Dear Reader,

High throughput screening in the development of new drugs leads to compounds with higher molecular weight and mostly poor water solubility. The latest developments in the pharmaceutical industry show that a dramatic 41% of New Chemical Entity developments fail due to poor bio-pharmaceutical properties.

Solutol® HS 15, a solubilizer developed by BASF, meets the requirements of an effective modern solubilizer and is approved for parenteral applications. It has just been monographed in the European Pharmacopoeia under the monograph name “Macrogol 15 hydroxystearate”.

Besides the outstanding toxicological characteristics like a low histamine release compared to other solubilizers also the good solubilizing capacity and the possibility to sterilize solutions with Solutol® HS 15 make it an expicient of choice for your formulation development. An article in this issue of ExAct is addressing some practical aspects for the production of solubilizes with Solutol® HS 15.

Yours sincerely,

BASF Aktiengesellschaft
Strategic Marketing
Pharma Excipients

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Dr. Thorsten Schmeller
Kollicoat® SR 30 D

Coated drug delivery systems.
K. Kolter, S. Gebert

Introduction
Sustained release dosage forms include single-unit and multiple-unit forms as well as coated forms and matrix forms [1]. Up to now, with the exception of the OROS System [2], the production of coated single-unit forms has been regarded as a malpractice, as the risk of dose dumping due to an incorrectly applied coating, or damage to a coating was too high. The OROS System is used in several products that are available on the market, but it has major disadvantages, such as the tricky operation of laser drilling, the use of organic solvents, high cost, and a low concentration of the drug in the core.

Objective
The aim of this project was to develop a coated, sustained release single-unit form that is simple to manufacture and poses no risk of dose dumping.

Experimental
Materials
Kollicoat® SR 30 D (polyvinyl acetate dispersion, BASF Aktiengesellschaft), metoprolol tartrate (Moehn S. A.).

Methods
Metoprolol tartrate was granulated with Kollidon® 30 solution, mixed with the other excipients for 10 minutes in a Turbula mixer, and compressed into tablets on a Korsch PH 106.
Tablet cores in batches of 5.0 kg were spray-coated with a pigmented Kollicoat® SR 30 D dispersion in a 24” Accela Cota.

Mechanical testing of the tablets
The film-coated tablets were subjected to a friability test (500 revolutions, drop height 15.5 cm) in an Erweka Friabilator, allowed to fall 20 times from a height of 1.5 m, and pricked with a needle.

Results and Discussion
From theoretical considerations, it is clear that a controlled release coating on a tablet must possess a high degree of flexibility, to ensure that any swelling of the core – whether in storage or during drug release – does not crack the film. It was found in tests on isolated films that polyvinyl acetate (Kollicoat® SR 30 D) has far greater elasticity than ethyl cellulose or ammonio methacrylate copolymer.

The permeability of the film coating can be adjusted by adding water-soluble or water-swellable substances, polymers if possible. As is to be expected, the release rate slows with increasing thickness of the coating. The release curve is S-shaped, as, initially, water has to penetrate the coating and enter the core in order to at least partially dissolve the drug substance before this can diffuse out through the coating. The time lag between first contact with water and drug release also depends on the thickness of the coating and the quantity of water-soluble excipients.

The coated tablets were subjected to strong mechanical stress.
Neither a friability test (500 revolutions, 15.5 cm drop height) nor 20 drops from a height of 1.5 m had any noticeable effect on the release characteristics. Surprisingly, the film-coated tablets can even be pricked with a needle without affecting drug release. Kollidon® SR possesses enormous plasticity that ensures that small holes are self-sealing, particularly when the tablet is introduced into an aqueous medium. As a result, such coatings have a previously unknown self-repair mechanism.

**References**


**Conclusions**

- Film coatings based on Kollicoat® SR 30 D are very resistant to mechanical stress and possess a self-repair mechanism.
- The release rate can be adjusted by using water-soluble polymers and by varying the coating thickness.
- Film coatings based on Kollicoat® SR 30 D allow the simple manufacture of coated controlled release single-unit forms without the risk of dose dumping.

