Dear reader,

You have probably heard A. T. Florence’s well-known question, “Where are the new pharmaceutical excipients?” The background to this question is that there have been no major advances in the field of pharmaceutical excipients in recent years. This is to change, as BASF AG has greatly increased research and development for excipients. We are developing entirely new innovative excipients for which comprehensive toxicological studies will be necessary, and this is entailing high development costs. BASF AG is well placed to carry out this work, as it has both extensive experience in the manufacture of polymers and great expertise in their use in pharmaceutical formulations. These new products will make BASF one of the most innovative manufacturers of excipients.

The new products will be in the fields of solid as well as liquid dosage forms. They will have considerable advantages and will make life easier for formulators of pharmaceutical preparations.

BASF already has a wide range of modern excipients for a great diversity of pharmaceutical applications. With the new excipients we will even more be able to offer complete system solutions from a single source.

This issue of ExAct presents Kollicoat SR 30 D, a polyvinyl acetate dispersion with excellent technical properties for controlled-release coatings.

Take the opportunity to improve your pharmaceutical development and manufacture.

Yours sincerely,

BASF Aktiengesellschaft
Product Development
Health and Nutrition

Dr. Kolter
Kollicoat® SR 30 D

A new sustained release excipient.
K. Kolter and F. Ruchatz

Introduction

Sustained release products are gaining interest due to a long lasting drug action with low side effects and a better compliance related to immediate release dosage forms. However, for the manufacturing of coated sustained release dosage forms only three polymers can be used: ethylcellulose (EC), ethyl acrylate-methyl methacrylate copolymer (EMM) and ammonio methacrylate copolymer.

Each of these polymers has certain disadvantages. Ethylcellulose shows curing effects and needs a high amount of plasticizer for a sufficient film formation. The plasticizer migration within the film and between the film and the core, often causes a change in the dissolution profile [1]. As an aqueous dispersion ethylcellulose is a very expensive coating material. The cationic character of ammonio methacrylate copolymer is responsible for the interaction with anionic drugs or the counterion of cationic drugs. This can strongly change the permeation of the drug through the film and therefore the release rate [2]. Based on the weaknesses of the established products there is a strong demand for a new coating polymer in this application field.

Objective

The objective of this study was to evaluate the physicochemical properties of the new product Kollicoat SR 30 D and its suitability for sustained release coating.

Materials and Methods

Materials
Kollicoat SR 30 D (BASF AG), Spherofillin 0.8 – 1.3 mm (Knoll AG), Kollicoat SR 30 D is polyvinyl acetate dispersion stabilised with polyvinylpyrrolidone and sodium lauryl sulfate. Composition:

- Polyvinyl acetate 27 %, polyvinylpyrrolidone 2.7 %, sodium lauryl sulfate 0.3 % (solids 30 % [w/w])

Methods
Particle size, Malvern Autosizer 2 C (Malvern); minimum film forming temperature, Thermostatir (Coefield); dissolution, Pharmatest PTW 5 (Pharma test); viscosity, Brookfield RVT (Brookfield); Shear stability test: the dispersion was treated with a stirrer equipped with 8 pins at a speed of 2 000 rpm for 15 minutes. Afterwards, the coagulate was determined by passing the dispersion through a sieve of 125 μm. The residue was dried, weighed and calculated in percent of the total polymer mass.

Results and Discussion

Polyvinyl acetate possesses lipophilic character. Therefore it is insoluble but slightly swellable in water creating a permeation barrier. Polyvinylpyrrolidone acts as a protective colloid to stabilize the polyvinyl acetate dispersion.

Physicochemical properties of Kollicoat SR 30 D:

- mean particle size 160 nm
- pH 4.5
- minimum film forming temperature (MFT) 18°C
- with 5% triethyl citrate 8°C
- with 10% propylene glycol 14°C
- with 5% triethyl citrate 8°C
- with 10% triethyl citrate 1°C
- coagulate in the shear stability test
- viscosity 54 mPas

The physicochemical properties of two-phase systems (i.e. aqueous dispersions) are of great importance. The small particle size of 160 nm is a prerequisite for the stability of the dispersion. Therefore, Kollicoat SR 30 D passes the shear stability test, where a stirrer with pins rotates generating a high shear force. No coagulate was found after this treatment.

The low viscosity of the dispersion (approx. 50 mPas) enables an easy handling and an atomization into fine droplets during the spraying process. The dispersion does not necessarily require a plasticizer, since the minimum film forming temperature is at 18°C. The addition of a small amount of plasticizer decreases the MFT and strongly increases the flexibility of the film. With 5% triethyl citrate or 10% propylene glycol the elongation of the film was improved up to 250%.

