Dear reader,

You may have known ExAct for four years as a customer’s newsletter for people who are working in the pharmaceutical industry area.

In one of the last editions we reported on the re-organisation of our pharma active ingredients business within BASF. Our goal was to provide a whole range of tools from one source to the pharmaceutical industry. One tool was still missing, namely Contract Manufacturing.

BASF’s drug business was sold effective March 1st, 2001.

Major parts of the chemical infrastructure and manufacturing facilities for active ingredients were retained after divestiture of the pharma business. Also retained was the know-how and experience of 30 years process development and manufacturing of active ingredients. The pharmaceutical know-how combined with BASF’s strong chemical expertise will now be dedicated to contract manufacturing projects for pharmaceutical clients.

BASF is entering the contract manufacturing arena with an unequivocal, long-term and exclusive commitment to the pharmaceutical industry.

BASF’s contract manufacturing resources will not be diluted by activities for other industries.

Detailed information on this new service is given on page 7 within this ExAct edition.

Yours sincerely,

BASF Aktiengesellschaft
Marketing Contract Manufacturing

Wolfgang E. Falkenberg
An Advantageous Combination for Taste Masking: Kollicoat®

S. Scheiffele and K. Kolter

Purpose

For several reasons taste masking of active drugs in oral dosage forms is gaining increasing importance. To satisfy the different requirements of taste masking, new coating formulations based on the sustained release dispersion Kollicoat SR 30 D in combination with soluble and / or swellable polymers were developed [1,2].

Experimental Methods

Materials:
Kollicoat SR 30 D, Kollidon 30, Kollidon CL-M, Kollidon CL, Kollidon VA 64, propylene glycol [BASF Aktiengesellschaft], acetaminophen, ibuprofen DTP [Knoll], Avicel PH 102, 105 [Lehmann & Voss], Karion Instant [Merck], magnesium stearate [Bärlocher].

Apparatus:
Fluid bed coater [Aeromatic-Fielder], tablet press [Korsch EK0], dissolution tester [Pharmatest Apparatebau].

Spray suspension:
First the pore former (Avicel PH 105, Kollidon CL-M, Kollidon 30) is dissolved or suspended in the given amount of water. Then the plasticizer (triacetin, propylene glycol) is added. Finally the calculated amount of Kollicoat SR 30 D dispersion is carefully stirred in.

Table 1: Tablet formulation

<table>
<thead>
<tr>
<th>%</th>
<th>mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coated active</td>
<td>37.91</td>
</tr>
<tr>
<td>Karion Instant</td>
<td>28.44</td>
</tr>
<tr>
<td>Kollidon VA 64</td>
<td>9.00</td>
</tr>
<tr>
<td>Avicel PH 102</td>
<td>14.22</td>
</tr>
<tr>
<td>Kollidon CL</td>
<td>9.48</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.95</td>
</tr>
<tr>
<td>Total</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Table 2: Process parameter

<table>
<thead>
<tr>
<th></th>
<th>Ibuprofen</th>
<th>Acetaminophen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inlet air temperature</td>
<td>40 °C</td>
<td>60 °C</td>
</tr>
<tr>
<td>Outlet air temperature</td>
<td>20-22 °C</td>
<td>33-35 °C</td>
</tr>
<tr>
<td>Nozzle diameter</td>
<td>0.8 mm</td>
<td>0.8 mm</td>
</tr>
<tr>
<td>Air pressure</td>
<td>1.2 bar</td>
<td>1.2 bar</td>
</tr>
</tbody>
</table>

Table 3: Coating formulations

<table>
<thead>
<tr>
<th></th>
<th>Acetaminophen</th>
<th>Ibuprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>38.10</td>
<td>45.98</td>
</tr>
<tr>
<td>B</td>
<td>1.38</td>
<td>49.38</td>
</tr>
<tr>
<td>C</td>
<td>8.57</td>
<td>4.83</td>
</tr>
<tr>
<td>D</td>
<td>53.33</td>
<td>47.81</td>
</tr>
</tbody>
</table>

Coating process:
The coating was applied in a fluidized bed coater (Aeromatic Strea 1) on 0.3 kg granules or pellets (ibuprofen, acetaminophen).

Methods:
Taste and dissolution rates at different coating levels were determined.
Results and Discussion

Both the coating level and the content of soluble and/or swellable pore formers influence the dissolution rate of the granules and thus also the taste masking properties.

