Dear reader,

With the 3rd edition of ExAct we presented to you Kollicoat® SR 30 D, a new aqueous polyvinyl acetate dispersion for controlled-release coatings. The present edition contains an article about a recent study on compaction of controlled release pellets coated with Kollicoat SR 30 D.

The preparation of controlled-release pellets and their subsequent compression into rapidly disintegrating tablets is of increasing interest. To obtain tableted reservoir-type pellets having the same release properties as the original, uncompacted pellets, requires a coating polymer with particular properties.

Kollidon® SR is another new excipient presented in this issue of ExAct. Kollidon SR is designed for the manufacture of sustained release matrix tablets by direct compression. It combines the useful properties of a hydrophilic matrix-forming agent, avoiding the drawbacks of many well established products for this purpose.

We trust that, besides the articles about novelties in the pharmaceutical excipients field, the information on actives like vitamins or pancreatin given in this issue will meet your interest.

Yours sincerely,

BASF Aktiengesellschaft
Marketing Pharma Ingredients

Dr. Folttmann
Compaction of controlled-release pellets

R. Bodmeier and A. Dashevsky, College of Pharmacy, Freie Universität Berlin, Kelchstraße 31, 12169 Berlin, Germany

Abstract
Oral sustained/controlled-release multiple unit dosage forms are becoming more popular when compared to single unit dosage forms. With regard to the final dosage form, the multiparticulates are formulated into single unit dosage forms such as hard gelatin cap-sules or tablets. This article discusses the compaction of coated pellets into tablets and presents results on the compaction of pellets coated with a new aqueous polymer dispersion, Kollicoat® SR 30 D.

Introduction
Multiple unit sustained/controlled-release dosage forms such as pellets offer several advantages when compared to single unit dosage forms such as coated tablets or capsules [1,2]. The multiparticulates spread uniformly throughout the gastrointestinal tract, resulting in less variable bioavailability and a reduced risk of local toxicity. Various drug release profiles can be obtained by simply mixing pellets with different release characteristics or incompatible drugs can be easily separated.

The compaction of pellets is a challenging topic. Ideally, the compacted pellets should disintegrate rapidly in the individual pellets in gastrointestinal fluids. The pellets should not fuse into a non-disintegrating matrix during compaction. The drug release should not be affected by the compaction process. With reservoir-type coated pellet dosage forms, the polymer coating must be able to withstand the compression force; it can deform, but should not rupture.

This article reviews the key variables affecting the compaction and performance of coated pellets (reservoir-type drug delivery systems) including the type of polymer coating and the proper selection of pellet core and tableting excipients. In addition, results are presented on the use of a new colloidal polymer dispersion, Kollicoat SR 30 D, which, because of the flexibility of its films, has great applicability for the preparation of controlled release pellets, which are subsequently compressed into tablets.

Polymer coating
Polymers used in the film-coating of solid dosage forms fall in two broad groups based on either cellulosic or acrylic polymers [3,4]. The acrylic polymers are marketed under the trade name Eudragit® or Kollicoat® and the major cellulosic polymer used for controlled release is ethyl cellulose. Many of these polymers have been formulated into aqueous colloidal dispersions (e.g. latexes or pseudolatexes) in order to overcome problems associated with the use of organic polymer solutions. A recently introduced new colloidal polymer dispersion is Kollicoat SR 30 D, which is a poly(vinylacetate) dispersion stabilized with polyvinylpyrrolidone and sodium lauryl sulfate.

The polymeric coating of the pellets must remain intact during compression in order to control the drug release. Besides its permeability properties, which govern the drug release, the mechanical properties of the particular polymer coating have to be determined in order to investigate its suitability for the coating of pellets to be compressed into tablets.

Ethyl cellulose
Most studies on the compaction of pellets coated with ethyl cellulose revealed a damage to the coating with a loss of the controlled-release properties. The drug release from compressed niacin/microcrystalline cellulose pellets coated with the aqueous colloidal ethyl cellulose dispersion, Surelease® (7% w/w), was much faster when compared to the release of the uncompressed pellets [5]. At higher compression pressures, the pellets were fractured and simultaneously underwent fusion. This resulted in a slight decrease in drug release when compared to the release from compacts compressed at lower compression pressures.

Propranolol HCl pellets were coated with an aqueous ethylcellulose dispersion, Aquacoat®, which was plasticized with 25% triethylcitrate. Irrespective of the pellet content or compression force, the drug release from compressed pellets was significantly faster than from the original pellets (figures 1 and 2). This is not surprising because of the weak mechanical properties of ethyl cellulose. Ethyl cellulose films cast from the plasticized pseudo-latexes, Aquacoat and Surelease, were very brittle and weak with low values for puncture strength and elongation (< 5%) [6].

Acrylic polymers
When compared to the ethyl cellulose films, films prepared from acrylic polymers are more flexible and therefore more suitable for the coating of pellets to be compressed into tablets [6]. Crystals, granules and pellets were coated with various aqueous acrylic polymer dispersions (Eudragit NE 30D, RS/RL 30D and L 30D-55) and compressed into fast disintegrating tablets [7,8]. Multiparticulates coated with flexible polymers (Eudragit NE 30D) and plasticized Eudragit RS/RL 30D could be compressed without significant damage to the coating. Enteric coatings based on Eudragit L30D-55, a methacrylic acid-ethylacrylate copolymer, were brittle and the compression of the pellets resulted in film damage. This damage could be avoided by mixing the enteric polymer with the flexible Eudragit NE 30D. New, more flexible, enteric polymers were developed for the compression of coated pellets [9].

Kollicoat SR 30 D
Kollicoat SR 30 D is a new colloidal poly(vinylacetate) dispersion for the preparation of controlled dosage forms. Kollicoat SR 30 D has several advantages when compared to other colloidal polymer dispersions. Kollicoat SR 30 D – coated pellets usually do not require a curing step (thermal aftertreatment), they have a pH-independent drug release and are easily processed.

Kollicoat SR 30 D was evaluated for the coating of propranolol HCl pellets, which were subsequently compressed into tablets. First, the drug release was determined from pellets coated with the plasticizer-free dispersion.