Composition and preparation of the spray suspension:

<table>
<thead>
<tr>
<th>Polymer dispersion</th>
<th>Kollicoat SR 30 D</th>
<th>Water</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50.0 (= 15.0 solids)</td>
<td>35.0</td>
</tr>
</tbody>
</table>

The pigment dispersion was homogenized using a corundum mill and added slowly to the polymer dispersion while stirring.

Coating process

The coating suspension was applied in a fluidized bed coater (Aeromatic Strea 1, Aeromatic AG) on 0.5 kg theophylline pellets under the following conditions:

- Inlet air temperature 60°C
- Outlet air temperature 31°C
- Atomizing pressure 1.0 bar
- Spraying rate 11.0 g/min
- Drying 50°C/5 min
- Coating level 0.5/1.0/2.0 mg/cm²

<table>
<thead>
<tr>
<th>Plasticizer</th>
<th>Triethyl citrate</th>
<th>Propylene glycol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration</td>
<td>5%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Elongation of Kollicoat SR 30 D films in relation to plasticizer concentration. (Figure 1)
To investigate the coating performance of Kollicoat SR 30 D, theophylline pellets were coated with increasing amounts of polymer. As expected, drug dissolution slows down with increasing film thickness. The coating level of 2 mg/cm² corresponds to an increase in weight of approx. 10%. During the coating process no agglomeration or stickiness of the pellets occurred.

Comparing the dissolution profiles in 0.08 N–HCl and 0.08 N–HCl followed by a pH-change, it can be concluded, that the new coating delivers drugs without any influence of the pH. This is mainly caused by the absence of ionizable groups in the polymer.

Curing effects are negligible, since storing the coated pellets under stress conditions (60°C/24 h) reduced the dissolution only slightly. This coating was applied without any plasticizer. Curing effects should be less pronounced if a small amount of plasticizer is added, due to the greater difference between product temperature/outlet air temperature and MFT, resulting in a completely homogeneous film.

**Conclusions**

- Kollicoat SR 30 D has demonstrated to be a stable aqueous dispersion with good handling properties for coating and a strong sustained release activity.
- The drug release rate is independent of the dissolution medium’s pH.
- The excellent film forming properties result in a negligible curing effect and a high stability of the drug release rate after storage.
- Kollicoat SR 30 D films exhibit an enormous flexibility, particularly with small amounts of plasticizer.

**References**


Copovidone


V. Bühler

Copovidone is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate in the mass proportion of 3:2. The nominal K-value of Copovidone as stated in the labeling is not less than 90.0 percent and not more than 110.0 percent.

- Packaging and storage
  Preserve in tight containers, protected from moisture.

- USP Reference standards (11)
  USP Copovidone RS.

- Labeling
  Label it to indicate its nominal K-value.

- Clarity and color of solution
  Dissolve 1.0 g in 10 ml of water: the solution is clear or slightly opalescent and colorless to pale yellow or pale red.

- Identification
  A: Infrared Absorption (187k).
  B: To 5 ml of a solution (1 in 50) add a few drops of iodine TS: a deep red color is produced.

- Loss on drying (731)
  Dry it at 105°C for 3 hours: it loses not more than 5.0% of its weight.

- Residue on ignition (281)
  Not more than 0.1%.

- Limit of aldehydes
  Enzymatic method see Povidone monograph of USP 23. Not more than 0.05% is found.

- Limit of hydrazine
  TLC method see Povidone monograph of USP 23. Not more than 1 µg per g is found.

- Limit of peroxides
  Specific method see Povidone monograph of USP 23. Not more than 0.04%, expressed as hydrogen peroxide.

- Limit of monomers
  Dissolve the equivalent of 5.0 g of dried Copovidone in 20 ml of methanol, and slowly add 20.0 ml of iodobromide TS. Allow to stand for 30 minutes, protected from light, with repeated shaking. Add 5 ml of potassium iodide solution (1 in 10), and titrate the liberated iodine with 0.1 N sodium thiosulfate VS until the solution is yellow. Continue the titration dropwise until the solution is colorless. Perform a blank determination (see Residual Titrations under Titrimetry (541)): the difference between the volumes of 0.1 N sodium thiosulfate consumed in the blank and the specimen titrations is not more than 0.9 ml, corresponding to not more than 0.1% of monomers calculated as vinylpyrrolidone.

- K-value
  Method see Povidone monograph of USP 23. The K-value is not less than 90.0% and not more than 110.0% of the K-value stated on the label.

- Content of copolymerized vinyl acetate
  Determine the saponification value as directed for Saponification Value under Fats and Fixed Oils (401). Calculate the percentage of copolymerized vinyl acetate in the Copovidone taken by the formula: 0.1(86.09/56.11)(S), in which 86.09 and 56.11 are the molecular weights of vinyl acetate and potassium hydroxide, respectively, and S is the saponification value: not less than 35.3% and not more than 41.4% of the copolymerized vinyl acetate component, calculated on the dried basis, is found.