For a good taste masking effect it is essential to deliver only a small amount within the first few minutes, but after 30–60 minutes dissolution should be complete (> 80 %).

Figure 1 clearly demonstrates the correlation between the coating level (A) and dissolution rate. As expected, dissolution slows down as the coating level increases. A coating level of 5 % can already delay the dissolution compared to uncoated acetaminophen.

Figure 2 compares the dissolution rates of the coated granules with those of the tablet formulation. Coating levels of 5, 10 and 15 % are compared.

The correlation between dissolution rate and coating level is observed with both formulations. Delayed dissolution is also apparent for the tablet formulation compared to the granules. This indicates that the coating suffers no appreciable damage during the tableting process.

The content and type of water soluble and/or swellable pore formers has an impact on the dissolution rate.

Figure 3 shows the dissolution rates of taste masked granules containing Avicel PH 105 (C), Kollidon CL-M (D) and Kollidon 30 (B) as pore formers. Dissolution is more rapid with Kollidon CL-M than with the same content of Avicel PH 105.

The dissolution profiles of the tableted ibuprofen pellets show a marked correlation with the compression force. While a rapid dissolution profile is seen at low compression force, a delay is achieved by increasing the pressure.

Conclusions

- Excellent taste masking can be achieved with Kollicoat SR 30 D and addition of soluble and/or swellable pore formers.
- Due to the enormous flexibility of plasticized Kollicoat SR 30 D films coated granules or pellets can be compressed without damaging the film. This allows the manufacture of taste masked lozenges or chewing tablets.

References

Lycopene - an Update

K. Kraemer, S. Ohnesorg, B. Nowakowsky

BASF has recently expanded its carotenoid portfolio by launching LycoVit 10%, a microencapsulated lycopene formulation used for dietary supplements and LycoVit Dispersion 20%, an oily dispersion used for fortification of food and for dietary supplements. They contain 10% and 20% lycopene respectively and thus offer a higher potency than other products found in the market place. Find below an update on bioavailability, scientific research and recommended intake levels.

Introduction
Carotenoids confer fruits and vegetables their yellow and pink color. Figure 1 shows the chemical structures of important dietary carotenoids. A diet rich in carotenoids is associated with a number of health benefits including reduced risk of chronic diseases. Some carotenoids, in particular β-carotene, are an important source of vitamin A. Lycopene, a carotenoid without pro-vitamin A activity, found almost exclusively in tomatoes and tomato-based products and imparting their red coloration, has attracted special interest in recent years. Lycopene is, besides β-carotene and lutein, the most abundant carotenoid in human plasma. Consumption of tomatoes and tomato-based products is inversely associated with the risk of certain cancers, mainly cancers of the prostate or gastrointestinal tract, and cardiovascular disease risk. The epidemiological evidence of lycopene in disease prevention has been extensively reviewed by Giovannucci (1999) and Arab & Steck (2000). This synopsis is intended to give a brief update on recent findings further corroborating the beneficial properties of lycopene.

Cis- and trans-Isomers and Occurrence in Human Tissue
Dietary lycopene exists both in the cis- and trans-isomeric form. Small amounts of cis-lycopene occur in fresh tomato. However, upon heating cis-isomers can increase up to 30% (Shi & Le Maguer 2000). Naturally occurring lycopene, including tomato oleoresin and ketchup, has varying amounts of cis isomers (table 1). In human plasma, however, the proportion of trans- and cis-isomers is about 50% each. BASF’s LycoVit 10% with approximately 15% cis isomers lies well within that range. An even greater percentage of approximately 80% cis-lycopene is found in prostate tissue (Clinton 1998). A recent study in ferrets showed that cis-isomers of lycopene are preferentially taken up into mixed micelles and into the lymph, respectively, indicating that cis-lycopene is more bioavailable than the trans-form (Boileau et al. 1999).