**Drug release of metoprolol tablets as a function of coating thickness** (Figure 2)

- cores
- 4 mg/cm² coating
- 6 mg/cm² coating
- 8 mg/cm² coating
- 10 mg/cm² coating

**Influence of mechanical stress on drug release of metoprolol tablets** (Figure 3)

- punctured
- friability test
- untreated
Kollicoat® MAE 100 P
A redisperisible powder of methacrylic acid copolymer type C.
S. Scheiffele, H. Ascherl, F. Ruchatz, K. Kolter

Introduction
Kollicoat® MAE 100 P is a non-dusting redisperisible powder grade of Kollicoat® MAE 30 DP (methacrylic acid copolymer type C) for enteric coating. It is not necessary to add NaOH to redisperse this product, since it is already partly neutralized.

Purpose
The objective of this study was to investigate the enteric coating properties of the product and to compare them with those of the dispersion.

Methods
Materials
Methacrylic acid ethyl acrylate copolymer (Kollicoat® MAE 30 DP; Kollicoat® MAE 100 P); Sicovit® Red 30; titanium dioxide; propylene glycol, BASF Aktiengesellschaft; talc, Riedel de Häen; triethyl citrate, Merck.

Apparatus
Accela Cota 24" (Manesty Machines Ltd.), dissolution apparatus (PTW-S, Pharmatest Apparatebau), straight-arm paddle agitator.

Composition and preparation of propranolol-HCl cores
Propranolol-HCl 40 mg (Knoll Aktiengesellschaft), Ludipress® 97.5 mg (BASF Aktiengesellschaft), Avicel PH 102 97.5 mg (FMC), Kollidon® VA 64 12.5 mg (BASF Aktiengesellschaft), magnesium stearate 2.5 mg (Bärlocher).
The ingredients of the formulation were mixed in a Diosna mixer and compressed with a force of 15 kN into cores with the following parameters: 9 mm diameter, 12 mm radius of curvature, 250 mg weight.

Composition and preparation of the spray dispersion

Polymer dispersion
Kollicoat® MAE 30 DP: Propylene glycol or triethyl citrate was mixed with water and then Kollicoat® MAE 30 DP was added under stirring.
Kollicoat® MAE 100 P: The powder was introduced into the water with stirring. After redispersal was complete (about 3 h) the plasticizer was stirred in.

Spray suspension (Table 1)
The pigment dispersion was mixed under stirring into the polymer dispersion.

Results
S. Scheiffele, H. Ascherl, F. Ruchatz, K. Kolter

Coating process (table 2)
Test on stirring-in behavior of Kollicoat® MAE 100 P and determination of viscosity
9 kg Kollicoat® MAE 100 P (= 20% (w/w) dispersion) were stirred into 36 kg water with immediate wetting of the powder. The stirrer torque and the viscosity were determined over a period of 3 h.

Determination of dissolution
According to USP 23, apparatus 2, method B using 0.1 N HCl and phosphate buffer 6.8. Propranolol-HCl was determined spectrophotometrically at 289 nm.

Conclusions
Kollicoat® MAE 100 P is a flowable non-dusting powder that can be incorporated rapidly and without problems with stirring. Immediate wetting of the powder should be ensured. During redispersion of the powder, the viscosity increased to 100 mPas in 5 minutes. This is because the particles swell, producing an intermediate viscous phase on the surface, which causes friction between the particles. The viscosity decreased to 30 mPas upon further stirring beyond 150
minutes. No problems occurred when preparing the spray suspensions from the redispersible powder with or without pigments, or in the coating process.

Spraying process
No modification of process parameters was necessary for application of the spray suspension of Kollicoat® MAE 30 DP and Kollicoat® MAE 100 P. The spraying behavior was identical for both products.

Dissolution
At a coating weight of 6 mg/cm$^2$ polymer, propranolol-HCl-tablets exhibited a dissolution rate of < 1% after 2 h in 0.1 N HCl. In phosphate buffer pH 6.8 more than 90% dissolved after 30 minutes. The application of Kollicoat® MAE 30 DP resulted in similar dissolution characteristics. Visual inspections of all tablets after the acidic treatment showed that no swelling or other defects occurred. Even a reduced coating level of 4 mg/cm$^2$ (3.9% after 2 h) easily fulfilled the requirements of the USP (< 10% drug dissolution). The dissolution rate in buffer pH 6.8 increases with decreasing coating level. Even with a high coating level of 12 mg/cm$^2$ more than 80% was released after 30 minutes. A coating of the same weight without pigments gave slightly higher dissolution rates in the acidic medium (2.4 % after 2 h).