- Nitrogen
  Specific method see Povidone monograph of USP 23. The Nitrogen content, on the dried basis, is not less than 7.0% and not more than 8.0%.

- (11) USP Reference Standards
  Add the following:
  USP Copovidone RS – dry portion at 105°C for 3 hours before using. Keep container tightly closed.

Our comment to this draft monograph:
1. This draft monograph is almost completely harmonized with the Ph. Eur. monograph “Copovidone”.
2. Kollidon VA64 meets all requirements of this monograph.
3. For the determination of the monomers the USP Commission asked us for a HPLC method to substitute the titration method. We proposed the limit of †10 ppm for vinylpyrrolidone and †20 ppm for vinyl acetate applying our HPLC method sent to USP. Kollidon VA64 meets also these requirements.

Add the following:
Copovidone: White to yellowish-white powder or flakes. Is hygroscopic. Freely soluble in water, in alcohol, and in methylene chloride; practically insoluble in ether. NF category: Tablet binder; coating agent.
Poloxamers (1)

Lutrol® F 68 (Poloxamer 188).

B. Fussneisser

Introduction

The poloxamers are a group of surface active compounds widely used in the pharmaceutical industry. As newly developed active drugs are often water insoluble substances, their formulation together with the interest to design new drug dosage forms in order to increase the effectiveness of already existing formulations, promoted a variety of delivery vehicles such as controlled or sustained release systems, gels, microemulsions and nanoparticles. These dosage forms support the claim for enhanced solubility and bioavailability, for lengthened contact at specified selected sites in the body, combined with the reduction in quantity of applied drug. All these aspects could optimize systemic and minimize side effects of active drugs.

Structure

These products are described as block polymers of the type ABA, consisting of a central, hydrophobic block of polypropylene oxide, which is edged by two hydrophilic blocks of polyethylene oxide. The polymers are derived from the sequential polymerization of propylene oxide and ethylene oxide. A general formula is shown in figure 1.

Due to the possibility to combine blocks of different molecular weights, the properties of the resulting polymers vary in a wide range. The poloxamer grid (see figure 2) demonstrates the spectrum of the molecular weight, the different appearance (liquid, paste and solid) and variations in the hydrophilic or hydrophobic character of the individual compounds.

Lutrol F 68 has an average molecular weight of about 8600. The polyoxyethylene units represent about 81% of the molecular weight whereas that one of polyoxypropylene stands for about 19%. Due to the composition Lutrol F 68 is readily water soluble.

Pharmacopeial situation

Up to now the products for pharmaceutical use have been characterized on one hand in the family-monograph ‘Poloxamers’ in the USP/NF, on the other hand in individual monographs cited in JPE (Japanese PharmaceuticalExcipients, 1993). In the ‘Third (2000) Supplement’ to the ‘Third (1997) edition of the European Pharmacopoeia’ a family-monograph on ‘Poloxamers’ was published. In contrast to the USP/NF eight different products are listed there [2].

Applications of Lutrol F 68

Lutrol F 68 is primarily applied as an emulsifier, solubilizer, and suspension stabilizer in liquid oral, topical and parenteral dosage forms. In solid preparations it acts as wetting agent, plasticizer, and to enhance the solubility and bioavailability of sparingly water soluble active drugs.

Lutrol F 68 in solid pharmaceutical dosage forms

Since the mid 70s Lutrol F 68 has been applied to improve the dissolution behaviour and intestinal absorption of hardly water soluble substances. Dipiron, digoxin, sulfadiazine, sulfisoxazole, phenylbutazone, spiranocloactone, diazepam and griseofulvin were among the first actives tested. Improvement of dissolution of solid dispersions was attributed to either modifications of the crystalinity or the facilitation of wetting through lowering the surface tension in formulations with increased surface. In coprecipitates of Spirinolacton and Diazepam the solubility of both actives was significantly increased. Differential thermograms and infra red spectra gave no indication of polymorphs during the preparation. [3].

After administration to volunteers solidified melts of 20% griseofulvin in Lutrol F 68 showed a 62% higher urinary excretion of the metabolite 6-demethyl-griseofulvin than micronized griseofulvin, compared to 33% of a physical blend of the same composition. X-ray diffraction experiments revealed that directly after preparation the active is partially present as amorphous material. However during time recrystallization took place [4]. Similar findings on the enhancement of dissolution of nifedipine from solid dispersions prepared using a fluidized bed for solvent evaporation were recently published. In this case, DSC measurement did not reveal the formation of amorphous nifedipine in the solid dispersion [5].