Table 1: Cis Isomers in Lycopene Products

<table>
<thead>
<tr>
<th>Sample</th>
<th>Lycopene (Percentage cis-Isomers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LycoVit 10%</td>
<td>15</td>
</tr>
<tr>
<td>Ketchup</td>
<td>11</td>
</tr>
<tr>
<td>Tomato Paste</td>
<td>10</td>
</tr>
<tr>
<td>Pizza Fix</td>
<td>3</td>
</tr>
<tr>
<td>Tomato Oleoresin</td>
<td>10</td>
</tr>
</tbody>
</table>

Source: BASF Aktiengesellschaft

Bioavailability
In a pilot trial, the group of R. Russell of Tufts University in Boston compared the bioavailability of lycopene from tomatoes to that of synthetic lycopene from BASF (Ferreira et al. 2001). Both lycopene sources were deuterium labeled. Tomatoes were steamed and pureed and synthetic lycopene was administered in corn oil. Two subjects each, received either the natural or synthetic lycopene with a liquid meal (35% fat). Labeled plasma lycopene was determined with a LC-MS method and the area under the plasma time curve (AUC) was calculated. Synthetic lycopene was found to be almost three times more bioavailable than lycopene from cooked pureed tomatoes. However, this data could not be confirmed in an unpublished study in human subjects, where lycopene in a beadlet preparation (LycoVit 10%) exhibited a similar bioavailability compared to lycopene from tomato oleoresin. This shows that the form of application may be important for the bioavailability of lycopene.

Prostate Cancer
The initial data from Kucuk et al. (1999) that lycopene-containing products may play a role in the prevention and treatment of prostate cancer, could

Table 2: Concentrations of Lycopene in Human Tissue

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Lycopene (nmol/g wet weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testes</td>
<td>4.4-21.4</td>
</tr>
<tr>
<td>Adrenal gland</td>
<td>1.9-21.6</td>
</tr>
<tr>
<td>Liver</td>
<td>1.3-5.7</td>
</tr>
<tr>
<td>Prostate gland</td>
<td>0.80</td>
</tr>
<tr>
<td>Breast</td>
<td>0.78</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.70</td>
</tr>
<tr>
<td>Lung</td>
<td>0.22-0.57</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.15-0.62</td>
</tr>
<tr>
<td>Colon</td>
<td>0.31</td>
</tr>
<tr>
<td>Skin</td>
<td>0.42</td>
</tr>
<tr>
<td>Ovary</td>
<td>0.30</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Source: Agarwal & Rao (2000)
be substantiated by two further trials. In one study, a mixture of several dietary factors, including lycopene, implicated in the progression of prostate cancer were used (Schroeder et al. 2000). Men with rising prostate specific antigen (PSA) after radical prostatectomy were enrolled in the study. The primary endpoint of the study, the PSA doubling time, was reduced in the active treatment. This improvement may translate to a relevant benefit for the patients and encourages the investigators to further study lycopene in the prevention of prostate cancer. P. Bowen from the University of Illinois at Chicago used tomato sauce as a source of lycopene in men with prostate cancer (figure 2). The purpose of the study was to assess lycopene uptake in prostate tissue and to determine if lycopene can reduce oxidative damage to leucocyte and prostate DNA. Further, the effects of the dietary intervention on PSA levels were investigated. Administration of 30 mg lycopene from tomato sauce for 3 weeks to prostate cancer patients significantly increased lycopene levels in serum and prostate and reduced oxidative damage to DNA. Serum PSA levels declined, indicating that the treatment interfered with the tumor. Further research is needed to show that these changes clearly translate to benefits for the patients.

Several mechanisms for lycopene in the prevention of cancer are proposed by Agarwal & Rao (2000) (figure 3). Lycopene has to be bioavailable in order to increase lycopene status. Then, lycopene may act as an antioxidant, and thus lower oxidative damage to DNA, lipids and proteins. In particular, oxidized DNA bases such as 8-hydroxy-deoxyguanosine (8OHdG) may cause mutations, and hence, are implicated in the development of cancer. In addition, lycopene is involved in gene regulation and stimulates gap-junctional communication. Gap-junctional communication is involved in the control of precancerous cells, i.e. stimulated gap-junctional communication is correlated with growth inhibition of tumor cells.

Lycopene may also interfere with the mitogenic pathway of insulin-like growth factor (IGF)-1 and slow down cell cycle progression (Sharoni et al. 2000).

UV Protection

β-Carotene is widely used as an oral sun protecting agent, and has been extensively tested in human studies. The usefulness of lycopene to prevent UV-induced skin damage has been evaluated only recently (Stahl et al. 2001). The group from the University of Duesseldorf used tomato paste as a bioavailable lycopene source. Tomato paste equivalent to 16 mg lycopene was taken together with 10 g olive oil by human volunteers.
The control group only ingested the olive oil. After ten weeks UV-induced erythema was 40% lower in the lycopene-treated group. This was paralleled by a significant increase in plasma lycopene. Even though, the efficacy of the treatment does not compare to a sunscreen with a high protection factor, the dietary intervention may confer a basic protection for times when the skin is not protected.