Effect of pellet content on the drug release in 0.1 N HCl from propranolol HCl pellets coated with Aquacoat (plasticized with 25% triethylcitrate, coating level-20%, 15 kN compression force, filler-Vivapur® 102). (Figure 1)
Effect of compression force on the drug release in 0.1 N HCl from propranolol HCl pellets coated with Aquacoat (plasticized with 25% triethylcitrate, coating level-20%, 50% pellet content, filler - 50% Vivapur 102).  
(Figure 2)

Effect of compression force on the drug release in 0.1 N HCl from propranolol HCl pellets coated with Kollicoat SR 30 D (plasticizer-free, coating level-20%, 50% pellet content, filler - 50% Vivapur 102).  
(Figure 3)

Effect of pellet content on the drug release in 0.1 N HCl from propranolol HCl pellets coated with Kollicoat SR 30 D (plasticized with 10% triethylcitrate, coating level-20%, 15 kN compression force, filler-Vivapur 102).  
(Figure 4)

**Mechanical properties of Kollicoat SR 30 D films.**  
(Table 1)

<table>
<thead>
<tr>
<th>Plasticizer</th>
<th>%</th>
<th>Puncture strength, MPa</th>
<th>Elongation, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>no plasticizer</td>
<td></td>
<td>0.10</td>
<td>1.1</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>5</td>
<td>0.06</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.38</td>
<td>21.4</td>
</tr>
<tr>
<td>Triethyl citrate</td>
<td>5</td>
<td>1.12</td>
<td>31.3</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.93</td>
<td>136.8</td>
</tr>
</tbody>
</table>

The drug release from the compressed pellets was higher than the release from the original pellets (figure 3), indicating insufficient flexibility and rupturing of the polymeric coating.

The mechanical properties (puncture strength and % elongation) of films prepared with Kollicoat SR 30 D are shown in table 1. Plasticizer-free films have low elongation values and therefore low flexibility. This explained the rapid release from compressed pellets coated with the non-plasticized Kollicoat SR 30 D. The inclusion of propylene glycol or triethylcitrate as plasticizers significantly increased the elongation values and flexibility. The addition of only 10% TEC resulted already in elongation values of more than 130%. Plasticized films prepared from Kollicoat SR 30 D have suitable mechanical properties in order to result in flexible coatings and therefore in compressible coated pellets.

The effect of pellet content and compression force on the release from propranolol HCl pellets coated with Kollicoat SR 30 D, which was plasticized with 10% triethylcitrate, are shown in figures 4 and 5. These pellets were compressible without a significant change in release profile for different compression forces and pellet contents. Plasticized Kollicoat SR 30 D results in flexible coatings. Coated pellets could be compressed without film damage. No changes in the drug release were observed when compared to the release from the uncompressed, original pellets.

**Pellet core**

Besides the coating, the pellet core will affect the compaction behavior of the coated pellets. The pellet core should also have some degree of elasticity, which can
accommodate changes in shape and deformation during tableting. It should deform and recover after compression without damage to the coating. Several studies have shown that the compaction of pellets and the mechanical properties of the resulting compacts are quite different from the powdered excipients [10, 11].

Harder pellets coated with Eudragit L30D-55 were able to resist the compression forces better when compared with softer, more porous pellets, which deform easier and therefore resulted in a higher degree of film rupture [12]. Minimal damage to coated pellets was found when the elastic and tensile properties of the coating and the uncoated pellet were similar [13].

The size of the pellets also affects the compaction properties and the drug release from the compacted pellets. At the same coating level, smaller pellets were more fragile than larger pellets. This was attributed to the reduced film thickness of the smaller pellets because of the larger surface area [14]. On the contrary, other researchers found that increasing the particle size resulted in more damage to the coating, as indicated by larger differences between the release profiles of tableted and uncompressed pellets [15].

**Tableting excipients**

The ideal filler used for the tableting of pellets should prevent the direct contact of the pellets (e.g. polymer coatings) and act as a cushion during compression. The excipients should result in hard and rapidly disintegrating tablets at low compression forces and should not affect the drug release. Besides their compaction properties, the excipients have to result in a uniform blend with the coated pellets, avoiding segregation and therefore weight variation and poor drug content uniformity of the resulting tablets. In order to avoid segregation during the flow of the pellet-excipient mixture, excipients with a larger particle size or drug-free placebo pellets could be used as diluents.

The variation in weight and drug content uniformity was minimized when using higher pellet concentrations or larger particle size fractions (e.g. granules) of the inert excipients [12]. Coated pellets could be prepared with a smaller size in order to approach the particle size of the inert excipients. Smaller pellets would also improve the content uniformity of low dose drugs.

The protective effect of different tableting excipients on the compression of theophylline granules coated with Eudragit RS was studied indirectly through dissolution studies [16]. The order of the least damage to the coating was: polyethylene glycol 3350 < microcrystalline cellulose < crospovidone < lactose < dicalcium phosphate. These results were in good agreement with the yield pressure of the excipients. A patent has been issued on the use of microcrystalline cellulose in concentrations between 10 and 50% w/w with coated granules in order to prevent fracture of the coated granules and to result in a tablet matrix of sufficient hardness [17].

**Conclusions**

The challenges in preparing tablets from coated pellets are evident. Various formulation and process parameters have to be optimized in order to obtain tableted reservoir-type pellets having the same properties, and in particular, release properties as the original, uncompressed pellets. The most important variable is the type of polymer selected for the coating of the pellets. The polymer coating must remain intact during compaction in order to extend the drug release. Traditionally used polymers for the coating of solid dosage forms which do not resist the mechanical stress during compaction (e.g. ethyl cellulose) are not suitable for the preparation of compacted pellets. The polymers have to be flexible enough to not rupture.

Kollidur SR 30 D, a new aqueous colloidal dispersion of poly(vinylacetate), results in flexible coatings with small amounts of plasticizer and therefore is highly suitable for the compression of controlled release pellets. The drug release from Kollidur SR 30 D-coated pellets was unaffected by the compaction into tablets.
Kollidon® SR

A new excipient for sustained release matrices.
F. Ruchatz, K. Kolter, S. Wittemer, W. Fraunhofer

Introduction
The manufacture of matrix tablets by direct compression is a cost saving simple process bearing a high attractivity. Polymers utilized as hydrophilic excipients for controlled release formulations (i.e. HPMC, alginates, xanthan gum) are well known and widely used [1, 2]. There are, however, some distinct disadvantages for some of these hydrogel formers, which complicate the development and production of matrix tablets: the lack of polymer flowability hampering the direct compression process, the influence of the pH value (alginites, xanthan gum) and the ionic strength (HPMC) on the release profile and the poor compressibility of the hydrogel formers. This will result in tablets with a low hardness (xanthan gum, alginates).