Lutrol F 68 in liquid pharmaceutical dosage forms

Due to its low toxicity, Lutrol F 68 proved to be a very useful excipient, even for parenteral applications. In addition to standard tests intravenous administration studies in dogs revealed, in contrast to other widely used surfactants, least distinctive side effects such as histamine release and hypotension [6]. Solid lipid nanoparticles (SLN) or nanosuspension formulated with Poloxamer 188 were investigated extensively and found their way into various patents. A nanosuspension of N-benzoylstaurosporine, a protein kinase C inhibitor and antitumor agent for intravenous application, is described [7,8]. The diameters of the resulting microparticles range from 5–20 nm. The SLN system (Compritol-Poloxamer 188) was examined and demonstrated excellent long-term stability and was autoclavable under optimized conditions. Controlled drug delivery could be achieved by varying the composition of the formulation and the production parameters. Designedipdin microemulsion for intravenous injection are patented in [10]. The microemulsion comprises designedipdin, poloxamer 188, lecithin, a liquid triglyceride, PVP, propylene glycol or polyethylene glycol, and water.
Aqueous microdispersion of perfluorocarbons

An echographic contrast agent composition is described. The first group comprises e.g. nanoparticles of a

system, for computed tomography (CT) or magnetic resonance (MR) and as phase shift colloids in ultra-sound contrast examination. The formulations have been formulated either in liquid or lyophilized form. The second group includes Lutrol F 68 preparations. In recent years numerous patents and papers have been published on the application of poloxamer 188 in the stabilization of contrast media preparations for oral or retrograde x-ray examination of the gastro-inte-stinal tract, for imaging the blood pool and lymphatic system, for computed tomography (CT) or magnetic resonance (MR) and as phase shift colloids in ultrasound contrast examination. The formulations have been formulated either in liquid or lyophilized form. The first group comprises e.g. nanoparticles of a barium salt which is formulated with 5% of Poloxamer 188 [11]. The latter one, for example, is based on an aqueous microdispersion of perfluorocarbons [12].

An echographic contrast agent composition is described in [13]. A solution of 30.0 g Poloxamer 188 and 54.0 g mannitol in 900 ml water was added with vigorous stirring to a solution of 30.0 g phosphatidyl-glycerol and 20.0 g cholesterol in 100.0 g petroleum ether. Water for injection was added to 1 l, and the liquid was homogenized until the particle size reached < 4 µm. The emulsion was dispensed into vials and lyophilized. These lyophilizates are characterized by a remarkable storage stability. When reconstituted with water, they produce microbubble-containing echo-contrast agents characterized by microbubbles having a very small diameter and a surprisingly high stability.

The development of liquid formulations, thermogelling at the administered site, is of increasing interest. This includes e.g. drug delivery systems for parenteral use. When injected i.m., the formulation forms a depot for the controlled release of drug by gelling at body temperature [15]. In such combinations Lutrol F 68 strongly influences the thermorheological properties of F 127 preparations. In contrast to the effect of commonly used salts (e.g. NaCl) the addition of Lutrol F 68 to Lutrol F 127 formulations resulted in an increase of the sol-gel-transition temperature, probably due to the formation of mixed micelles as shown in figures 3 and 4 for different Lutrol F 68 concentrations. At constant amounts of Lutrol F 127 the viscosity and the thermo-reversible gelling temperature are functions of the Lutrol F 68 concentration. The latter one can be adjusted in a range of about 25°C by varying the quantity of Lutrol F 68 to a maximum of 20%. At this concentration the gelling temperature is within a very narrow range. A strong increase in viscosity can be observed coincidently.

Formulation and manufacturing of the granules is as follows:

1. Formulation
   - Acceclofenac: 1.3 g
   - Orange flavour: 4.3 g
   - Sorbitol, crystalline: 85.6 g
   - Lutrol F 68 [1]: 4.4 g
   - Cremophor RH 40 [1]: 4.4 g
   - Water: about 50.0 g

2. Manufacturing
   - Granulate mixture I with solution II, pass through a 0.8 mm screen, dry and sieve again.
   - 3.9 g of the granules correspond to 50 mg acceclofenac.

Lutrol F 68 for taste-masking

The unpleasant taste or smell of actives such as indomethacin-HCl, Aceclofenac or Albendazole can be masked by either using polymeric film formers or Lutrol F 68 alone or by combining it with hydrophobic compounds. An example is given in [14] for rapid-release coated pharmaceuticals. The above given example of Aceclofenac instant granules is excerpted from the compilation of “Generic Drug Formulations” of BASF.