**Safety and Recommended Intake Levels**
Based on the scientific information provided above, lycopene may offer important health benefits. Safety of LycoVit 10% has been studied extensively in state-of-the-art toxicological studies. At the recommended intake of maximal 10 mg per day, LycoVit 10% is a safe nutritional supplement.

**Lycopene**

**LycoVit 10%**
- **Characteristics**
  - excellent flowability
  - high stability in bulk and dietary supplements
  - uniform particle size distribution
  - very good resistance to pressure during tabletting (no bleeding)
  - GMO-DNA-free
- **Application**
  - single dose tablets
  - multivitamin tablets
  - mixed carotenoid supplements
  - hard gelatine capsules

**LycoVit Dispersion 20%**
- **Characteristics**
  - dispersion of microcrystalline lycopene in sunflower oil
  - GMO-free
- **Application**
  - soft gelatine capsules
  - fortification of food*
*available as of 2002

If you are interested in receiving samples, please contact the following colleagues:
- NAFTA - Mr. Kaufman, +1 973 426 5376
- Asia - Ms. Yap +65 398 5021
- South America - Ms. Assis + 55 11 4343 2380

**References**


Kucuk O, Sakr W, Sakar F et al. Lycopene supplementation in men with prostate cancer (PCa) reduces grade and volume of preneoplasia (PIN) and tumor, decreases serum prostate specific antigen (PSA) and modulates biomarkers of growth and differentiation. Abstract. 12th International Carotenoid Symposium, Cairns, Australia, July 1999
Contract Manufacturing by BASF

Your Expertise Advantage.

BASF decided to expand its activities in the fields of exclusive process development and manufacture of active ingredients and advanced intermediates. BASF offers the whole range of supporting technologies.

Our multiproduct plants offer nearly all technologies that are now necessary for the production of advanced intermediates and active ingredients.

BASF is keen to develop processes that are specifically tailored to the customers’ needs.

Plant Services and Major Equipment
- Ecological labs
- Fully biological wastewater treatment
- Analytical equipment of all kinds available
- Evaluation of process safety data
- DMF and regulatory assistance and know-how
- Stainless steel, Hastelloy and glass-lined reactors varying from 50 L to 16000 L
- Pendulum and horizontal centrifuges, pressure filters
- Vacuum paddle dryers, filter dryers
- Milling, sieving, and blending facilities
- Chambered equipment for handling highly toxic substances and processes

Materials handled
- Dimethyl sulfate
- Crotonaldehyde
- Nitromethane
- Thiouryl chloride
- Ketene
- Phosgene
- Methyl vinyl ketone
- Hydrogen chloride gas
- Cyanides
- Phosphorus oxychloride

Experience in the handling of narcotic drugs and controlled substances up to ton-quantities.

Technologies/Chemical Processes
- Chloromethylation (Blanc Reaction)
- Catalytic hydrogenation and dehydrogenation
- Reductive amination
- Grignard reactions
- Halogenations
- Dealkylation of phenol ethers
- Optical resolution
- Hydroformylations
- Carbonylations
- Ketene and diketene chemistry
- Phosgene chemistry
- Acetylene chemistry
- Hydrocyanic acid, cyanides
- Organic photochemistry
- Selective alkylation of urea
- Bromination with bromine
- All types of standard batch reactions

Ludwigshafen pilot plant
Synthesis of heterocycles like indoles, quinolines (figure 1), isoquinolines, xanthines, uracils, imidazolines (figure 2)

Electrochemistry

Reduction with lithium aluminum hydride and other complex hydrides

Phase transfer catalyzed reactions

Suzuki coupling

Diazotization

Gomberg arylation (figure 3)

Oxidations with H$_2$O$_2$, peracids and persalts

Prins reaction

Enzymatically catalyzed reactions

Phosphorous and sulfur chemistry

With our know-how in

Exciipients and Pharmaceutical formulations

Crystal engineering

Nanotechnology

We support you in developing

Drugs with enhanced bioavailability

Powders with adjusted particle size

Formulations with increased dissolution rate

Sustained release formulations

Direct compressible formulations

Taste masked active formulations

Enteric coated formulations

Solubilization of water insoluble drugs

We have accrued vast experience in developing advanced formulations for the pharmaceutical market and can draw on our superior expertise in traditional physical processing (e.g., blending, sieving, milling) and crystal engineering of active ingredients.