Conclusions
There was no difference in the gastric resistance and drug dissolution rate of Kollicoat® MAE 30 DP (dispersion) and Kollicoat® MAE 100 P (powder). In order to minimize the viscosity of a 20% suspension of Kollicoat® MAE 100 P it should be stirred for at least 3 h.
Kollidon® SR

Compression behavior.
K. Kolter

Introduction
Sustained release matrix formulations are gaining increasing importance because of their low manufacturing costs. Kollidon® SR is a relatively new matrix retarding agent consisting of 80% polyvinyl acetate and 20% polyvinylpyrrolidone [1]. With its excellent flowability, this formulated combination allows sustained release dosage forms to be manufactured by the simple direct compression tabletting technique. Although tablet formulations are known to be easily producible with Kollidon® SR, no detailed studies have yet been performed on the behaviour of Kollidon® SR during tabletting.

Objective
This study was undertaken to characterize the compression behaviour of pure Kollidon® SR, correlate the results with the tablet properties and examine the influence of admixed drug substance.

Experimental Methods
Materials
Kollidon® SR (polyvinyl acetate – polyvinylpyrrolidone, BASF Aktiengesellschaft), caffeine 0.2–0.5 (BASF Aktiengesellschaft).

Methods
All starting materials were blended for 10 minutes in a Turbula mixer and compressed into flat tablets with a diameter of 10 mm on a Korsch EKO instrumented tablet press. The compression force was varied between 5 and 25 kN. The tabletting rate was 30 tablets/minute. The compression data were evaluated using a BASF in-house software program which calculates the parameters listed in tables 1 and 3.

Plasticity (%)
plastic energy/total energy x 100.

Elastic relaxation
tablet thickness without load – tablet thickness under load.

K-value (compression resistance)
\[ \frac{\Delta \log p}{\Delta \log q} \]
where p is the compression pressure, and q is the apparent density.

Results and Discussion
Compression of pure Kollidon® SR produced tablets of exceptional hardness. A compression force of only 4.8 kN already gave a hardness value of 250 N, which increased to more than 500 N at compression forces of 9.7 kN and above. The values could not be measured since they exceeded the limit of the measuring range of the hardness tester. These enormous strengths were due to the plastic behavior of polyvinyl acetate which softens at increasing temperatures – occurring locally during the tabletting process – and becomes easily deformable under pressure. This creates extremely strong bonds between the particles. The hollow conical structure of Kollidon® SR further enhances the plastic deformability and makes the particles easy to compress. No overcompression effects were observed up to a compression force of 25 kN or 320 MPa, since the strength was always above

Table 1: Tablet formulations

<table>
<thead>
<tr>
<th></th>
<th>K-SR tablets</th>
<th>K-SR/caffeine tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kollidon® SR</td>
<td>323.4 mg</td>
<td>160.0 mg</td>
</tr>
<tr>
<td>Caffeine</td>
<td></td>
<td>160.0 mg</td>
</tr>
<tr>
<td>Aerosil 200</td>
<td>1.6 mg</td>
<td>3.5 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.5 mg</td>
<td></td>
</tr>
<tr>
<td>Tablet weight</td>
<td>325.0 mg</td>
<td>325.0 mg</td>
</tr>
</tbody>
</table>

Table 2: Compression data of caffeine tablets (Kollidon® SR/caffeine 1:1)

<table>
<thead>
<tr>
<th></th>
<th>9.9 kN</th>
<th>17.2 kN</th>
<th>25.0 kN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hardness [N]</td>
<td>185</td>
<td>235</td>
<td>270</td>
</tr>
<tr>
<td>Friability [%]</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ejection force [kN]</td>
<td>0.17</td>
<td>0.13</td>
<td>0.12</td>
</tr>
<tr>
<td>Residual force [kN]</td>
<td>0.09</td>
<td>0.08</td>
<td>0.04</td>
</tr>
<tr>
<td>Energy of compression [J/g]</td>
<td>29.3</td>
<td>33.4</td>
<td>26.5</td>
</tr>
<tr>
<td>Plasticity [%]</td>
<td>95.8</td>
<td>95.7</td>
<td>70.5</td>
</tr>
<tr>
<td>Tablet thickness under load [mm]</td>
<td>3.82</td>
<td>3.80</td>
<td>3.32</td>
</tr>
<tr>
<td>Relaxation in die [%]</td>
<td>0.28</td>
<td>0.42</td>
<td>0.56</td>
</tr>
<tr>
<td>Porosity under load [%]</td>
<td>33.3</td>
<td>38.1</td>
<td>24.9</td>
</tr>
<tr>
<td>K-value</td>
<td>4.7</td>
<td>4.6</td>
<td>5.6</td>
</tr>
<tr>
<td>Heckel constant (1/MPa)</td>
<td>0.0030</td>
<td>0.0023</td>
<td>0.0019</td>
</tr>
<tr>
<td>Heckel A-value</td>
<td>0.0009</td>
<td>0.0005</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Table 3: Compression data of Kollidon® SR

