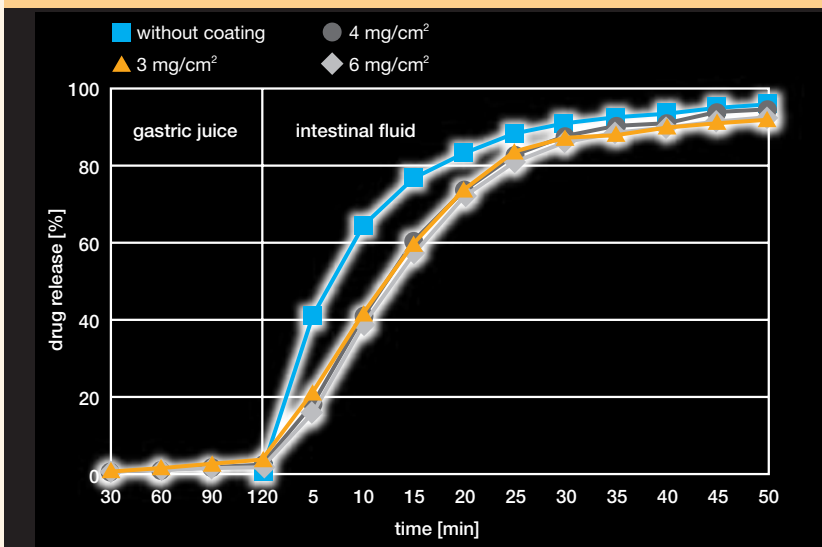
At 6 mg/cm<sup>2</sup>, the coated Aspirin crystals passed the stress test (40°C/75% r.h./3 months), whereas the 4 mg/cm<sup>2</sup> coating level failed. From a stability point of view a higher coating level should be used (**figure 4**).



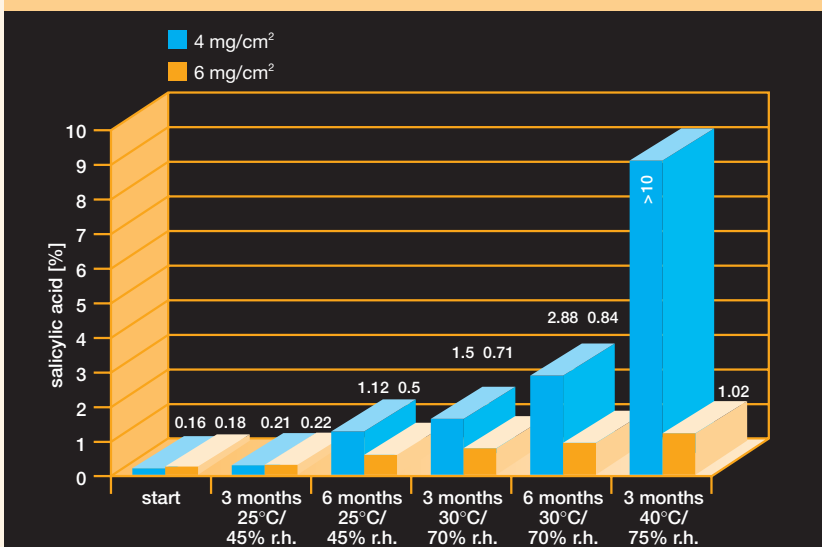
Weight increase of film-coated tablets after the enteric resistance test according to USP 23 (**figure 1**)



Drug release of enteric-coated and uncoated Aspirin tablets (figure 2)



Drug release of enteric-coated and uncoated Aspirin crystals (figure 3)



Degradation of Aspirin in enteric-coated crystals at different coating levels and storage conditions (figure 4)

**Conclusion**

- › Aspirin tablets and crystals can be enteric coated using aqueous Kollicoat® MAE 30 DP without degradation of the drug.
- › Initially a reduced spraying rate should be used resulting in a “dry” process.
- › A higher stability of Aspirin during storage is achieved by applying higher coating levels.
- › The manufacturing process is easy to handle, fast and cost saving.

**References**

[1] S. Scheiffelle, K. Kolter und G. Schepky, Drug Dev. Ind. Pharm. 24 (9), 807-18 (1998)  
 [2] E. R. Hackmann, N. R. Vals and M. I. Santaro, Rev. Farm. Bioquim. Univ. São Paulo (1), 53-58 (1997) 33

# Kollidon® SR

## Properties of Kollidon® SR as a New Excipient for Sustained Release Dosage Forms

K. Kolter, W. Fraunhofer and F. Ruchatz

### Introduction

Sustained release of active drugs is highly attractive and consequently controlled release formulations are gaining more and more interest. In particular the manufacture of matrix tablets by direct compression is a cost saving simple process preferably suitable for economic production of controlled release formulations. However, prerequisites for an easy processing and a reliable release control are a good flowability and sufficient binding properties accompanied by a strong prolongation of the drug release provided by the matrix former. Some drawbacks of directly compressed matrices using the well known hydrogel formers such as HPMC, HPC, xanthan gum, alginates amongst others are the poor flowability and the insufficient compressibility hampering the direct compression process. Tablets with a low hardness and a high friability were achieved in particular when using alginates and xanthan gum.

### Objective

As a new direct compressible excipient for sustained release matrices offering several advantages Kollidon® SR was developed. Kollidon® SR is a spray formulated, free flowing, non-hygroscopic powder consisting of 8 parts (w/w) polyvinyl acetate and 2 parts (w/w) polyvinylpyrrolidone.

The intention of the presented study was to characterise Kollidon® SR, with respect to the compression behaviour and to the influence of different tableting processes, speeds and tablet dimensions on the properties of Kollidon® SR formulations. Furthermore the impact of different variables on the release profile of Kollidon® SR tablets using caffeine as model drug was investigated.

### Materials and Methods

By varying the dimensions (10, 11, 12 mm diameter, convex and flat beveled edge) tablets were manufactured using a rotary press under constant conditions. Furthermore tablets were produced using different types of machinery (single punch and rotary press) and different tableting speeds as shown in table 2.