References:
[16] WO 95/01410, B. Kapp, L. Lüben, A. Doenicke, Histamine release and hypotensive reaction in dogs by solubilizing agents and fatty acids: Analysis of various compounds in Cremophor EL and development of a compound with reduced toxicity; Agents and Actions, 1/2 (12), 1982, 64 – 80.
Introduction
The solubilizer Solutol HS 15 (polyethylene glycol 660 - 12-hydroxystearate) is a non-ionic surfactant used for pharmaceutical purposes produced from 1 mol 12-hydroxystearic acid and 15 mol ethylene oxide. The product is very efficient in solubilizing substances like fat-soluble vitamins, and active ingredients of hydrophobic nature.

Application
The solubilizing capacity for some tested drugs (Clotrimazole, Carbamazepine, 17ß-Estradiol, Sulfathiazole, and Piroxicame) increased almost linearly with enlarging concentration of solubilizing agent (Fig. 1) due to the formation of spherical micelles even at high concentrations of Solutol HS 15. Tests have revealed that the viscosity increased with increasing amount of solubilizer, but the amount of solubilized drugs did not have any additional influence on the kinematic viscosity (Fig. 2).

In contrast to Solutol HS 15 the viscosity of PS 80 strongly increased at higher concentrations, whereas the viscosity of Solutol HS 15 remained fairly low. Therefore an uncomplicated administration of a 30% solution of Solutol HS 15 is possible. Many drugs are manufactured under aseptic conditions but this can be avoided, because steam sterilization (121°C/20 min) of pure Solutol HS 15 is possible. Tests did not reveal any changes of properties indicating that no considerable hydrolyzation process took place. The sterilization process performed with solubilizates of 20% Solutol HS 15 in demineralized water and a drug loading of 7.5% tocopherol acetate did not influence the properties of the solubilizate except a minor change of the pH-value. After the sterilization process a phase separation occurred which can be overcome by shaking the solutions moderately during cooling. Also the micelle diameter remained unchanged.

Regulatory status/toxicology
The commission of the German Pharmacopoeia has decided to include polyoxyl 15 hydroxystearic acid as monograph in the next edition of the DAB. BASF has applied for the monographs in the USP and the Ph. Eur. Solutol HS 15 is approved by the HPB (Canada) for human application. Active ingredient is vitamin K1. The reason to have a deeper look in Solutol HS 15 is the improved tolerance after parenteral application. Based on the toxicity studies it can be concluded, that i.e. histamine release in dogs is roughly 10 times lower compared to Cremophor EL.

Conclusion
Solutol HS 15 meets the requirements of an effective modern solubilizer for parenteral use. Combined are the high solubilizing capacity and low toxicity of Solutol HS 15.
Ibuprofen, more than 30 years killing pain.

M. Black

Ibuprofen (I) is a chiral propionic acid derivative belonging to the class of non-steroidal anti-inflammatory drugs (NSAIDs), having a range of analgesic, antipyretic and anti-inflammatory actions. Racemic Ibuprofen was originally developed by Boots as one of the first NSAIDs with the potency of aspirin but with an improved side effect profile, particularly with regard to gastro-intestinal toxicity. Boots launched the first tablet form as Brufen in the UK in 1969. Following the release of Ibuprofen to OTC status it was established as one of the major products in the analgesic market, competing against aspirin and paracetamol. In 1995 BASF Pharma acquired the bulk Ibuprofen business and the Brufen prescription product through the fusion with the Boots Pharmaceutical division.

BASF Manufacturing Process

Crude Ibuprofen is manufactured at BASF Bishop, in Texas, USA. Final purification and crystallization is then carried out in Bishop and in Beeston, UK. A computer-controlled crystallization process is employed at both plants to ensure that standard grades have identical physical parameters and characteristics. Products from both sites are controlled to ensure they comply with the United States, European and Japanese Pharmacopoeias. The Bishop facility has been recognized for environmental excellence. The technology utilizes a three-step catalytic synthesis (II) involving acetoacetylation of isobutylbenzene using HF as solvent, followed by a catalytic reduction to the alcohol which then undergoes a palladium - facilitated carbonyl-insertion affording the racemic propionic acid derivative (Ibuprofen).

The process has a high atom utilization ratio and earned recognition from “Chemical Engineering” as the 1993 winner of the Kirkpatrick Chemical Engineering Achievement Award. This award is presented biannually for the most notable chemical engineering technology commercialized in the preceding two years. Similarly, in June 1997, this process received the US Presidential Green Chemistry Challenge Award.

Therapeutic Activity

Ibuprofen is used in the treatment of painful and inflammatory conditions such as rheumatoid arthritis, Osteo-arthritis, ankylosing spondylitis, mild to moderate pain, dysmenorrhea, vascular headache and also for the reduction of fever. It is characterized by its rapid absorption in the stomach with relatively little associated gastro-intestinal toxicity and by its rapid onset of pharmacological action.