<table>
<thead>
<tr>
<th></th>
<th>4.8 kN</th>
<th>9.7 kN</th>
<th>14.4 kN</th>
<th>17.7 kN</th>
<th>25.0 kN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hardness [N]</td>
<td>280</td>
<td>&gt; 500</td>
<td>&gt; 500</td>
<td>&gt; 500</td>
<td>&gt; 500</td>
</tr>
<tr>
<td>Friability [%]</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ejection force [kN]</td>
<td>0.19</td>
<td>0.04</td>
<td>0.03</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Residual force [kN]</td>
<td>0.05</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Energy of compression [J/g]</td>
<td>23.1</td>
<td>33.7</td>
<td>37.6</td>
<td>39.1</td>
<td>41.3</td>
</tr>
<tr>
<td>Plasticity [%]</td>
<td>96.6</td>
<td>96.7</td>
<td>96.9</td>
<td>97.1</td>
<td>71.2</td>
</tr>
<tr>
<td>Tablet thickness under load [mm]</td>
<td>4.41</td>
<td>3.78</td>
<td>3.07</td>
<td>3.46</td>
<td>3.31</td>
</tr>
<tr>
<td>Relaxation in die (mm) [%]</td>
<td>0.24</td>
<td>0.32</td>
<td>0.45</td>
<td>0.56</td>
<td>0.60</td>
</tr>
<tr>
<td>Porosity under load [%]</td>
<td>5.5</td>
<td>8.2</td>
<td>12.7</td>
<td>14.3</td>
<td>19.8</td>
</tr>
<tr>
<td>K-value</td>
<td>7.3</td>
<td>12.0</td>
<td>19.0</td>
<td>13.2</td>
<td>19.6</td>
</tr>
<tr>
<td>Kollidon® SR</td>
<td>41.1</td>
<td>25.1</td>
<td>24.6</td>
<td>24.1</td>
<td>24.2</td>
</tr>
<tr>
<td>Kollidon® SR/caffeine tablets</td>
<td>2.3</td>
<td>4.1</td>
<td>5.7</td>
<td>6.3</td>
<td>6.3</td>
</tr>
<tr>
<td>Heckel constant (1/MPa)</td>
<td>0.0059</td>
<td>0.0076</td>
<td>0.0090</td>
<td>0.0128</td>
<td>-</td>
</tr>
<tr>
<td>Heckel A-value</td>
<td>0.1684</td>
<td>0.1871</td>
<td>0.1928</td>
<td>0.1560</td>
<td>-</td>
</tr>
</tbody>
</table>

Heckel constant [1/MPa] = \[ \frac{\Delta \log p}{\Delta \log q} \]

Heckel A-value = \[ \frac{A}{B} \]

where A and B are constants specific to the tablet and the compaction process.
500 N and no friability was present. The admixture of caffeine, as expected, reduced the strength to values between 185 and 270 N. The easy deformability of Kollidon® SR is also manifested in the marked decrease in porosity of the tablets at low compression forces, and the negligible change in porosity at moderate and high compression forces. The porosity without load no longer changed from about 10 kN onwards, while the porosity under load still showed a certain decrease. In contrast, the K-value increased from a very low initial level.

The plasticity of Kollidon® SR decreases markedly with rising compression force. This result also illustrates that Kollidon® SR is highly deformed even by slight pressure, but the elastic component increases considerably at higher pressures. This increase in the elastic component of the energy is associated with a greater elastic relaxation of the tablet in the matrix when the upper punch returns upwards and the compression force decreases (0.24 mm at 4.8 kN and 0.65 mm at 25 kN). Surprisingly, these considerable elastic relaxations have no influence at all on the strength of the tablet matrix.