Objective
To address these concerns, Kollidon SR was developed as a new direct compressible excipient for sustained release matrices. Kollidon SR is a formulated, free flowing, non-hygroscopic powder consisting of 8 parts (w/w) polyvinyl acetate and 2 parts (w/w) polyvinylpyrrolidone. Kollidon SR should retain the useful properties of an hydrophilic matrix forming agent, avoiding the drawbacks of the commercially available products. The intent of the presented study is to characterize Kollidon SR, with respect to the compression behavior and to determine the influence of different media on the release profile of tablets, with different model drugs.

Materials and Methods
Materials
Kollidon SR (BASF); propranolol-HCl (A), caffeine (B) (Knoll); Mg-stearate (Bärlocher); Aerosil 200 (Degussa).

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

Manufacture of the tablets
The ingredients were weighed (see table 1), blended for 10 min in a tubula mixer and passed through a 800 µm sieve. The mixtures were compressed using an instrumented rotary press Korsch PH 106, rotation speed 30 rpm, with the compression forces 10, 18 and 25 kN, tablet diameter 10 and 12 mm, beveled edge.

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

Release studies
The dissolution experiments were performed using a PTS-W, Pharmatest with different buffer solutions [a] 0.08 N HCl USP XXIII, b) phosphate buffer solution pH 7.4 (PBS 7.4, USP XXIII), c) PBS 7.4 + 2.5 % NaCl] at 50 rpm and 37°C. The release profile in PBS pH 7.4 at 100 rpm was also recorded.

Results and Discussion
The excellent flow properties of Kollidon SR are shown in table 2. The angle of repose was far below 30° and the flow time of 150 ml powder through the funnel was fast and consistent. When considering the bulk and tap densities, only small variations of the tablet weight are expected.

This was confirmed by the evaluation of the tablet properties (table 3). A high content uniformity was achieved with both model drugs caffeine and propranolol-HCl although, the latter drug is known for its poor flow properties.

Table 1: Tablet compositions with Kollidon® SR and the model drugs (amount per tablet [mg])

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kollidon SR</td>
<td>160</td>
<td>160</td>
</tr>
<tr>
<td>Propranolol-HCl</td>
<td>160</td>
<td>160</td>
</tr>
<tr>
<td>Caffeine</td>
<td>3.4</td>
<td>3.4</td>
</tr>
<tr>
<td>Aerosil 200</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Mg-stearate</td>
<td>325.0</td>
<td>325.0</td>
</tr>
</tbody>
</table>

The direct compression resulted in tablets with an extremely high hardness and a low friability. According to the chemical composition and the adjusted particle size distribution, the marked dry binding capacity in combination with the good flow properties, are regarded as additional benefits when using Kollidon SR as sustained release excipient.

As shown in figure 1, a sustained release of the highly water soluble drug caffeine was obtained over a period of more than 16 h. Moderate swelling of the tablets was observed, but the tablet shape remained intact due to the water insoluble polyvinylpyrrolidone. The release mechanism can be assumed as diffusion controlled.

Neither different pH-values, the variation of the ionic strength or the change of the paddle speed simulating different hydrodynamic conditions, influenced the release profile of caffeine tablets with Kollidon SR. Overall, no influence of the compaction force on the release profile of caffeine and propranolol-HCl tablets could be detected (figures 2, 3).

The content uniformity of caffeine tablets was independent from the compression force.
Influence of compression force on the release profile of Kollidon SR tablets with propranolol-HCl. (Figure 2)

Influence of compression force on the release profile of Kollidon SR tablets with caffeine (diameter 10 mm). (Figure 3)

As expected, the tablet hardness increased with increasing forces. The variation of the compression force caused only minor changes affecting the production of propranolol-HCl tablets (figure 4).

**Conclusions**

Kollidon SR, a new excipient for drug delivery matrices, possesses good controlled release properties.

The release profiles of tablet formulations with Kollidon SR were not influenced by different dissolution media or compression forces.

The excellent flow properties and the dry binding activity of Kollidon SR, provide easy handling and effective development and production of sustained release tablets.

**References**


Poloxamers (2)

Lutrol® F 127 (Poloxamer 407).
B. Fussnegger

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 specifically selected sites in the body, combined with the reduction in quantity of applied drug [1]. All these aspects could optimize systemic and minimize side effects of active drugs.

Structure
The poloxamers 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, different appearances (liquid, paste and solid) and variations in the hydrophilic or hydrophobic character of the individual compounds. Lutrol F 127 has an average molecular weight of about 12200. The polyoxyethylene units represent about 73% of the molecular weight whereas that one of polyoxypropylene stands for about 27%. Due to the composition Lutrol F 127 is readily water soluble.

Pharmacopoeial Situation
Up to now the products for pharmaceutical use have been characterized on the one hand in the family-monograph 'Poloxamers' in the USP/NF, on the other hand in individual monographs cited in JPE (Japanese Pharmaceutical Excipients, 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].

The latest edition of the American Pharmacopoeia USP24/NF19 harmonizes the monomer contents in terms of ethylene oxide, propylene oxide and 1.4 - dioxane to the figures published in Ph.Eur.

General Properties of Lutrol F 127
The most important property for its application in pharmaceutical dosage forms is the capability of Lutrol F 127 to form thermo-reversible gels the rheological properties of which largely depend on their concentration. Dilute aqueous solutions display Newtonian flow. Above concentrations of 10% it changes to plastic flow with a pronounced change in flowability and viscosity.

Figure 3 shows the temperature influence on the viscosity of aqueous poloxamer 407 solutions at low temperatures, whereas figure 4 demonstrates the influence of the polymer concentration on the viscosity at constant temperatures. Both figures are taken from literature [3].