### Materials

Kollidon® SR (BASF Aktiengesellschaft);  
caffeine (BASF Aktiengesellschaft);  
Mg-stearate (Bärlocher);  
Aerosil® 200 (Degussa Aktiengesellschaft).

### Powder properties

The bulk and tap density were determined using an Erweka SVM volumeter, the angle of repose and the flow time were measured with a Pfrengle funnel. The particle size was investigated by means of a Malvern Mastersizer.

### Manufacture of the tablets

The ingredients were weighed (see table 1), blended for 10 min in a turbula mixer (T3C) and passed through a 800 µm sieve. The mixtures were compressed under the conditions listed in table 2.

### Determination of the tablet properties

Dimensions, weight and hardness using a Krämer tablet tester (HT-TMB), disintegration time (Krämer DES-5-AS), friability with an Erweka friabilator.

### Release studies

The dissolution experiments were performed using a PTS-W Pharma test with the buffer solutions

- 0.08 N HCl USP XXIII [2h]
- phosphate buffer solution pH 7.4 (USP XXIII [14h]).

**Table 1: Tablet composition with Kollidon® SR and the model drug caffeine (amount per tablet [mg])**

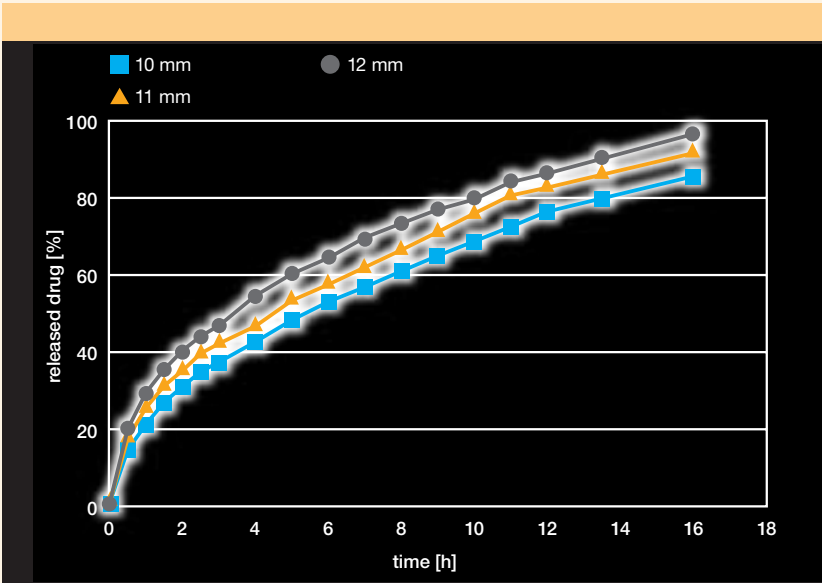
Kollidon® SR	160.0
Caffeine	160.0
Aerosil® 200	3.4
Mg-stearate	1.6

Tablet weight	325.0
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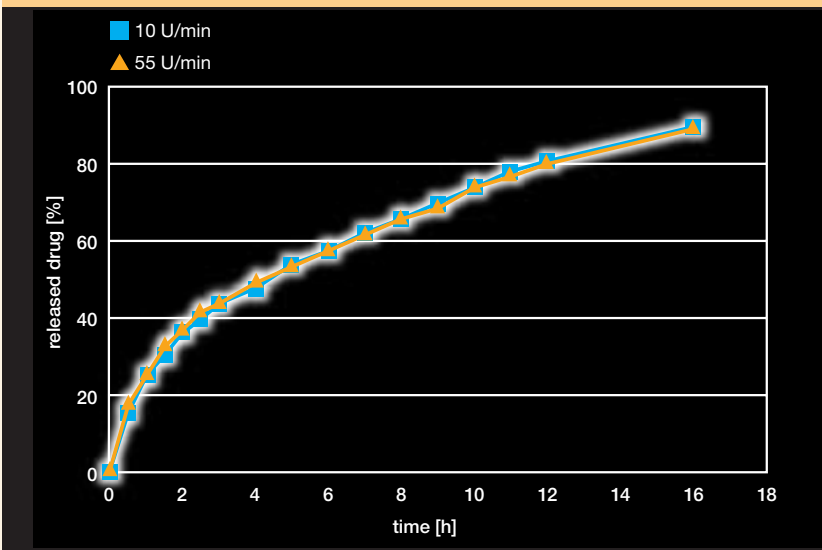


**Table 2: Production conditions for Kollidon® SR matrix tablets**

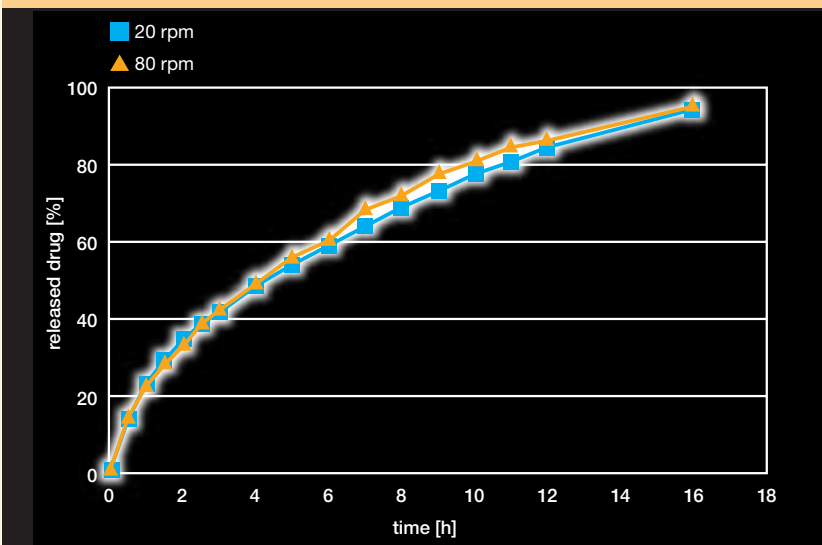
	Single punch press Korsch® EK0, instrumented	Rotary press Korsch® PH106, instrumented
Type		
Speed [rpm]	10/20/30/40/50/55	20/40/60/80
Compression force [kN]	15	15
Tooling	10 mm flat	10 mm flat