The addition of caffeine leads to lower plasticity values and lower elastic relaxations in the die. Surprising results were also measured for the ejection forces, since these values (0.10 to 0.02 kN) were at an extremely low level yet still continued decreasing as the compression force increased. The same applies for the residual force (0.05 to 0.00 kN). From this it can be concluded that Kollidon® SR does not adhere to the die and that the relaxation occurs rapidly and completely in the direction of die opening.

> **Conclusions**
> Kollidon® SR yields tablets of exceptional strength even at low compression forces. The ejection forces and residual forces are very low and, surprisingly, continue decreasing as the compression pressure increases. Porosity, plasticity, elastic relaxation and K-value show that Kollidon® SR is an extremely easy to compress substance. Admixture of caffeine reduces the strength, elastic relaxation and plasticity, but increases the porosity and also – slightly – the ejection force. Kollidon® SR exhibits almost ideal tabletting properties.

> **References**
Solutol® HS 15

Practical aspects for the production of solubilizates.
K. Kolter, F. Ruchatz

Introduction
An increasing number of drugs (especially new entities) show a poor water solubility causing serious formulation problems for injectables. This has created a strong demand for formulation aids to overcome the dissolution problems.

A simple and effective method to dissolve drugs is their solubilization using non-ionic surfactants. Among these surfactants, Solutol® HS 15 proved to have superior properties as a solubilizing agent because of its good physiological tolerance and high solubilizing capacity for a wide range of drugs. Solutol® HS 15 has been approved in parenteral formulations for human use in several markets.

Objective
The purpose of the study was to show some practical aspects of the production of micellar solutions with Solutol® HS 15. Two different formulation methods of solubilizates were investigated with respect to the dissolution kinetics of various model drugs. The maximum amount of drug load using different batches of Solutol® HS 15 was evaluated. The physiological tolerance of Solutol® HS 15 solubilizates was compared with polysorbate 80 (PS 80).

Materials and Methods
Preparation method
Method A (RT): 20% (w/w) Solutol® HS 15 was dissolved in phosphate buffer (PB) pH 7.0 (USP XXIII) at room temperature. An excess of drug was added at the same temperature under stirring. The dissolution kinetics of the dispersion were monitored for 7 days.

Method B (65°C): The drug was suspended in the molten solubilizer (20% w/w) under stirring at 65°C. Phosphate buffer (PB) pH 7.0 (USP XXIII) was added dropwise and the solutions were allowed to cool to room temperature under stirring.

Drugs
Clotrimazole, estradiol, sulfathiazole, nifedipine, riboflavin, carbamazepine, procainamid, acetaminophen and tocopherol acetate were used as model drugs.

Drug content
The dispersions were filtered through a 0.22 µm membrane resulting in clear/opalescent solutions. After diluting the solubilizates with a 1:1 mixture of methanol/PB, the amount of drug was measured using a photometer (Hewlett Packard).

Laser light scattering
The micelle diameters were measured at an angle of 90°, by means of a set up from ALV (Germany), equipped with a 400 mW Nd-Yag Laser at 532 nm and a correlator (ALV 5000). The time correlation function was recorded for 15 minutes and the hydrodynamic diameter was evaluated using a CONTIN software program.

Table 1: Comparison of micellar diameter and molecular weight [Mw] of solubilizates with different drugs and formulation methods

<table>
<thead>
<tr>
<th></th>
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<th></th>
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<th></th>
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<tbody>
<tr>
<td>Clotrimazole</td>
<td>12.7</td>
<td>13.0</td>
<td>206000</td>
<td>193400</td>
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<td>13.8</td>
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<td>13.0</td>
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<td>193400</td>
<td>13.6</td>
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<td>12.9</td>
<td>12.8</td>
<td>183400</td>
<td>179000</td>
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<td>13.8</td>
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<td>12.8</td>
<td>183400</td>
<td>179000</td>
<td>13.6</td>
<td>13.8</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>12.7</td>
<td>12.7</td>
<td>185700</td>
<td>165400</td>
<td>13.3</td>
<td>24.5</td>
</tr>
<tr>
<td>Tocopherol acetate</td>
<td>13.3</td>
<td>24.5</td>
<td>202000</td>
<td>1445700</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Influence of the production method on the maximum amount of solubilized drug after 7 days and on the kinematic viscosity of the solubilizates