Ibuprofen's mode of action in man is believed to involve the reversible inhibition of the enzyme system responsible for the biosynthesis of prostaglandins from arachidonic acid in the cellular membrane. This system is called Cyclooxygenase (Cox), therefore Ibuprofen and related NSAIDs are also known as Cox-inhibitors.

Prostaglandins (PGs) are naturally occurring fatty acid derivatives distributed in the tissues, and have, among other properties, a powerful effect upon the smooth muscle. PGs appear to be synthesized locally in increased amounts in response to an inflammatory stimulus or to a blood flow disturbance. Evidence supports the view that PGs then sensitize the tissues to the action of other agents such as histamine and kinins thereby resulting in pain and inflammation.

The inhibitory action of NSAIDs on PG synthesis is the most probable cause of the gastro-intestinal side effects generally associated with this class of drug. However over 30 years of clinical data reveal that in comparison to related products, Ibuprofen has the lowest incidence of serious gastro-intestinal reactions.
Ibuprofen, break-through in formulation technology.

H. Einig

BASF Pharma is a major manufacturer of the analgesic drug substance ibuprofen. The characteristics of an active drug substance are determined not only by pharmacological attributes but also by the pharmaceutical formulation of the drug. It is commonly observed that different formulations of the same drug substance can show wide variances in bioavailability. Therefore, in recent years developers have concentrated both on improving the physical properties of active ingredients and the optimization of pharmaceutical formulations.

Although ibuprofen is most frequently administered in the form of tablets, it is not particularly suitable for tabletting processes. Its compressibility is poor, and therefore it is not possible to manufacture tablets by the cost-saving direct tabletting process. A more cost-intensive pretreatment such as granulation or compaction is generally necessary. However, none of the known granulation processes is suitable for producing very small dosage forms containing extremely high concentrations of the active ingredient. Such small dosage forms are advantageous in terms of cost reduction and increased user-friendliness. An investigation of ibuprofen tablets marketed in the USA showed that such tablets have a maximum active ingredient content of slightly more than 60%. Another drawback of ibuprofen is its slow dissolution rate in digestive juices. For these reasons ibuprofen is regarded as a difficult active ingredient in the pharmaceutical industry.

Intensive pharmaceutical work on this substance has eliminated these unfavourable properties and provided the pharmaceutical industry for the first time with intermediate formulations and finished preparations which permit economic and simple manufacture of new ibuprofen tablets and which no longer exhibit any of the well-known disadvantages of ibuprofen.

The following 3 new types of ibuprofen will be available in future:

- Ibuprofen DTP
- Ibuprofen DC 80
- Ibuprofen DC 92

1. Ibuprofen DTP

The poor compression characteristics of the active ingredient ibuprofen were successfully remedied by means of a special coating process. This led to the development of an intermediate formulation of the active ingredient, known as ibuprofen DTP, with very good direct tabletting properties. The abbreviation DTP stands for Direct Tabletting Preparation. Ibuprofen DTP has an active ingredient content of 97 ± 1%. Only small amounts of filler, disintegrant, flow-conditioning agent and lubricant need to be added to the active DTP-ingredient and then the mixture is homogenized. Tablets characterized by their hardness, rapid disintegration and favourable release of the active ingredient can be manufactured using a low compression force.

The table shows the range of standard grades produced by BASF Pharma and the recommended uses in each case.
This is illustrated in Table 1:

<table>
<thead>
<tr>
<th>Table 1. Example of a 200 mg ibuprofen tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composition</strong></td>
</tr>
<tr>
<td>Ibuprofen DTP 206 mg</td>
</tr>
<tr>
<td>+ Ibuprofen 200 mg</td>
</tr>
<tr>
<td>AcDiso 12 mg</td>
</tr>
<tr>
<td>Avicel PH 200 6 mg</td>
</tr>
<tr>
<td>Magnesium stearate 1 mg</td>
</tr>
<tr>
<td>Aerosil 200 1 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compression force</th>
<th>Tablet hardness</th>
</tr>
</thead>
<tbody>
<tr>
<td>A = 4.2 kN</td>
<td>A = 79.1 N</td>
</tr>
<tr>
<td>B = 8.2 kN</td>
<td>B = 104.7 N</td>
</tr>
<tr>
<td>C = 11.6 kN</td>
<td>C = 104.8 N</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Release (in accordance with USP XXIII)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample B after:</td>
</tr>
<tr>
<td>5 min</td>
</tr>
<tr>
<td>10 min</td>
</tr>
<tr>
<td>15 min</td>
</tr>
<tr>
<td>30 min</td>
</tr>
</tbody>
</table>

Ibuprofen DTP is especially suitable for the development of combination preparations, whereas ibuprofen DC 80 and DC 92 (described below) are mainly suitable for monopreparations with a rapid release. The advantages of ibuprofen DTP for the manufacture of combination preparations are demonstrated in Table 2, taking ibuprofen DTP in combination with caffeine as an example.