Influence of different tablet diameters on the release profile of Kollidon® SR matrices (figure 1)



Release rate of caffeine from Kollidon® SR matrices produced via single punch press (figure 2)



Release rate of caffeine from Kollidon® SR matrices produced via rotary press (figure 3)

**Table 3: Powder properties of Kollidon® SR**

Bulk density	0.37 g/ml
Tap density	0.44 g/ml
Hausner ratio	1.13
Angle of repose	21.9°
Flow time	9.50 s
Medium particle size	appr. 100 µm

**Table 4: Tablet properties of Kollidon® SR matrices with varying tablet dimensions**

Parameter	10 mm	11 mm	12 mm
Compression force [kN]	18	18	18
Compression pressure [MPa]	229	189	159
Dev. tablet mass [%]	1.1	0.9	0.5
Hardness [N]	279	172	187
Friability [%]	0.03	0.02	0.02

**Table 5: Tablet properties using a single punch press**

[Tablets/min]	Drug amount [mg]	Mass [mg]	S <sub>rel</sub> [%]	Hardness [N]
10	159.2	323.0	1.0	221
20	158.5	321.9	0.9	218
30	158.6	322.6	0.8	199
40	158.7	322.6	0.7	198
50	159.9	324.5	0.6	215
55	159.4	324.1	0.5	217

**Table 6: Tablet properties using a rotary press**

Speed [rpm]	Drug amount [mg]	Mass [mg]	S <sub>rel</sub> [%]	Friability [%]	Hardness [N]
20	160.4	324.2	1.0	0.06	242
40	158.0	321.5	0.9	0.06	210
60	158.8	322.4	1.1	0.10	203
80	158.2	320.9	1.8	0.11	184

**› Results and Discussion**

The outstanding flow properties of Kollidon® SR are shown in table 3. The angle of repose was below 25° and the flow time of 150 ml powder through the funnel was fast and consistent.

The direct compression resulted in tablets with a high hardness and low friability (table 4). The hardness was reduced with increasing tablet dimension caused by the reduction of the compression pressure when keeping the compression force constant. According to the chemical composition and the adjusted particle size distribution, the dry binding capacity in combination with the flow properties can be regarded as additional benefits when using Kollidon® SR as a sustained release excipient.

Different dimensions of the tablets influenced the release rate only slightly due to the different surface areas as shown in figure 5. A sustained release of the water soluble drug caffeine was obtained over a period of more than 16 hours.

Due to the good flowability of the powder mixture no influence of the tableting speed could be observed when using a single punch press. The tablet hardness (> 200 N) and friability (0.02%) were excellent. The standard deviation of weight and drug content were below 1% as shown in table 5.

Again a diffusion controlled release of caffeine for a period of more than 16 hours was obtained. The different tableting speeds did not influence the release profile of the tablets.

The variation of rotation speed did not influence the release rate (figure 7) or the tablet weight and content uniformity when using a rotary press. However with increasing rotation speed the tablet hardness was reduced and the friability increased. But again the tablet hardness was considerably high (> 180 N).

**Conclusion**

› Kollidon® SR could be shown as a promising new excipient with good sustained release capacity, excellent flowability and dry binding properties.

› Therefore it is in particular suitable for direct compression of sustained release matrices.

# (+)-Pseudoephedrine

## A Potent and Well Tolerated Decongestant

H. Einig

### › Introduction

The common cold is not only a very unpleasant disorder for those affected; it is also one of the main causes of loss of working hours. Allergic rhinitis also poses a great problem today.

Therefore, nasal decongestants are being successfully used for colds with a congested or stuffy nose and for allergic reactions of the nose. They are either applied locally in the form of a solution or are increasingly administered as systemically acting agents.

At present, the main decongestants available for oral administration are as follows: Ephedrine, phenylpropanolamine, phenylephrine, and pseudoephedrine.

Recently it has been published that ( $\pm$ )-phenylpropanolamine (PPA) increases the incidence of stroke as a result of bleedings in the brain. Meanwhile the FDA requested manufacturers of pharmaceuticals containing PPA to take these products off the market or to replace PPA by another active ingredient. Accordingly (+)-pseudoephedrine got into the focus of attention as a potent and well tolerated decongestant.

### › Chemistry

(+)-Pseudoephedrine is one of the alkaloids occurring in the cultivated plant *Ephedra vulgaris*. BASF manufactures (+)-pseudoephedrine free of isomeric contaminants in a biotechnological process with the biocatalyst yeast and produces an active ingredient identical with that found naturally. BASF is the largest producer of (+)-pseudoephedrine in the world.