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug amount [%]</th>
<th>Diss. Enhance. Factor</th>
<th>Kinematic Viscosity [mPas]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clotrimazole</td>
<td>0.27</td>
<td>0.28</td>
<td>270</td>
</tr>
<tr>
<td>Estradiol</td>
<td>0.16</td>
<td>0.16</td>
<td>160</td>
</tr>
<tr>
<td>Sulfathiazole</td>
<td>0.59</td>
<td>0.60</td>
<td>10</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>0.33</td>
<td>0.25</td>
<td>330</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>0.36</td>
<td>0.36</td>
<td>36</td>
</tr>
<tr>
<td>Tocopherol acetate</td>
<td>&lt; 5%</td>
<td>7.3</td>
<td>290</td>
</tr>
</tbody>
</table>

Table 3: Haemolytic activity of human erythrocytes and serum histamine level in dogs after i.v. application

<table>
<thead>
<tr>
<th>Drug</th>
<th>Haemolytic activity [% Haemolysis]</th>
<th>Serum Histamine level [nM/l]</th>
</tr>
</thead>
<tbody>
<tr>
<td>HS 15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PS 80</td>
<td>0</td>
<td>&gt; 50000</td>
</tr>
</tbody>
</table>

Drug content
The dispersions were filtered through a 0.22 µm membrane resulting in clear/opalescent solutions. After diluting the solubilizates with a 1:1 mixture of methanol/PB, the amount of drug was measured using a photometer (Hewlett Packard).

Laser light scattering
The micelle diameters were measured at an angle of 90°, by means of a set up from ALV (Germany), equipped with a 400 mW Nd-Yag Laser at 532 nm and a correlator (ALV 5000). The time correlation function was recorded for 15 minutes and the hydrodynamic diameter was evaluated using a CONTIN software program.
Kinematic viscosity
The solutions were investigated at 25 °C using a capillary viscometer (Löbel and Höll, Germany), capillary No. 1.

Haemolytic activity
Different concentrations of the solubilizers were incubated with isolated human erythrocytes for 60 minutes. The degree of damage of the red blood cell membranes was quantified by spectrophotometry of released haemoglobin after centrifugation of the intact erythrocytes [1].

Blood histamine level in dogs
Solubilizes of Solutol® HS 15 and PS 80 in a concentration of 5 % in an aqueous solution of 10 % sorbitol were administered i.v. to beagle dogs (100 mg/kg). The blood histamine level was monitored by sampling the blood in intervals over a period of 60 minutes. The amount of released histamine was analyzed using an ELIZA test.

Results and Discussion
In all cases, with the exception of tocopherol acetate formulation produced at room temperature, clear micellar solutions with a low viscosity were obtained.

The comparison of the production methods revealed different dissolution kinetics for the drugs (figure 1). Using method B, the elevated temperature of 65 °C led to more or less supersaturated micellar drug solutions. However, the drug dissolution was finished after cooling to room temperature with the exception of piroxicam within 24 h, resulting in saturated micellar solutions. It can be expected that the manufacture of solubilizes with drug amounts below the saturation point is finished shortly after cooling to room temperature. The maximum drug load was reached in 6 of 8 cases at 24 h when preparing the solubilizes with method A.

Generally after a period of 24 h, the drug concentrations in the micellar solutions were equal using both methods with the exception of tocopherol acetate. It seems that there is no influence of the production method on important properties of the solubilizes. As can be seen in table 2 at a concentration of 20 % Solutol® HS 15, the water solubility of the different drugs could be enhanced by a factor of 10–100, depending on the structure of the drug molecule. The micelle diameter and the viscosity were consistent, regardless of the chemical structure of the drug or maximum amount of solubilized drug by using Solutol® HS 15 (table 1, 2).

The kinematic viscosity of the solubilizes was rather low. It can be concluded that it is easily possible to produce micellar solutions of drugs using different methods. The diffusion and dissolution of drugs in a micellar solution at room temperature takes place very quickly. For the handling of vitamins like tocopherol acetate the dispersion in the molten solubilizer is needed, because mixed micelles of vitamin/solubilizer are built.