Due to the reversibility of the thermoviscosimetric behaviour of Lutrol F 127, gels could be prepared either by dissolving the polymer at temperatures exceeding 70°C or in the cold at around 5°C to 10°C. The latter possibility is always recommended in cases of a heat sensitive active. The sol-gel transition temperature of aqueous solutions of Lutrol F 127 ranges from around 15°C to 25°C at polymer concentrations exceeding 16% and is highly influenced by co-formulated components such as organic or inorganic salts, PEGs, solvents, etc. Certain salts with multivalent anions, at characteristic concentrations, prevent poloxamer 407 solutions completely from forming gels [4].

In contrast to Lutrol F 68 with its property to form micelles, this capability is not known of Lutrol F 127. Its gelling however can be attributed to structures formed by hydrophobic interactions of its polypropylene oxide units. This effect has been widely used with actives to modify their dissolution properties and stability.

Applications of Lutrol F 127
Lutrol F 127 and its effects on formulated actives [5] When indomethacin was formulated in gels containing Poloxamer 407 at concentrations from 0–30% w/v the hydrolysis rates of the active were slower in the gels than in a buffer solution alone. It is predicted that at pH 7.0 and 20°C, the time required for 10% indomethacin degradation is 2.7 years in 20% w/v Poloxamer 407 gel, while it is 48 days in the aqueous solution.

The degradation of indomethacin in different gel systems was studied [6] at different concentrations of each gelling agent at pH 10.2 and at 35°C and 45°C. The results indicate that no protection against indomethacin hydrolysis was provided by the viscous carbopol and CMC-sodium gels. Protection was observed however in case of nonionic poloxamer 407 gels, which consists of structured three-dimensional hydrophobic areas, where actives can be enclosed and thus sheltered from hydrolysis.
To increase or to modify the release characteristic of poorly soluble drugs, solid dispersions were obtained by melting Lutrol F 127 and adding the actives to the molten compound. In a second step tablets were formulated by blending these solid dispersions with e.g. Methocel K15M, Avicel PH101 and Magnesium stearate. The blends are compressed to obtain modified-release formulations for oral administration. Examples of active ingredients whose solubility and therapeutic effectiveness can be improved with the formulations are among others cisapride, cyclosporin, diclofenac, felodipine, ibuprofen, indomethacin, nicardipine, nifedipine, terfenadine and theophylline [7].

The in vitro release characteristics of various actives depend on the parameters poloxamer concentration, temperature and pH. When diclofenac and hydrocortisone were used as model drugs and the release rates from Poloxamer 407 gels were studied in an in vitro membraneless release model [8], the release rate decreases with increasing Poloxamer 407 concentration, but increases with increasing temperature. A linear relation was obtained between the apparent release rate and the initial drug concentration, but increases with increasing temperature and pH. When diclofenac and hydrocortisone, no pH-dependency was observed. Thus, the drug is released upon the gel pH and was maximal at pH around 7, whereas in the case of hydrocortisone, no pH-dependence was determined with wound models [10]. As all the additives studied resulted in deletious effects on EGF stability aqueous topical preparations of EGF additives studied resulted in deleterious effects on EGF stability aqueous topical preparations of EGF formulations containing various stabilizers have been evaluated and the pharmacological activity of gel preparations was determined with wound models [10]. All as the additives studied resulted in deletious effects on EGF stability aqueous topical preparations of EGF formulations containing various stabilizers have been evaluated and the pharmacological activity of gel preparations was determined with wound models [10]. As all the additives studied resulted in deleterious effects on EGF stability aqueous topical preparations of EGF were formulated with Poloxamer 407 as a gel base in saline in combination with gelatin or amastatin as a protease inhibitor. The pharmacological effect of EGF gel studied with open wound model in mice revealed significant higher healing effects compared to the gel without a protease inhibitor. The EGF gel made of Poloxamer 407 containing a protease inhibitor would be a promising aqueous topical preparation for EGF.

The enhancement in wound healing by transforming growth factor-β1 (TGF-β1) was studied by [11] in relation to the release characteristics from different topical delivery systems such as phosphate-buffered saline, a poloxamer 407 gel, DuoDERM hydroactive paste, and poly(ethylene oxide) hydrogel. When the release of 125Iodine-labeled TGF-β1 from carriers was measured in full-thickness wounds in rats and the healing of the wounds was analyzed by histological and wound area measurements it became obvious that these effects were most prominent when TGF-β1 was formulated with a poloxamer 407 gel formulation, which provided the most sustained release of TGF-β1. The finding that the enhancement in wound healing by TGF-β1 was significantly dependent on the carrier used for its topical delivery to the wound site shows the importance of using adequate delivery systems when growth factors but also other proteins are used to enhance wound repair and wound healing.

In [12] topical preparations such as hydrophilic ointments for local treatment of deep skin burns were evaluated. Local anesthetics carbizocaine and lidocaine were used as drugs. Tests were performed among others using Poloxamer 407 as gel forming component.

Lutrol F 127 in dental formulations and oral rinses Not only a variety of dental formulations, oral rinses and dentifrices are known to be formulated using Lutrol F 127 but also semi-solid tetracycline-containing formulations based on Poloxamer 407 were prepared for the treatment of periodontitis by direct periodontal intrapocket administration. The formulations are easily administered by a syringe equipped with a needle appropriate for intrapocket delivery. They are characterized by a sol-gel transition, becoming semi-solid once in the periodontal pocket and, finally, they represent biocompatible formulations eliminated from the body by normal routes [13].

Lutrol F 127 in ophthalmic formulations Formulations containing poloxamer 407 for ophthalmic use are well documented not only in patent literature such as [14], where the ophthalmic drug delivery with thermoreversible polyoxalkylenे
gels adjustable for pH is claimed. The composition is a liquid at room temperature or below and a gel with a desired osmolality at body temperature. For example, a solution containing neomycin sulfate 0.55%, polymyxin B sulfate 0.12%, glycerin 0.7%, poloxamer 407 10.0%, methyl/paraaben/propy/paraaben 0.1%, and Tris-HCl buffer 70/53% exhibited gelation at approximately 33°C and osmolality of approximately 650 mOsm/kg in the liquid state at pH 7.5 and calculated osmolality in the gelled state was approximately 290 mOsm/kg.