An Integrated Approach

Efficient life cycle management of active ingredients will become tremendously important once the patent protected period has expired. In addition to Contract Manufacturing of advanced intermediates and bulk active drugs, we offer our sound expertise in formulation and engineering technologies to extend the life cycle of our customers' products. From lab to full-scale production – Rely on BASF’s outstanding services.

The world's largest chemical complex
Theophylline

A drug for the standard therapy of bronchial asthma and chronic diseases of the respiratory tract

H. Einig

BASF manufactures a large number of different grades of theophylline at its factory in Minden, Germany to fulfil the wide variety of requirements from the pharmaceutical industry. Nevertheless, BASF often receive enquiries as to which grade is most suitable for the special requirements of developing a new dosage form.

Theophylline is used mainly in solid oral dosage forms, particularly slow release forms, and, to a lesser extent, instant-release forms. Theophylline has a very narrow therapeutic range; i.e. the range between ineffective plasma levels and plasma levels that result in serious side effects and toxic reactions is very small. It is given as 6 - 12 µg/ml plasma by E. Mutschler (Arzneimittelwirkungen, Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart 1991), though upper values of 15 - 20 µg/ml Plasma are often quoted in the literature.

Instant release forms that must be taken several times a day are prescribed less frequently, as patient compliance is poor if 3 - 4 doses have to be taken per day.

Some examples are given below of tablets that can be manufactured straightforwardly, including both rapid-release and the nowadays more usual slow-release forms. Judicious adjustment of the release rate of theophylline from such slow release forms makes it necessary to take only one or two doses per day.

Of the many grades of theophylline that BASF can offer its customers, Theophylline Anhydrous Granules 0.2/0.7 are particularly suitable for direct compression. This grade denotes granules with the following specification: at least 90 % of the granules must pass through a sieve with a mesh size of 0.710 mm and at most 10 % may pass through a sieve with a mesh size of 0.212 mm. Thus the particle size distribution of this grade lies within the range for granules that generally give good results in tablet manufacture.

The following table (table 1) documents the good tabletting properties of Theophylline Anhydrous Granules 0.2/0.7. Mixtures of 99.5 % theophylline and 0.5 % magnesium stearate were compressed into 300-mg tablets in an eccentric press, and their hardness and friability were measured. (Magnesium stearate is intended to prevent the mixture adhering to the punches.) Practically without other pharmaceutical excipients, at a compression force of 8.31 kN, the substance produces tablets with a hardness of 58 N and a friability of 0.36 %. This shows how easy it is to manufacture tablets without prior granulation. This method of production allows real cost savings in tablet manufacture. It should also be noted that Theophylline Anhydrous Granules 0.2/0.7 have very good flow properties with an angle of repose of 36°.

The agglomerated particles of Theophylline Anhydrous Granules 0.2/0.7 have very good flow properties with an angle of repose of 36°. A typical particle size distribution for Theophylline Anhydrous Granules 0.2/0.7, determined by laser light scattering on a stream of dry particles, is shown below. (figure 1)

The following formulation for a 100-mg theophylline tablet is a typical instant-release formulation.

Recipe with Ludipress®

Ludipress® is a direct compression excipient of BASF AG, in which the disintegrant is incorporated

| Composition per tablet: |  |
|-------------------------|--
| Theophylline 02/07       | 100 mg |
| Ludipress®              | 147 mg |
| Magnesium stearate      | 3 mg   |

Preparation: dry blending of all ingredients

| Tablet weight | 250 mg |
| Tablet size   | 8 mm diameter round tablet |
| Tablet press  | Rotating press Korsch |

The agglomerated particles of Theophylline Anhydrous Granules 0.2/0.7 have very good flow properties with an angle of repose of 36°. A typical particle size distribution for Theophylline Anhydrous Granules 0.2/0.7, determined by laser light scattering on a stream of dry particles, is shown below. (figure 1)
Table 2: Compression-hardness-relationship of Ludipress-theophylline tablets

<table>
<thead>
<tr>
<th>Compression force</th>
<th>Hardness</th>
<th>Friability</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.21 kN</td>
<td>49 N</td>
<td>0.15 %</td>
</tr>
<tr>
<td>10.28 kN</td>
<td>97 N</td>
<td>0.10 %</td>
</tr>
<tr>
<td>15.32 kN</td>
<td>124 N</td>
<td>0.11 %</td>
</tr>
</tbody>
</table>

Dissolution
1000 ml of 0.08 N HCl, paddle apparatus 50 rpm, 37 °C. (figure 2)

Recipe with Ludipress® LCE and testing of the influence of disintegrant

Ludipress® LCE is a direct compression ingredient of BASF AG without a disintegrant.