<table>
<thead>
<tr>
<th>Table 2. Combination preparation consisting of 200 mg ibuprofen and 65 mg caffeine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composition</strong></td>
</tr>
<tr>
<td>Ibuprofen DTP 206.0 mg   = Ibuprofen 200.0 mg   + Caffeine 65.0 mg</td>
</tr>
<tr>
<td>AcDiso 14.0 mg</td>
</tr>
<tr>
<td>Avicel PH 200 10.0 mg</td>
</tr>
<tr>
<td>Hydroxypropylmethylcellulose 2.5 mg</td>
</tr>
<tr>
<td>Magnesium stearate 1.25 mg</td>
</tr>
<tr>
<td>Aerosil 200 1.25 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Content of active ingredients per tablet</th>
<th>82.8%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compression force:</td>
<td></td>
</tr>
<tr>
<td>A = 3.6 kN</td>
<td></td>
</tr>
<tr>
<td>B = 77 kN</td>
<td></td>
</tr>
<tr>
<td>C = 11.4 kN</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3. Ibuprofen 200 mg tablet from Ibuprofen DC 80</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composition</strong></td>
</tr>
<tr>
<td>= Content of DC 80 250 mg</td>
</tr>
<tr>
<td>= Content of ibuprofen 200 mg</td>
</tr>
<tr>
<td><strong>Weight of tablets</strong></td>
</tr>
<tr>
<td>250 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quantity of active ingredient</th>
<th>80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compression force:</td>
<td></td>
</tr>
<tr>
<td>A = 4.6 kN</td>
<td></td>
</tr>
<tr>
<td>B = 6.9 kN</td>
<td></td>
</tr>
<tr>
<td>C = 11.7 kN</td>
<td></td>
</tr>
<tr>
<td>Friability:</td>
<td></td>
</tr>
<tr>
<td>A = 1.5%</td>
<td></td>
</tr>
<tr>
<td>B = 1%</td>
<td></td>
</tr>
<tr>
<td>C = 0.6%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>In vitro dissolution of drug (according to USP XXIII)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample B after:</td>
</tr>
<tr>
<td>5 min</td>
</tr>
<tr>
<td>10 min</td>
</tr>
</tbody>
</table>

The ibuprofen DC 80 granulate can be compressed directly into tablets on a rotary press without any previous processing steps. In spite of the low compression force, the high degree of tablet hardness that is attained, allow the tableting process to run at high speed (see Table 3). The active ingredient is released in vitro within 10 minutes. Similarly, other doses of the active ingredient can also be produced from ibuprofen DC 80, as shown in the case of a 600 mg tablet in Table 4.

<table>
<thead>
<tr>
<th>Table 4. Combination preparation consisting of 600 mg ibuprofen and 100 mg paracetamol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composition</strong></td>
</tr>
<tr>
<td>Ibuprofen DTP 800.0 mg = Ibuprofen 800.0 mg + Paracetamol 100.0 mg</td>
</tr>
<tr>
<td>Avicel PH 200 20.0 mg</td>
</tr>
<tr>
<td>Hydroxypropylmethylcellulose 6 mg</td>
</tr>
<tr>
<td>Magnesium stearate 1.25 mg</td>
</tr>
<tr>
<td>Aerosil 200 1.25 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Content of active ingredients per tablet</th>
<th>82.8%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compression force:</td>
<td></td>
</tr>
<tr>
<td>A = 3.6 kN</td>
<td></td>
</tr>
<tr>
<td>B = 77 kN</td>
<td></td>
</tr>
<tr>
<td>C = 11.4 kN</td>
<td></td>
</tr>
</tbody>
</table>

**Please note:** When formulating combination products of ibuprofen and caffeine, pay attention to existing patents, especially patent No. US 4, 565, 249.

As in the ibuprofen monoblock, ibuprofen is quantitatively dissolved after 10–15 minutes. In addition to tablets with an active ingredient content of 200 mg, all other common doses (400 mg, 600 mg and 800 mg) can also be produced in this way.

The use of ibuprofen DTP is especially favorable for sustained-release preparations (SR) in conjunction with highly viscous hydroxypropylmethyl celluloses or the new excipient developed by BASF, Kollidon SR, which is used as excipient to control the rate of release. In this way SR preparations of ibuprofen can be produced using the direct tableting process without a previous granulation step. In addition extremely high concentrations of the active ingredient are achieved in this process.