The role of tear deposits on hydrogel contact lenses-induced bacterial keratitis and possibilities for its prevention was determined in [15]. Among other polymers of poloxamer series tested, poloxamer 407 decreased Pseudomonas aeruginosa adherence to new hydrophilic contact lenses by 94%. This poloxamer is non-toxic, stable, water-soluble, and lacks antimicrobial activity. Thus, it could be used to prevent bacterial attachment to contact lenses and, may be therefore, a potential candidate to reduce the incidence of contact lens-induced keratitis.

**Lutrol F 127 and the formulation of nanoparticles**

Some years ago solid lipid nanoparticles (SLN) have been developed as new drug delivery systems. Although many particulate drug carriers, such as microspheres, liposomes, niosomes, emulsions, etc., have been introduced, they have some disadvantages, e.g., low efficiency of incorporation, poor stability and lack of reproducibility. Meanwhile, SLN as new drug delivery systems entraps drugs with a high efficiency and a good reproducibility. Also, small size SLN can circulate in blood for a prolonged time. A preparation of ketoprofen-incorporated solid lipid nanoparticles (Keto-SLNs) by ultrasonication and microfluidization and their evaluation was performed in [16]. Keto-SLN was evaluated by the measurement of particle size and zeta-potential, efficiency of entrapment, sedimentation volume, and in vitro release pattern. The mean particle size was about 0.1 µm, and the size was dependent on the type and amount of the emulsifier. Zeta-potential was negative, entrapment efficacy was very high and stability was good for at least 60 days in the respect of particle size and sedimentation. The analgesic effect was also comparable to that of ketoprofen-loaded suspension. Therefore, keto-SLNs delivery systems can be used for anti-inflammatory agents such as ketoprofen and in addition for other actives such as antioxidant drugs, analgesics, etc.

Solid lipid nanoparticles (SLN) as alternative i.v. colloidal drug carriers were produced by high pressure homogenization of melted lipids. In order to reduce the phagocytic uptake by the reticuloendothelial system (RES) after i.v. injection their surface was modified [17] by using hydrophilic polymers such as Poloxamer 407. Viability determinations revealed the SLN to be 10 fold less cytotoxic than poly lactide nanoparticles and 100 fold less than Bucymanoate particles. Poloxamer 407 surface-modified solid lipid nanoparticles (SLN) for drug targeting purposes as alternative colloidal carrier systems for controlled drug delivery are discussed in [18]. The surfactant polymers are directly incorporated in the production process. Production parameters were optimized to obtain nanoparticle sizes required for the envisaged targets, e.g. < 150 nm for endothelial cells. Drug loading capacities of 9.8% of the lipid matrix were obtained, prolonged in vitro drug release was achieved over 5 wk (prednisolone). SLN of optimized composition proved to be physically stable during sterilization (autoclaving) and on long-term as aqueous dispersion.

The influence of coatings with surfactants such as poloxamer 407 on the body distribution of nanoparticles after intravenous injection to rats was studied in [19]. After i.v. injection, nanoparticles or other colloidal drug carriers such as liposomes are rapidly removed from the blood by the reticuloendothelial system (RES) and distributed in the body organs. Since it was shown that the surface properties have an important influence on the body distribution. An evaluation of Poloxamer 407 gels alone or in combination with polyactic-co-glycolic acid (PLGA) nanoparticles containing peptides or proteins for parental delivery was performed using insulin as active [20]. In vitro techniques were applied and in vivo evaluations were performed after s.c. application. The in vivo results demonstrated that higher concentrations of poloxamer 407 in the gel resulted in slower release of insulin from the matrices, independent of the vehicle used. Compared to an insulin solution, in vivo administrations of insulin loaded to a poloxamer 407 gel resulted, in a slower and more prolonged hypoglycemic effect of insulin which was inverse proportional to the polymer concentration. Poloxamer 407 gels containing insulin-PLGA nanoparticles had the most long-lasting hypoglycemic effects of all formulations. This in vitro and in vivo study revealed that gel formulations containing either drug or drug-nanoparticle formulations could be useful for the preparation of controlled delivery systems for peptides and proteins having short half-lives.

**Lutrol F 127 in combination with gel-forming polymers**

The development of liquid formulations, thermo-gelling at the administered site, is of increasing interest. This includes e.g. drug delivery systems for parental use. When injected i.m. the formulation forms a depot for the controlled release of drug by gelling at body temperature. The addition of F 68 strongly influenced the thermo-rheological properties of F 127 formulations. In contrast to the effect of common used salts (e.g. NaCl) the addition of F 68 to F 127 formulations resulted in an increase of the sol-gel-transition temperature, probably due to the formation of mixed micelles [21]. Further arguments for the use of these polymers are their solubilizing capacity and the good compatibility with drugs.

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Lycopene

BASF's new carotenoid.

B. Michelsen, U. Sindel

Introduction

The awareness of the tight link between diet and health is ever increasing and new research data keep emerging showing beneficial effects of specific food components. Carotenoids are among the components that have received special attention, in particular provitamin A carotenoids such as beta-carotene.

Lycopene was ignored for a long time due to its lack of vitamin A activity. This, however, has changed dramatically during the last 5 years and lycopene is now receiving major attention. Lycopene has unique properties and research data show that lycopene may have beneficial health effects.

BASF is expanding its product range with this promising carotenoid and will be offering high concentrated and stable lycopene products for dietary supplements in 2000.

Origin

Lycopene is found almost exclusively in tomatoes where it is the major carotenoid, giving tomatoes their characteristic color. Watermelons, pink grapefruits, papayas and guavas contain lycopene as well, but tomatoes and tomato products such as ketchup are the main dietary lycopene sources providing more than 85% of the dietary lycopene.

Structure

Lycopene is a non-polar hydrocarbon with 11 conjugated and 2 non-conjugated double bonds. In contrast to beta-carotene, lycopene lacks the ring system and therefore does not contribute to vitamin A activity.

Carotenoids exist in both cis- and trans-isomeric forms. The trans-isomeric form can be converted to the cis-isomer by exposure to light or heat or by chemical reaction. Lycopene obtained by extraction from tomatoes contains approximately 85% of the trans-isomeric form. Chemically synthesized lycopene has a similar content of the trans-isomeric form and can thus be considered as nature-identical lycopene.