### › Pharmacology

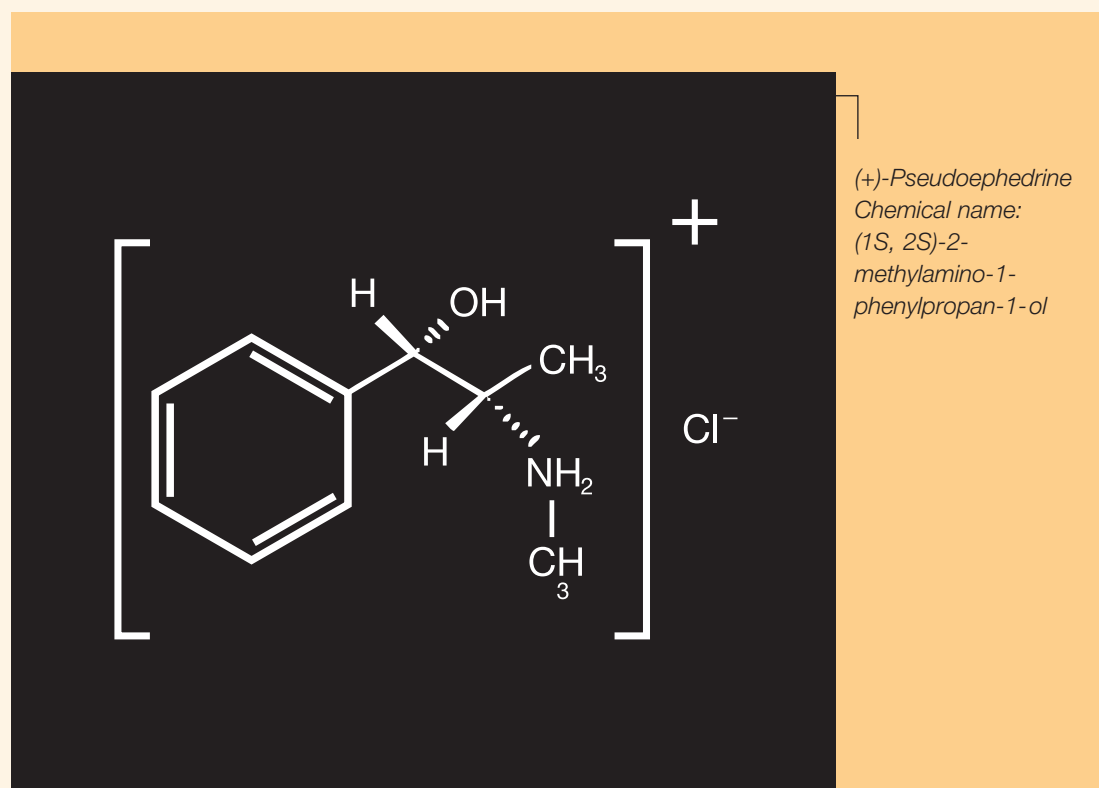
The oral decongestants are sympathomimetics and have the same structural elements as the chemically similar natural hormones adrenaline or noradrenaline. The decongestant effect on the nasal mucosa is based on the general vasoconstrictive properties of adrenergic substances. The  $\alpha$ -adrenergic receptors of the smooth vascular muscles in the nose are stimulated, the dilated arterioles of the mucosa are constricted, the flow of blood in the nasal mucosa is reduced and a contraction of the mucosa is induced. In this way, the nose becomes clear again (John F. Cormier and Bobby G. Bryant, Cold and Allergy Products, Handbook of Nonprescription Drugs, Am. Pharmac. Assoc., Washington 1973, page 73).

Sympathomimetics may activate  $\alpha$ -,  $\beta_1$ - and  $\beta_2$ -adrenergic receptors to a more or less considerable degree and thus have different effects and side effects depending on their chemical structure. For example, in the case of (-)-ephedrine, the decongestant effect on the nasal mucosa is very pronounced. However, (-)-ephedrine also has the pronounced effect of increasing blood pressure and has considerable effects on the central nervous system so that its use as a nasal decongestant is limited.

### › Tolerance of (+)-pseudoephedrine

In spite of the chemical similarity with other sympathomimetic decongestants, no increase in blood pressure was observed in clinically controlled double blind trials with (+)-pseudoephedrine involving simultaneous administration of a placebo in patients with controlled hypertension. Even in cases where toxic doses of up to 4,500 mg (+)-pseudoephedrine were ingested, no dramatic increase in blood pressure was observed.

The side effects of (+)-pseudoephedrine on the central nervous system are also considerably less pronounced than those of (-)-ephedrine or ( $\pm$ )-phenylpropanolamine. Such serious side effects as schizophrenia, mania, psychoses or suicide attempts, as reported for ( $\pm$ )-phenylpropanolamine, do not occur with pseudoephedrine. In placebo-controlled double blind trials, reports of side effects such as anorexia, anxiety or disorientation have been very rare and, apart from general difficulties in sleeping, were not statistically significant.



› Pharmacokinetics

The absorption of (+)-pseudoephedrine is nearly quantitative. The maximum plasma peaks can be reached within 0.5 to 2 hours. The substance is distributed in the extracellular space. The apparent distribution volume is between 3 and 5 l/kg. The elimination of (+)-pseudoephedrine is predominantly renal. The biological half-life of (+)-pseudoephedrine is approximately 6 hours whereas that of phenylephrine is approximately 2.5 hours. Therefore, to reach effective phenylephrine plasma levels a frequent and inconvenient administration is indicated.

› Dosages

The American FDA OTC Panel on Cold, Cough, Bronchodilator and Antihistaminic Products recommends the following doses as safe and effective (Category I) for pseudoephedrine:

	every 4 hours	maximum amount
Adults	60 mg	360 mg
Children 6-12 years	30 mg	180 mg
Children 2-6 years	15 mg	90 mg

› Therapeutic use

(+)-Pseudoephedrine is in most cases used as the salt in the form of the hydrochloride or sulfate. As a **monoproduct**, it is used in doses of about 10 to 60 mg as an instant release form usually in tablets. Slow release preparations with doses of 120 mg and 240 mg once or twice daily have recently been receiving considerable attention.

Most (+)-pseudoephedrine is used for **combination products**. However, instant release formulations used to treat common colds and allergic rhinitis predominate here.

Such combinatory active ingredients may be: Paracetamol, acetylsalicylic acid, ibuprofen, codeine, dextromethorphan, guaifenesin, diphenhydramine, chlorpheniramine, loratadine, terfenadine, etc.