Tablets are produced according to (table 3) by dry blending process and compressed on a Korsch rotary press with a compression force of 9.45 kN. The resulting hardness is 95 - 101 N. The influence of the amount of the disintegrant Kollidon CL is demonstrated by the following dissolution curve: (figure 3)

Nowadays, however, slow-release dosage forms of theophylline are more often used. In addition to pellets, bolus formulations are also widely used for slow-release dosage forms. Bolus forms are particularly suitable when they release the drug independently of the pH and the time spent in the stomach. A drug that has dissolved in the stomach can pass through the pylorus, which is always open by as much as 3 - 4 mm, and into the small intestine where it is readily absorbed. The manufacturing costs for bolus forms are particularly low. The necessary excipients that ensure pH-independent release of the drug are now available.

The use of Kollidon® SR to delay the release of Theophylline Anhydrous Granules 0.2/0.7

Kollidon® SR from BASF AG is an 8:2 mixture of polyvinyl acetate and Kollidon® 30 (povidone K30). It is a special formulation of two excipients with excellent flow and tablet-making properties that are used in the pharmaceutical industry.

According to (table 4) Kollidon SR is mixed dry with Theophylline Anhydrous Granules 0.2/0.7 and compressed into tablets directly without further processing. (Lit. BASF internal report, Fraunhofer 1999)

Drug release of Lots 24.1 - 24.4

Medium: 0.8 N HCl solution, readjusted after 2h to pH 6.8 with buffer, USP paddle apparatus 50 rpm, 900 ml solution. (figure 4)

The chart (figure 4) above shows that the rate of release of theophylline depends on the quantity of Kollidon® SR in the formulation.
The use of Kollicoat® SR 30 D to delay the release of Theophylline Anhydrous Granules 0.2/0.7

Kollicoat® SR 30 D is a 27% aqueous dispersion of polyvinyl acetate stabilised with 2.7% Kollidon® 30 and 0.3% sodium lauryl sulphate.

Kollicoat® SR 30 D is mainly intended for coating pharmaceutical dosage forms with a film that does not dissolve in water, but releases the drug through pores at a controlled rate (see also separate information material of BASF AG). However, Kollicoat® SR 30 D is also eminently suitable for granulation.

Drugs granulated with Kollicoat® SR 30 D can be pressed into tablets with an insoluble matrix structure from which the drug usually diffuses out at a rate proportional to square root of the time. Theophylline Anhydrous Granules 0.2/0.7 have proved particularly suitable for this purpose (BASF internal report, dissertation by Flick 1999). It must be added, however, that it is recommended to include a filler such as microcristalline cellulose or lactose in the granulating mixture. The granulation is best carried out in a fluidised-bed granulator, but it is also possible to use a high-shear mixer.

Batch size for granules 10 kg.
Tablet form: oblong 19 x 8.5 mm
Compression force: 12 - 18 kN (table 5).
The release curve can be seen in the following chart (figure 5).
The release of theophylline is determined by the same method as described above.
Medium: 0.8 N HCl solution, readjusted after 2h to pH 6.8 with buffer, USP paddle apparatus 50 rpm, 900 ml solution.

The release rate can be adjusted very simply by varying the amount of polymer in the formulation. This applies to both Kollidon® SR and Kollicoat® SR 30D.

The properties of the 2 polymeric excipients (Kollidon SR and Kollicoat SR 30D) can be summarised as follows:

The release of theophylline is

- independent of the compression rate
- independent of the pH value of the dissolution medium
- independent of the ionic strength of the dissolution medium
- independent of the storage time and conditions (humidity, temperature)
- proportional to the square root of the time

Summary
BASF is the world’s largest manufacturer of theophylline and theophylline derivatives.