**Which advantages does ibuprofen DTP offer for the manufacture of rapidly soluble combination preparations?**

- No need for an expensive and time-consuming granulation
- A mixing process with a few inactive retarding components is the only intermediate step required before tableting
- A high tableting speed can be attained, as only a low compression force is required
- Rapid release of the active ingredient in vitro
- A high content of the active ingredient in the tablet corresponding to a smaller amount of excipients results in a larger number of tablets per batch
- Major cost reductions compared to the conventional processes
- Applicable for all dosage strengths

**Which advantages does ibuprofen DTP offer for the manufacture of sustained-release preparations?**

- No need for an expensive and time-consuming granulation

2. Ibuprofen DC 80

DC grades are ready-to-use mixtures which can be compressed into tablets without any further processing. DC grades are used for many active ingredients. For example, there are many DC grades available for the active ingredient paracetamol (acetaminophen). Now, such DC grades can also be made available for ibuprofen. DC 80 means that the tableting mixture contains 80% of the pure active ingredient. A 200 mg ibuprofen tablet produced from ibuprofen DC 80 is described in Table 3.
Which advantages does Ibuprofen DC 80 offer to monopreparations?

- No need for customers to develop their own formulations
- All intermediate steps in manufacturing prior to tabletting are rendered superfluous
- A high tabletting speed can be attained, as only a low compression force is required
- Manufacture of all doses from ibuprofen DC 80 is possible
- Very rapid release of the active ingredient
- A high content of the active ingredient in the tablet corresponding to a smaller amount of excipients results in a larger number of tablets per batch

Ibuprofen 600 mg tablets from Ibuprofen DC 80.

(Product 4)

<table>
<thead>
<tr>
<th>Which advantages does Ibuprofen DC 80 offer to monopreparations?</th>
</tr>
</thead>
<tbody>
<tr>
<td>- High patient compliance because of the small size of the tablets</td>
</tr>
<tr>
<td>- Major cost reductions compared to the conventional method of producing tablets</td>
</tr>
</tbody>
</table>

3. Ibuprofen DC 92

The development of DC grade ibuprofen has reached its culmination in the DC 92 grade. A patented production process makes it possible to manufacture ibuprofen tablets in all sizes from 200 to 800 mg with the following characteristics:

- Highest active ingredient content with 92% ibuprofen
- Shortest disintegration time only 30 seconds in water

LycoVit 10% – A new lycopene powder grade for dietary supplements

BASF has for several years marketed BetaVit 10% and BetaVit 20% especially suitable in tablet preparations. Today our BetaVit grades are widely used in multivitamin tablets.

A natural extension is the inclusion of the carotenoid lycopene into our product range. Lycopene is the carotenoid giving the tomato its beautiful red color. Lycopene is an emerging antioxidant in disease prevention and health enhancement as many studies suggest that the intake of tomato products can be associated with lower incidences of prostate cancer, digestive tract cancers and cardiovascular diseases. The inclusion of lycopene along side beta-carotene and vitamins in dietary supplements is thus a natural evolution. For this purpose BASF has developed LycoVit 10% which is a powder for dietary supplements.

LycoVit 10% contains 10% lycopene and shows the same excellent stability and powder properties as the well known BetaVit grades.

The potency of LycoVit 10% is higher than other products found in the market place thus taking up less space in the dietary supplements products. The nature-identical lycopene from BASF is produced based on several years BASF experience in terms of manufacturing of carotenoids. This in combination with our competence regarding micro-encapsulation of active ingredients has enabled us to bring LycoVit 10% into the market place.

A scientific booklet on lycopene can be ordered with the attached reply card.
Kollidon® SR – A new excipient for sustained release matrices.

With the ExAct edition in hand we presented to you Kollcoat SR 30 D, a real breakthrough in sustained release coating. Besides other topics, ExAct No. 4 will deal with Kollidon SR, a brand-new excipient for the manufacture of sustained release matrix tablets by direct compression.

Kollidon SR retains the useful properties of a hydrophilic matrix-forming agent, avoiding the drawbacks of the commercially available products. Should you require information on Kollidon SR in advance, please fill in the attached reply card or contact your local BASF company or one of our regional centers (addresses on the back of this newsletter).

New Media

Kollidon® Book and Generic Drug Formulations now available on CD-ROM.

Now BASF offers interested industry and university readers of ExAct a new service: Information on Kollidon and an extensive collection of pharmaceutical formulations on CD-ROM.

The Kollidon Book – which can also be ordered in book form – contains information on soluble and insoluble Kollidon grades. It also covers general subjects like registration in pharmaceuticals/food as well as toxicological data.

In Generic Drug Formulations, the user will find a selection of about 500 formulations of human and veterinary drugs which have all been developed by BASF’s Application Laboratories. The formulations included are in solid, liquid, and semi-solid form. However, emphasis is placed on tablets. These data can still be ordered in binder form.