› Pharmacopoeias, CoSs and DMFs

USP XXIII, EP Drug Master Files (DMF) and Certificates of Suitability (CoS) are available:

Sulfates:

AUS, B, D, F, GR, GB, FIN, IRL, I, NZ, NL, A, S, E, ZA, TR, DK and USA

Hydrochlorides:

AUS, DK, F, GB, IRL, I, NZ, NL, S, E, ZA, TR, CDN, USA and EU

› Physical properties

Compression behaviour

The compression behaviour of the 5 grades of (+)-pseudoephedrine hydrochloride was determined by producing pure active ingredient tablets containing 200 mg of pure substance. The resulting hardness of the specific tablet was determined at compression forces of about 12-16 kN. The higher the resulting hardness of a tablet at a constant compression force, the more suitable this grade is for direct compression. The results of the following table 1 show that, according to a cost-effective direct compression process, the grades "fine powder" and "powder 200" with the addition of suitable tableting ingredients such as Ludipress® are most suitable for the production of (+)-pseudoephedrine hydrochloride tablets.

(Punch parameters: Ø 9 mm; faceted and flat on both sides; filling quantity 200 mg)

Table 1: Compressibility of different grades of (+)-pseudoephedrine hydrochloride

	Fine powder	Powder 200	Coarse powder	Crystals 60/140	Crystals
Compression force as the mean from upper and lower punches	14.6 kN	13.9 kN	12.3 kN	16.3 kN	21.7 kN
Tablet hardness	34 N	24 N	14 N	7 N	9 N

Because of the extremely strong water sorption at high humidity, the containers always have to be tightly sealed as otherwise there will be considerable caking.

› Formulation examples

1. Tablet with 60 mg (+)-pseudoephedrine hydrochloride (granulation process)

Composition per tablet

(+)-Pseudoephedrine hydrochloride, fine powder	60.0 mg
Lactose monohydrate	30.0 mg
Avicel® PH 101	17.0 mg
Kollidon 30	5.0 mg
Kollidon® CL	7.0 mg
Magnesium stearate	0.5 mg
Aerosil® 200	0.5 mg

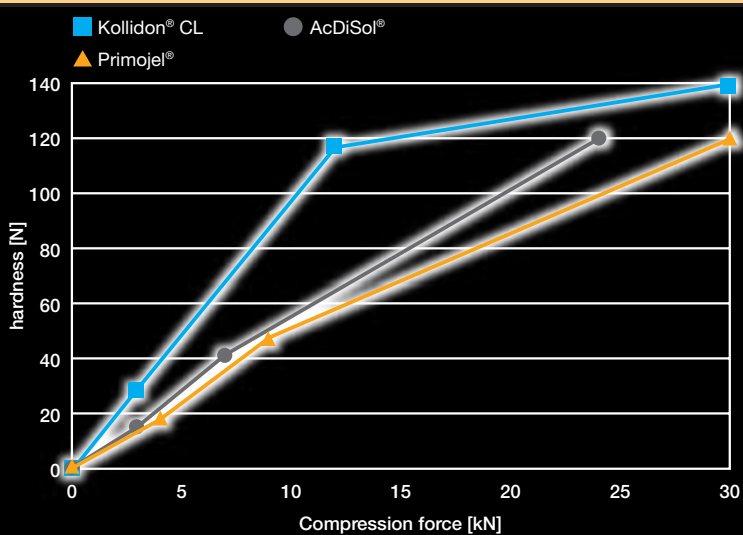
Batch size: 2.4 kg

1.2 kg (+)-pseudoephedrine HCl, fine powder, 0.60 kg lactose monohydrate, 0.340 kg Avicel® PH 101 and 0.10 kg Kollidon® 30 are vigorously mixed in a Stefan® granulator, subsequently thoroughly moistened with demineralized water until an earth-moist mass is obtained (snowball effect), stirred vigorously for a further 2 minutes and forced through a sieve of 3 mm mesh. The wet granules are dried in a fluid bed drier (laboratory drier of Glatt®, inlet air 60° C), homogenized through a sieve of 1 mm mesh and mixed into the granules ready for tableting with the additives 0.140 kg Kollidon® CL, 0.010 kg magnesium stearate and 0.010 kg Aerosil® 200.

Croscarmellose sodium, NF (AcDiSol®) and sodium carboxymethyl starch (Primojel®) were investigated as alternative disintegrants. Kollidon® CL led to distinctly higher hardnesses as demonstrated in the following diagram:

Tableting: Korsch® EK-0 excentric press

Weight	120 mg
Tablet punch	7 mm round
Compression force	10 kN
Hardness	90 N
Disintegration into 0.1 N HCl (37° C)	2 minutes
Release in vitro 0.1 N HCl (37° C) 50 rpm paddle app.	5 minutes: 85 % 10 minutes: 98 %



Compression force/hardness diagram on the basis of lactose/Avicel (figure 1)

2. Tablet with 60 mg (+)-pseudoephedrine hydrochloride (direct compression process)

Tabletting: Korsch® EK-0 excentric press  
 Tablet punch: 9 mm round

**Table 3: Compositions of the Ludipress® formulations (amount per tablet [mg])**

(+)-Pseudoephedrine hydrochloride, powder 200	60 mg
Ludipress®	138 mg
Magnesium stearate	1 mg
Aerosil® 200	1 mg
<b>Total</b>	<b>200 mg</b>

**Table 4: Pharmaceutical properties of the Ludipress® formulation at different compression forces**

Compression force	3.4 kN	8.9 kN	29.3 kN
Hardness of the tablet	20.4 N	80.6 N	98.9 N
Disintegration in water	6 min.	7 min.	8 min.
Release 10 min.	88.7 %	85 %	89.4 %
Release 20 min.	98.9 %	101.4 %	102.2 %

At request we will provide further formulation examples for (+)-pseudoephedrine salts especially in combination with other active ingredients.

Batch size: 3kg  
 All constituents of the above formulation are mixed in the specific ratio only in a dry form.



SEM photographs of (+)-pseudoephedrine hydrochloride (fine powder grade)



# Vitamins

## Broader product portfolio through Takeda vitamin acquisition

N. Maruyama

### › Introduction

At the beginning of this year BASF's and Takeda's vitamin businesses were combined under BASF's responsibility. This merger did not only substantially strengthen the product portfolio of water-soluble vitamins for food, but also to a large extent our range of speciality vitamin products for pharma: we can now supply vitamin C, B<sub>1</sub>, B<sub>6</sub> in direct compressible forms and B<sub>2</sub> and folic acid in a High Flow form. The agreement with Takeda does not only cover Takeda's vitamin products, patents & licenses and trademarks, but above all their staff, which contributes to our expertise in the pharma ingredients business. In a dedicated laboratory in Japan they are already working on technical services and improvements which will add value to your business. 2 former employees from Takeda Vitamin and Food in Japan have already started working in Germany and are reinforcing our human nutrition team in Ludwigshafen.