Theophylline is still widely used in the therapy of asthmatic complaints in spite of the appearance of new drugs. BASF produces a number of grades that differ in particle size distribution for different customer’s requirements. The common theophylline instant release tablets are still prescribed. Slow-release bolus forms and pellets are becoming more popular, now that suitable excipients for these dosage forms are available.

Methods of manufacture using the anhydrous 0.2/0.7 granular grade of theophylline are given above for the following dosage forms:

- instant release tablets
- various slow-release tablets made by direct compression and granulation

The new release-delaying excipients make drug release independent of the pH.

The Theophylline Anhydrous Granules 0.2/0.7 grade is particularly suitable for this method of tablet manufacture.

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Table 5: Tablet composition: (Kollicoat SR 30 D)

<table>
<thead>
<tr>
<th>Component</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theophylline 0.2/0.7</td>
<td>396 mg = 49.5 %</td>
</tr>
<tr>
<td>Kollicoat® SR 30 D*</td>
<td>396 mg = 49.5 %</td>
</tr>
<tr>
<td>Lactose</td>
<td>80 mg = 10 %</td>
</tr>
<tr>
<td>Substances added after fluidised-bed granulation</td>
<td>60 mg = 7.5 %</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>316 mg = 60.5%</td>
</tr>
<tr>
<td>Aerosil® 200</td>
<td>4 mg = 0.5 %</td>
</tr>
<tr>
<td>*(solids)</td>
<td>4 mg = 0.5 %</td>
</tr>
</tbody>
</table>

Dissolution rate of Theophylline (according to table 5) (figure 5)
Technical Marketing Services

In NAFTA

During the last two years, BASF’s new state of the art technical service center in Ledgewood, New Jersey has supported customers and partners in the pharmaceutical, cosmetic and nutritional industries. Conveniently located in Northern New Jersey - close to many R&D laboratories of pharmaceutical and consumer product companies, and only five miles away from BASF Corporation headquarters - the new facility is easily accessible via Interstate 80.

The entire NAFTA regional technical support for our active pharmaceutical ingredients and excipients, our vitamins, carotenoids, nutraceuticals and cosmetic chemicals is centralized in the facility. Here pharmacists, chemists and other specialists in pharmaceutical, cosmetic and nutritional science are available to provide for you the additional expertise that may be required for your product and process development.

Tablets, liquid preparations, semisolid drugs, nutritional and cosmetic goods - we can provide guidance to make the product better.

We also offer the opportunity for R&D staff of our customers and partners to spend time in our facility and gain hands-on experience in direct cooperation with BASF scientists.

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News

Kollidon SR

In ExAct editions no. 4 and 6 we reported about Kollidon SR, a new polyvinylacetate/povidone excipient for matrix sustained release dosage forms. In 2001 an USA-DMF has been submitted. The DMF no. is 15460.
Kollicoat IR

In 1999, BASF launched 2 new pharmaceutical excipients, Kollicoat SR 30 D and Kollidon SR, both based on polyvinyl acetate. These products have been well received by the market, as they provide a ready solution to a number of formulation problems that are encountered with sustained release solid dosage forms.

BASF has further innovations for 2001: We will introduce Kollicoat IR, a new polymer for coating instant release tablets and other rapid release dosage forms, that is still under development. This product will complete our range of coating materials, since it will enable us to offer sustained release coatings, enteric coatings and instant release coatings, with the best product in each class. Kollicoat IR features high water solubility, very low viscosity and enormous flexibility, which in combination make possible very fast coating processes and extremely stable dosage forms.

In the next issue of ExAct you will find more on this exciting innovative excipient. Don’t miss it!

New Media

Vademecum for Vitamin Formulations
(New: 2nd edition)

After 12 years the “Vademecum for Vitamin Formulations” by Volker Bühler has been revised. Even today there is still a gap in the knowledge of the formulation technology of vitamins.

In this book the emphasis is put on practical aspects. The reader has easy access to a wealth of information because of the alphabetical format. Many specific formulations are given. Vitamins and excipients with their influence on the stability of vitamin preparations are discussed in detail.

In this revised edition several new formulations, an index of these formulations, a lot of information about multi-vitamin preparations and some actualisation were added.

The enclosed CD-ROM offers even more practical aspects in form of the optimal access to all formulations and crosslinked information on excipients in conjunction with vitamins.

This book incl. CD-ROM can be ordered with the attached reply card.