Biological effects

Lycopene has the highest antioxidant capacity among all carotenoids tested which is attributable mainly to the 11 conjugated double bonds in the molecule. Lycopene is a very efficient quencher of singlet oxygen and was shown to be a potent radical scavenger as well [1]. Recent in vitro studies showed that lycopene protected human cells against radical damage [2, 3] and protected human LDL against oxidation [4].

Role of lycopene in health

Oxidative damage to DNA and lipids is believed to be involved in the initiation and progress of chronic diseases such as cancer and cardiovascular diseases. Prevention of oxidative damage is therefore in focus in research and being a strong antioxidant, lycopene is being investigated intensively. Many studies have already shown that lycopene may play a role in lowering the risk for some chronic diseases.

Tissue culture studies have shown that lycopene has anti-cell proliferative activity. Lycopene alone inhibits growth of different cancer cell lines [5] and when vitamin E was added, a synergistic inhibition in growth was observed in prostate cancer cell cultures [6]. Lycopene was shown to up-regulate cell-cell communication and thereby acts as an anti-carcinogen independent of its antioxidant properties [7, 8].

In addition to the effects in cell cultures, lycopene has been shown to have anti-tumorogenic activity in mice and rat cancer models [9]. The cell culture and animal studies support the findings in humans, that a high intake of lycopene containing products is associated with a lower risk of cancer and the intake of lycopene containing food products or blood lycopene levels [10]. The associations are particularly strong for prostate cancer.

In a study of some 48,000 male health professionals, those with a lycopene intake of more than 6.5 mg daily had a 21% lower risk of getting prostate cancer in comparison to those with a lycopene intake of less than 2.3 mg daily [10].

With respect to cancer, the notion of a tissue specific action of lycopene is intriguing. Lycopene is accumulated in the prostate and is the dominant carotenoid in this tissue [2]. Recently, dietary intervention studies in prostate cancer patients demonstrated that the lycopene concentration in the prostate can be increased significantly by an increased intake of a lycopene containing product [11, 12]. A decrease in serum levels of a prostate cancer biomarker was obtained as well [12].

BASF’s lycopene grades

All BASF’s lycopene grades are produced with nature-identical lycopene. The stability of crystalline carotenoids is in general very poor. Due to the influence of oxygen, moisture and heat, crystalline lycopene decomposes within a few weeks. Tests performed in our laboratory revealed that after 28 days storage at room temperature in open containers, only 6% of the lycopene content is remaining [13]. Remarkable is also the rapid decomposition of lycopene within the first days of storage. 25% of the lycopene disappeared after only 2 days which makes it absolutely necessary to stabilize the lycopene crystals by formulation.
The following lycopene grades will be offered by BASF:

- **LycoVit 10%**
- **Lycopene Dispersion 20**
- **Lycopene 10 CWD**

**LycoVit 10%**

Lycopene 10% is a red dark powder containing 10% of lycopene embedded in a matrix of gelatine and sucrose coated with modified starch. This microencapsulated form of lycopene shows excellent powder properties, and the microencapsulation ensures a high stability of lycopene both in bulk and in the final product (fig. 2, 3). Based on the physical properties of the microcapsules, LycoVit 10% shows high resistance towards pressure during tableting. LycoVit 10% is suitable for single entity as well as multivitamin tablet formulations. Enclosed is an example of a direct compressible formulation of single entity tablets containing LycoVit 10%.

**Lycopene Dispersion 20**

This product is designed for the application as ingredient in soft gelatine capsules. It contains 20% of microcrystalline lycopene dispersed in sunflower oil. 90% of the dispersed lycopene particles are smaller than 12 µm leading to a high stability of the dispersion. No additional stabilizers are used in the production of Lycopene Dispersion 20.

**Lycopene 10 CWD**

A cold-water-dispersible powder with excellent flow properties is obtained by embedding 10% of lycopene in a matrix of fish gelatine and glucose-syrup through fluidised spray-drying. 25 to 50 ppm of lycopene in a matrix of fish gelatine and glucose-syrup properties is obtained by embedding 10% of lycopene dispersed in sunflower oil.

**Direct compressible formulation of single entity tablets with LycoVit 10%**

<table>
<thead>
<tr>
<th>Property</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula</td>
<td>LycoVit® 10%</td>
</tr>
<tr>
<td>Ludipress® CL</td>
<td>60 g</td>
</tr>
<tr>
<td>Kollidon® CL</td>
<td>330 g</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>6 g</td>
</tr>
<tr>
<td>Microencapsulation</td>
<td>4 g</td>
</tr>
<tr>
<td>Pass the mixture through a 0.8 mm screen and press with medium compression force (about 20 kN).</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>400 mg</td>
</tr>
<tr>
<td>Diameter</td>
<td>11 mm</td>
</tr>
<tr>
<td>Hardness</td>
<td>80 N</td>
</tr>
<tr>
<td>Disintegration (water)</td>
<td>4 min</td>
</tr>
<tr>
<td>Friability</td>
<td>&lt; 0.1%</td>
</tr>
</tbody>
</table>

**Availability**

BASF lycopene grades are now available in sample quantities. Commercial quantities will be available by the end of the year.

**Conclusion**

Lycopene is raising considerable interest on the health and nutrition market. BASF has developed three different lycopene products. BASF lycopene grades are now available in sample quantities. Commercial quantities will be available by the end of the year.

**References**


* See page 12, 'Vitamins – an overview'.

'The microencapsulation technology'
Vitamins
An Overview
K. Petzelt, U. Sindel

Introduction
Vitamins are organic substances which are required to maintain vital functions such as growth, reproduction and energy conversion. As vitamins are not synthesized by the human body or only in insufficient amounts, they have to be supplied through food and supplements either as vitamins or provitamins [1].

During the last years, vitamin research has increasingly turned from classic vitamin deficiency towards risk reduction of chronic degenerative diseases. On the one hand there are correlations enjoying wide recognition, such as the use of folic acid supplementation to protect against neural tube defect. Also the inverse correlation between intake of vitamin E and cardiovascular disease has been shown in numerous studies. Others, like the possible protection of vitamin K against osteoporosis, are now gaining recognition [2].