### › Products

Our water-soluble product line is now nearly complete and provides a large variety of specialities for individual solutions. And they are especially suitable for the pharmaceutical area. The vitamin C portfolio alone contains now more than 10 specialities, tailor made to suit the specific requirements of the pharma and food industry. There are direct compressible formulations and coated products, either ascorbic acid, sodium ascorbate or calcium ascorbate with 90, 97 or 99% activity. Not to the same large extent but still remarkable are our two other direct compressible (DC) products B<sub>1</sub> and B<sub>6</sub> as well as our two High Flow products B<sub>2</sub> and folic acid, which are first choice products if it comes to tableting.

### › Future

The merger was only a starting point for a much more complex programme of investment in modern plants to provide our customers efficiently and on a long-term basis with reliable products. We will reach this target through our commitment to quality, technical support and know how, our global presence and above all through our dedicated staff. One important step on the way to our target is to achieve world-wide cost leadership through the realisation of world scale effects and the sustained enhancement of our cost, sales and above all our customer service.

### › Takeda's DC product portfolio

With the increasing population, and growing economy and health awareness, the vitamin supplement market is expected to continue to grow at a rate of more than 4.0% a year. The world population is expected to grow at a rate of 1.1% a year until 2015 according to the World Health Organisation. The population aged 65 and above will increase from 6.9% in 1998 to 7.9% in 2015. This will result in a higher medical care cost, especially in developed countries. Governments will try to cut on expenditure, resulting in a focus on preventive medicine and self medication, which will then lead to increased interest in vitamins. Due to these circumstances plus economic growth, the overall vitamin C demand has increased more than 1.3 times as much as per-capita GDP (PPP) growth world-wide from 1990 to 1998, and this trend is expected to continue.

The positive trends of preventive medicine and self medication will contribute to substantial growth of the dietary supplement market. The introduction of the Dietary Supplement Health and Education Act (DSHEA) in the USA in 1994 led to the classification of Dietary Supplement and to a liberalisation for the approval of new products, especially tablets, since a tablet is the most common form for dietary supplement. In EU member states and Japan, a classification similar to Dietary Supplement in USA is being discussed. If a similar classification is introduced in other countries, the demand for vitamin tablets will increase.

Direct Compressible (DC) products are the perfect solution to produce high-quality tablets. The material for the tableting must possess the following properties:

- Free-flowing
- Good cohesiveness
- Proper bulk density

The conventional method requires a separate granulation process to give the three properties to the materials. The DC method, on the other hand, by utilising new types of active ingredients, binders and fillers that have the required properties, does not require a granulation step. With DC products, we just need to mix active ingredients and additives, and then compress to make tablets.

*With the DC method, we can expect the following advantages:*

#### - Shortening of operating time

The only steps involved are mixing and compressing. Granulation and drying steps are not necessary and therefore the tablet processing time is considerably shorter than with the conventional method.

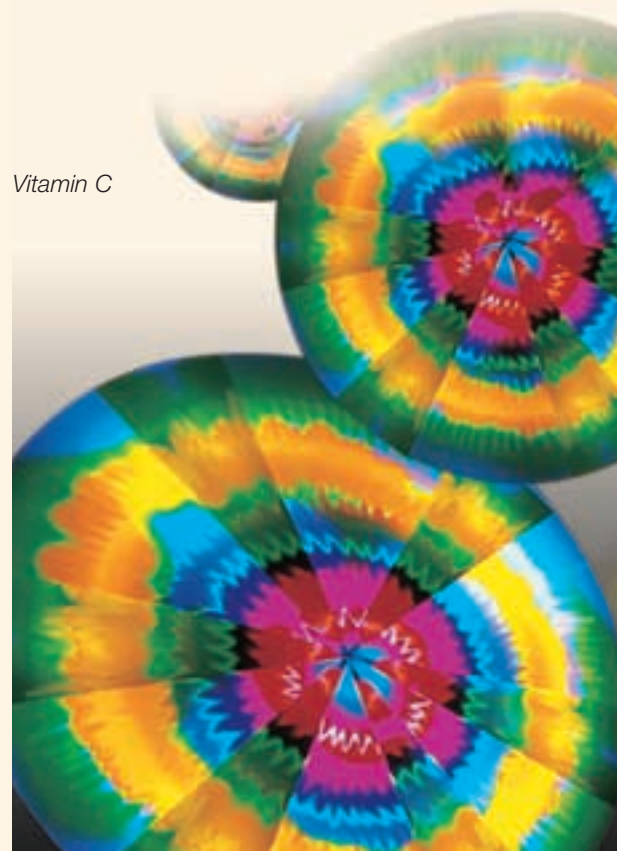
#### - Reduction of labor cost and energy cost

Short processing time is not the only factor for economical operation. DC saves cost by not requiring granulation equipment, man power for granulation, energy for granulation and drying, and space requirements for the granulation and drying process. All contribute to an economical tableting operation.

#### - Efficient quality control

The simple process makes it easier to acquire GMP certification. The lot-to-lot uniformity of finished products is excellent. DC is a completely dry process, therefore, there is no negative influence by water and heat to vitamin stability from the granulation. As a consequence, the tablets which are made by DC have better stability in both content and color. In general, less overage is necessary to compensate for loss compared to wet granulation.

Vitamin C



**- Simplification of equipment**

The process does not use organic solvents, whereas the wet-granulation method sometimes needs organic solvents when making granules. DC is also environmentally friendly.