As demonstrated in figure 2, different batches of Solutol® HS 15 showed the same solubilization capacity.

The results of the haemolytic study and the measurements of the histamine release after i.v. application, indicated a low toxicity of Solutol® HS 15 (table 3).

Conclusion
The production of micellar drug solutions with Solutol® HS 15 is very easy. Economically, method B is preferred but for thermosensitive drugs an alternative way of production exists. Solutol® HS 15 shows a low toxicity combined with a high solubilizing capacity. Thus it can be regarded as an excellent solubilizer for parenteral use.
News

A new multipurpose plant at Minden site.

BASF Fine Chemicals Division has recently decided to invest in a new plant in Minden. The new multipurpose plant entails the biggest investment ever made at Minden site. Building work started this summer and the plant will be operational by the end of 2004. Twelve active ingredients and two intermediates will be produced (toll-manufactured) for the pharmaceutical industry in this new plant. The Fine Chemicals Division has invested a double digit sum in this project. Twelve of the fourteen existing products are already produced in a multipurpose plant in Minden; two are manufactured in the pilot plants in Ludwigshafen. The two main reasons for construction of this plant are that the new plant will include state of the art technology and that it will lead to a much needed increase in capacity for the existing products. The Fine Chemicals Division intends to expand its contract manufacturing activities in order to produce more substances for the pharmaceutical industry. All products are manufactured under cGMP (current good manufacturing practice). In order to meet stringent cleanliness requirements, this plant will be almost hermetically sealed from the filling station of raw materials to the packing unit for finished substances. In this way contamination of the products will be avoided and employees will have absolutely no contact with the active ingredients. The plant has been built according to an “easy to clean” design because of frequent product turnarounds. Twelve employees are currently working in the multipurpose plant and the activities of the new plant will create six further jobs.
Solutol® HS 15 monographed in the European Pharmacopoeia.

In recent years problems caused by solubilizers in pharmaceutical development have become increasingly evident. In addition to toxicological problems, the solubilizing capacity of various solubilizers has also been the focus of research and development.

Solutol® HS 15, a solubilizer developed by BASF, meets the requirements of an effective modern solubilizer and is approved for parenteral applications. It has just been monographed in the European Pharmacopoeia under the monograph name “Macrogol 15 hydroxystearate”.

Beside the outstanding toxicological characteristics like a low histamine release compared to other solubilizers also the good solubilizing capacity and the possibility to sterilize solutions with Solutol® HS 15 without stability problems make it an interesting material for the pharmaceutical industry.

New Media

Edition 2003 now available.

Technical Information
In ExAct No. 10 we offered the first time the Technical Information “Products for the Food and Pharmaceutical Industry”.

It covers the main technical data on BASF vitamins, carotenoids and other nutritional ingredients for the pharmaceutical and food industries.

Now the 2003 edition of this Technical Information is available.

This book/CD ROM can be ordered with the attached reply card.
Preview

Sustained release floating systems based on Kollidon® SR.

Floating systems are particularly suitable when a drug is intended to exert its action locally in the stomach or is absorbed in the stomach or upper part of the small intestine. These systems prolong gastric and intestinal transit time and can thereby enhance bioavailability especially for drugs with an "absorption window". To date only few manufacturing techniques for floating systems are known, all of them very demanding.

ExAct No. 12 will include an article on a simple, low-cost process for the production of floating systems by direct tabletting using Kollidon® SR, a newly developed matrix sustained release excipient.

Calendar

8th to 10th December, 2003
CPHI China 2003
Shanghai, China

7th to 9th April, 2004
Eighth European Symposium on Controlled Drug Delivery
Noordwijk aan Zee, The Netherlands

21st to 23rd April, 2004
CPHI Japan 2004
Tokyo, Japan

29th May to 3rd June, 2004
2nd World Conference of the Board of Pharmaceutical Sciences, Pharmaceutical Sciences World Congress (PSWC 2004)
Kyoto, Japan

12th to 16th June, 2004
31st Annual Meeting & Exposition of the Controlled Release Society, Honolulu*, Hawaii, USA

4th to 9th September, 2004
World Congress of Pharmacy and Pharmaceutical Sciences, 64th Congress of FIP
New Orleans, USA

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