As a result, the importance of maintaining adequate intake of vitamins is widely accepted.

BASF range of vitamin products
BASF offers a wide range of highly pure crystalline vitamins and vitamin oils as well as microencapsulated fat- and water-soluble vitamin products all

Pass all components through a 0.8 mm sieve, mix and press with high compression force.
Particle size distribution of the microcapsules.

(Figure 3)

Matrix material

Oil drops (1 µm)

Starch layer

Microencapsulated vitamin oil.
(Figure 2)

showing excellent powder and tabletting properties. This product range is complemented by beta carotene as provitamin A.

Many products have been particularly developed to meet the requirements of the pharmaceutical and nutritional supplement industries. Also available are customized vitamin premixes with or without excipients in oily and powder form.

The Product Range [3]
- Water-soluble vitamins
- Fat-soluble vitamin oils
- Microencapsulated vitamins
- Microencapsulated vitamin combinations
- Vitamin premixes
- Carotenoids

All BASF vitamin products and mixes are manufactured under GMP conditions with stringent analytical control.

The Microencapsulation Technology

Some vitamins are sensitive to oxygen, light and moisture. Furthermore oily vitamins like vitamin A and E cannot be used directly for tablet formulations as the oil is extruded during tabletting. To overcome these difficulties – to protect the vitamins against atmospheric effects and to achieve a tabletable form – BASF has developed a sophisticated microencapsulation technology.

Manufacturing process

In the encapsulation process (fig. 1) an emulsion of the active ingredient and a suitable matrix material is atomised. The resulting fine droplets are caught by a fluidised powdering agent, usually starch. This coating is necessary to prevent the emulsion droplets from agglomeration during the drying process.

The final microcapsule (fig. 2) contains the vitamin in form of homogeneously distributed nanodroplets or nanoparticles, embedded in a protective matrix of natural carbohydrates and proteins.

Physical properties

Through microencapsulation a free-flowing, non-dusting powder with narrow particle size distribution is obtained. The mean particle diameter is about 250 µm (fig. 3). Due to their robust structure and elastic properties, the microcapsules show an excellent pressure resistance during tabletting. Therefore only a minimum of active ingredient is extruded during tabletting, leading to a high stability of the final product and a good tablet hardness.

Advantages of microencapsulated vitamins
- non-tablettable vitamins are transferred into powders with excellent tabletting properties
- uniform, free-flowing, non-dusting powder
- spherical particles with narrow particle size distribution
- High shelf life even with sensitive ingredients

Outlook

This overview of the BASF product range of vitamins will be followed by an article about recent additions to our vitamin product line in one of the next editions of ExAct.

References

The Vitamins brochure can be ordered with the attached reply card.
Knoll Pharma Active Ingredients

New Active Ingredients

Introduction
This new business brings together a portfolio of new active pharmaceutical ingredients tailored for the generics industry. The number of products is constantly enlarged and a range of new projects is under development. More detailed product and project information is available from the Internet pages as well as separate leaflets.

I Support for our customers is provided in various ways, for example:
- Patent/exclusivity searches
- Documentation (Product Information Packages, DMF)
- Formulation Support
- Customer Support
Around the world sales representatives of BASF Group or local agents are in close contact with our customers. Due to this network we are able to provide our customers with technical support and help whenever and wherever necessary. The vast spectrum of internal synergies of the entire BASF Group is to the benefit of our customers. For our products, up-to-date documentation, in the form of Customer Product Information Packages and DMF's according to European and US requirements, are available as well as suggested formulations. Patent/exclusivity information on various different issues is available to customers, e.g. products, processes, indications, formulations, etc. Formulation support is provided by our applications laboratories.

Pancreatin Knoll® – Product Profile
Pancreatin Knoll®
Pancreatin has been known to gastroenterology for a long time and is used to treat indigestion caused by exocrine pancreatic insufficiency. This occurs as a result of various pancreatic diseases: chronic pancreatitis, cystic pancreas, mucoviscidosis, lack of an enzyme, status after pancreas and stomach resection.

Pancreatin Knoll® is extracted from the porcine pancreas, using a special manufacturing process – it is a standardized and highly active enzyme combination from only one species, and is largely identical with the natural physiological enzyme pattern of human pancreatic secretes.

Pancreatin Knoll® is offered in various forms, differing only in their enzymatic activities, and all with outstanding technical properties. In addition we are able to meet special requests by customers regarding auxiliaries and particle size. The fine, almost fiber-free powder is characterized by good flowability. Pancreatin Knoll® powder.

Pancreatin Knoll® is an extract of the porcine pancreas and contains lipase, amylase and proteases available in an active state.

Enzyme activity
Pancreatin Knoll® is available with either high lipolytic or high proteolytic activity. The enzyme activity is adjusted according to the request of the customer with lactose, microcrystalline cellulose or saccharose.

Example Pancreatin N
Lipase 80,000 Ph. Eur. U/g
Amylase 60,000 Ph. Eur. U/g
Proteases 3,000 Ph. Eur. U/g
Enzymatic activities in USP – Units are available too.

Storage
Preserved in well-sealed containers, and protected from heat and moisture.

Pancreatin Knoll® in film-coated microtablets.

Pancreatin Knoll® in pellets.

Pancreatin Knoll® in powder.

This support not only saves our customers considerable time but also costs. However, patented products are not offered or supplied to countries in which they are under patent.

Production Facilities
Our production facilities are state-of-the-art and meet the requirements of national and international authorities, especially the FDA and are located all over the world. Highly motivated staff constantly look to improve our already advanced quality standards and reliability of Knoll products. All environmental and other regulatory requirements are at least met if not surpassed, and last but not least our flexibility is designed to ensure that customers are served according to their needs.

Customer Support
Around the world sales representatives of BASF Group or local agents are in close contact with our customers. Due to this network we are able to provide our customers with technical support and help whenever and wherever necessary. The vast spectrum of internal synergies of the entire BASF Group is to the benefit of our customers. For our products, up-to-date documentation, in the form of Customer Product Information Packages and DMF's according to European and US requirements, are available as well as suggested formulations. Patent/exclusivity information on various different issues is available to customers, e.g. products, processes, indications, formulations, etc. Formulation support is provided by our applications laboratories.
BASF – Expertise in Health and Nutrition.