*However, there are limitations to DC methods:*

- The number of additives and active ingredients for DC are limited.
- DC grade active ingredients and additives are granules and, therefore, low dosages of active ingredients must be considered carefully. The active is not “locked” into granules. DC mixtures are subject to separation in subsequent processing steps.
- Some of the DC grade additives are not available in certain countries.

BASF now has the following DC product range supplied by Takeda to meet various needs of pharmaceutical and dietary supplement industries (see tables on the right).

There are a total of five DC products in the vitamin C group: three with ascorbic acid as the active ingredient, one with sodium ascorbate and one with calcium ascorbate. C-97 has excellent colour stability, and is recommended for straight vitamin C tablets. C-97 SF has good compressibility and can be used for “sugar and starch free” formulations because it does not contain starch or sugar.

**Vitamin C**

<b>C-97</b>	<b>97 % ascorbic acid and 3 % corn starch</b>
<b>C-97 SF</b>	<b>97 % ascorbic acid and 3 % hydroxypropyl methylcellulose</b>
<b>TC-90</b>	<b>90 % ascorbic acid and 10 % corn starch</b>
<b>SA-99</b>	<b>99 % sodium ascorbate and 1 % corn starch</b>
<b>C-Cal-97</b>	<b>97 % calcium ascorbate, 3 % hydroxypropyl methylcellulose, and 0.1 % tartaric acid</b>

SA-99 can be used as a sodium ascorbate source for formulations such as chewable C tablets. The combination of SA-99 and C-97 result in excellent chewable vitamin C tablets. C-Cal-97 can be used as a calcium ascorbate source and to manufacture low-acidity products without excess sodium.

For B vitamins, we have two DC grade vitamin B<sub>1</sub>s and one DC grade vitamin B<sub>6</sub>. In addition, we have other B vitamins that can be used for dietary supplements along with DC products. They are riboflavin High Flow 95 and Folic Acid High Flow. These are high flow products with good flowability.

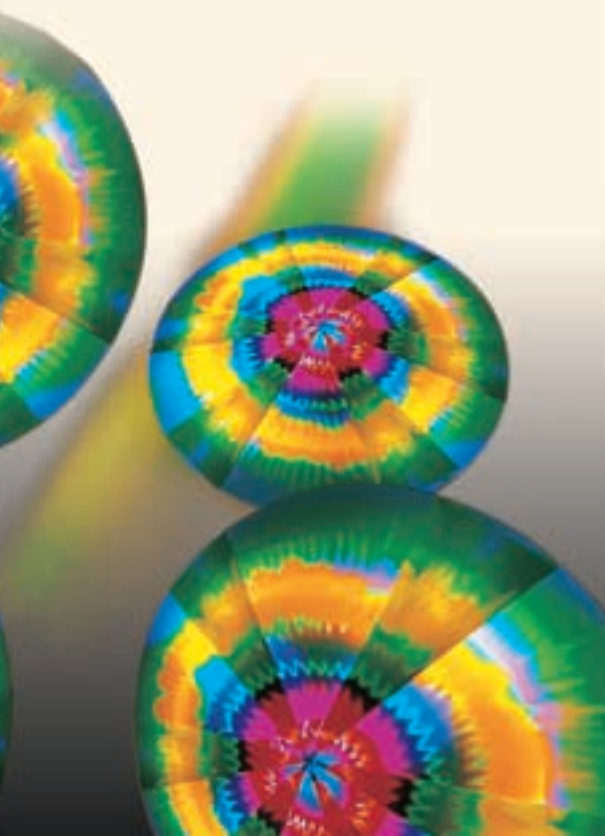
BASF can now supply a large variety of specialities to meet the various needs of pharmaceutical and dietary supplement industries. We can play a leadership role in the dietary supplement industry by offering solutions to ever growing health awareness and self-medication trends.

**Vitamin B<sub>1</sub>**

<b>TH-97</b>	<b>97 % thiamine hydrochloride and 3 % hydroxypropyl methylcellulose</b>
<b>TM-97</b>	<b>97 % thiamine mononitrate and 3 % hydroxypropyl methylcellulose</b>

**Vitamin B<sub>6</sub>**

<b>B6-97</b>	<b>97 % pyridoxine hydrochloride and 3 % hydroxypropyl methylcellulose</b>
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# Technical Marketing Services

## In the European Region

In the European Region the Technical Marketing Services have been re-organised to provide BASF customers with a direct contact person who will coordinate all customer support and all technical activities. The Technical Marketing Service will be prepared to discuss specific applications and projects using BASF Pharma Ingredients relating to customer needs.

### *The contact persons are:*

Mrs Maureen Mistry, based in Ballerup, Denmark. She is responsible for Scandinavia, UK, Ireland, Poland and the Netherlands.  
(tel: 0045 44 73 0166; fax: 0045 44 73 0102)

Mr Vincent Bettevy, located in France. He is responsible for France, Belgium, Spain and Portugal.  
(tel: 0033 1 49 64 5687; fax: 0033 1 49 64 5622)

Dr. Michael Black, situated at BASF AG in Ludwigshafen. He is responsible for Germany, Switzerland, Austria, Hungary, Italy and Greece.  
(tel: 0049 621 60 94830; fax: 0049 621 60 94789).



From the right side: Mr Vincent Bettevy, Mrs Maureen Mistry, and Dr. Michael Black

## News

### Caffeine

**“Association of coffee and caffeine intake with the risk of Parkinson disease”**

In May 2000 the above mentioned study was published in the Journal of the American Medical Association. Here are the important conclusions:

#### *Participants*

Data was analysed from 30 years of follow up of 8004 Japanese-American men (age 45-68 years) enrolled in the prospective longitudinal Honolulu Heart Program between 1965 and 1968.

#### *Context*

The projected expansion of the elderly population at highest risk for Parkinson disease (PD) in the next several decades makes identification of factors that promote or prevent the disease an important goal.

#### *Objective*

To explore the association of coffee and dietary caffeine intake with risk of PD.

See also the latest publishing “Study points to potential role for Caffeine in reducing the risk of Parkinson’s Disease” made by the Massachusetts General Hospital, USA under [www.massgeneral.org/DEPTS/pubaffairs/releases/050401parkinsons.htm](http://www.massgeneral.org/DEPTS/pubaffairs/releases/050401parkinsons.htm)

#### **Conclusion**

› Our findings indicate that higher coffee and caffeine intake is associated with a significantly lower incidence of PD. This effect appears to be independent of smoking. The data suggest that the mechanism **is related to caffeine intake and not to other nutrients contained in coffee.**

# News

## Caffeine

“Do caffeine-containing analgesics promote dependence?”

Another interesting conclusion was found during an expert review in January 2000. We believe that this information is of interest for those pharma customers which are using caffeine in analgesic combinations or intend to develop a new formulation.

### Participants

International scientists were jointly selected by the regulatory authorities of Germany, Switzerland and Austria and the pharmaceutical industry to meet in New York.

### Objective

Debates about the suspected association between renal disease and use of analgesics led to the question whether caffeine could stimulate an undesirable overuse of phenacetin-free combined analgesics. A committee was asked to critically review the pertinent literature in order to guide clinical practice and contribute to considerations of regulatory authorities.

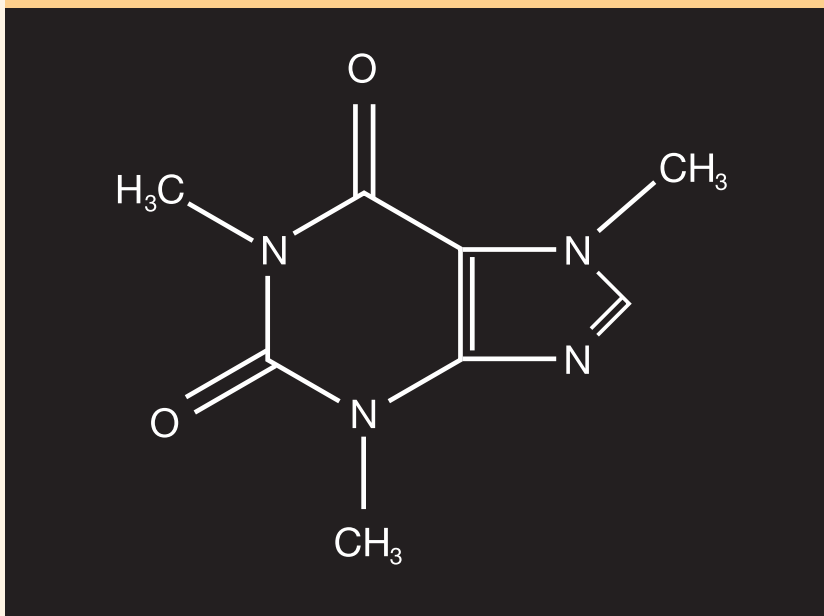
### Evidence

Published literature relevant to the subject was sent to all invited experts, who added further research.

### Conclusion

Although more experimental and longterm data on mechanisms of dependence would be desirable, the committee concluded that the available evidence **does not support the claim that analgesics coformulated with caffeine**, in absence of phenacetin, stimulate or sustain overuse.

We have the complete studies in our files and are prepared to mail them to you.



Caffeine



Equipment of the caffeine production in Minden, Germany.

## Preview

### Masking of unpleasantly tasting active ingredients

Launched as a film-forming polymer based on polyvinyl acetate for sustained-release coating, the properties of Kollicoat® SR 30 D are not completely highlighted. The combination with water-soluble excipients or at least a component that swells after being contacted with water make Kollicoat® SR 30 D a versatile excipient for taste-masking purposes: Integer coating combined with the fast release of the active ingredient.

ExAct No. 7 will inform you about the suitability of Kollicoat® SR 30 D in different formulations to cope with unpleasantly tasting actives or excipients.

For any information in advance please contact your local BASF office or our regional centres.

## Contact

Please contact your local BASF company or one of the following regional centres:

### Asia

#### **BASF Asia Pacific Regional HQ Pharma Solutions**

Dr. Danilo Mercado  
BASF South East Asia Pte Ltd  
9/F., Suntec Tower Three  
7 Temasek Boulevard  
**Singapore**  
Fax: \*\*65 / 4 30 98 12

### Europe

#### **BASF Aktiengesellschaft**

LN/FP – J 550  
Mr. Peter Hoffmann  
D-67056 Ludwigshafen  
**Germany**  
Fax: \*\*49 / 6 21 60 - 2 26 27

### NAFTA

#### **BASF Corporation**

Pharma Solutions  
Mr. Charles Dods  
3000 Continental Drive-North  
Mount Olive, NJ 07828-1234  
**USA**  
Fax: \*\*1 / 97 34 26 53 55

### South America

#### **BASF S.A.**

Human Fine Chemicals  
Mr. Claudio Lehmann  
Estrada Samuel Aizemberg, 1707  
09851-550 São Bernardo do Campo - SP  
**Brazil**  
Fax: \*\*55 / 11 43 43 22 55  
Phone: \*\*55 / 11 43 43 22 84

### Eastern Europe/Africa/West Asia

#### **BASF Aktiengesellschaft**

LRM/M – D 205  
Mr. Rolf Hanssen  
D-67056 Ludwigshafen  
**Germany**  
Fax: \*\*49 / 6 21 60 - 4 46 89

Or visit our website:  
<http://www.basf.de/pharma>

## News

### Kollicoat® SR 30 D

In previous editions we reported about Kollicoat® SR 30 D, a new aqueous polyvinyl acetate dispersion for sustained release film coating. In 2000 a USA-DMF has been submitted. The DMF no. is 15055.

## New Media

### CD-ROM "ExAct"

In November 1998 we published the first edition of ExAct. The number of readers is continuously growing. We often receive requests concerning previous ExAct editions. For this reason we are now offering the editions 1-6 on a CD-ROM that can be ordered with the attached reply card.