**Product Overview**

**BASF – Expertise in Health and Nutrition.**

- **Direct Compression Agents**
  - Ludipress®
  - Ludipress® LCE

- **Binders, Solubilizers**
  - Kollidon® 12 PF/77 PF
  - Kollidon® 25/30/90 F

- **Disintegrants, Suspension Stabilizers**
  - Kollidon® CL
  - Kollidon® CL M

- **(Dry) Binders, Film Formers**
  - Kollidon® VA 64

- **Sustained Release Excipients**
  - Kollidon® SR

- **Disintegrants**
  - PVP-lodine 30/06
  - PVP-lodine 30/06 M10

- **Enteric Film Coatings**
  - Kollicoat® MAE 30 DP
  - Kollicoat® MAE 100 P

- **Sustained Release Film Coatings**
  - Kollicoat® EMM 30 D
  - Kollicoat® SR 30 D

- **Colorants**
  - Sicovit®, soluble dyes
  - Sicovit®, lakes and pigments

- **Solubilizers/Emulsifiers**
  - Cremophor® RH 40
  - Cremophor® EL
  - Cremophor® A 6/8 A 25

- **PEGs, Poloxamers**
  - Lutrol® E grades
  - Lutrol® F grades

- **Solvents**
  - Propylene Glycol

- **Active Ingredients**
  - Crospovidone M
  - Tretinoin
  - Isotretinoin
  - Retinol 50P

- **Carotenoids**

- **Sustained relief!**
  - Kollidon® new excipient for smooth direct compression of sustained release dosage forms.

- **BASF – Your Global Commitment.**
  - Quality
  - Supply safety
  - Future

- **LycoVit 10%**
  - a microencapsulated product containing lycopene.
  - Dietary supplement with lycopene.

- **Vitamins**
  - Fat-soluble Vitamins
    - Vitamin A
    - Vitamin D₃, D₉
    - Vitamin E
    - Vitamin K₁
  - Water-soluble Vitamins
    - Vitamin C
    - Vitamin B₉ (Thiamin)
    - Vitamin B₁₂ (Bilobain)
    - Nicotinamide
    - Calcium-D-Pantothenate
    - Vitamin B₆ (Pyridoxine Hydrochloride)
    - Vitamin B₁₇ (D-Biotin)
Vitamin B₂ in a new shape — Riboflavin 100.
In general, direct-compressible actives have gained more and more importance. This is especially the case for substances which are difficult to handle in their pure form, like Riboflavin. Due to the appearance of crystalline Vitamin B₂ — a strongly staining powder with a low tap density — the application of the pure material is not very common in pharmaceuticals or nutritional supplements.

Direct-compressible Riboflavin formulations generally consist of granules with a certain amount of excipients in order to provide binding and disintegrating properties.

BASF offers a direct-compressible 100% preparation and combines the advantages of improved tablet properties and optimized release rates with the highest possible potency.

ExAct No. 5 will inform you about a well-known vitamin in a new shape. For information in advance: please contact your local BASF company or one of our regional centres.

**Contact**

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

**Asia**
BASF East Asia Regional Headquarters Ltd.
Dr. Danilo Mercado
7/F., Tower I, South Seas Centre East
Tsim Sha Tsui
P.O. Box 86427
Kowloon, Hong-Kong
Fax: **852/23122261**

**Europe**
BASF Health & Nutrition A/S
Ms. Rie Rosenstand
Malmparken 5
DK-2750 Ballerup
Denmark
Fax: **45/44730102**

**NAFTA**
BASF Corporation
Pharma Specialties, Mr. Richard Becker
3000 Continental Drive North
Mount Olive, NJ 07828-1234
USA
Fax: **1/973 426 5369**

**South America**
BASF S.A.
Fine Chemicals, Mr. Torsten Meid
Caixa Postal 139
09701-970 São Bernardo do Campo
Brazil
Fax: **55/11 751 21 99**

**Eastern Europe/Africa/West Asia**
BASF Aktiengesellschaft
LRV/CM – D 205
Mr. Matthias Hof
D-67056 Ludwigshafen
Germany
Fax: **49/621 60 446 89**

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

**Preview**

**News**

**New Ph.Eur. Monographs for Lutrol® Grades.**

**Lutrol® E grades**
In the Supplement 2000 to Ph. Eur. a new family monograph “Macrogols” was published. It includes all of our Lutrol E grades which meet the requirements of this monograph.
The following major changes can be found in the new monograph:

- **Reducing substances**
  A reaction with resorcinol substitutes the reaction with potassium permanganate because the results obtained with permanganate were not always clear.

**Kollidon 90 F — New Packaging.**
We have just finished in December 1999 the new packaging line for Kollidon 90 F. It is a card box with a PE/Alu-inliner with 20 kg net weight. It is filled under air and then vacuum and purging with nitrogen is applied.
The new packaging will improve the stability and expiration period. Stability tests with the new packaging according ICH-guideline will be started.

**PVP-Iodine.**
In the last 25 years PVP-Iodine 30/06 was made in Ludwigshafen. In 1996 we started a second production site in Geismar, Louisiana.
From the beginning of 2000 we will transfer the production completely to Geismar. That means in case of audits etc. the site will be in Geismar near New Orleans.

**Formaldehyde**
The functionality test of the presence of formaldehyde was introduced because macrogols are used in soft gelatin capsules and formaldehyde is not compatible with gelatin.

**Lutrol® F grades**
In the Supplement 2000 to Ph. Eur. also a family monograph “Poloxamers” was introduced. It is almost harmonized with the corresponding USP-NF monograph and our Lutrol F grades meet the requirements of this new Ph.Eur. monograph.

**Lutrol® Y grades**
In the Supplement 2000 to Ph. Eur. a new family monograph “Macrogols” was published. It includes all of our Lutrol Y grades which meet the requirements of this monograph.

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**Lutrol® Y grades**
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**Reducing substances**
A reaction with resorcinol substitutes the reaction with potassium permanganate because the results obtained with permanganate were not always clear.