BASF

The Chemical Company

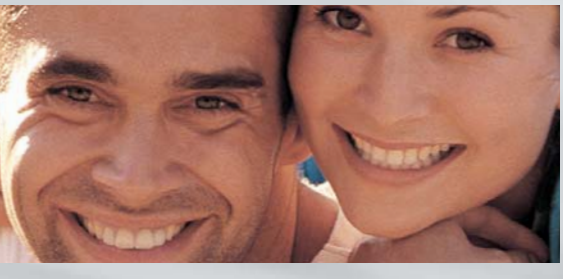
Content Uniformity

Lμtrol® micro

The new measure for bioavailability.

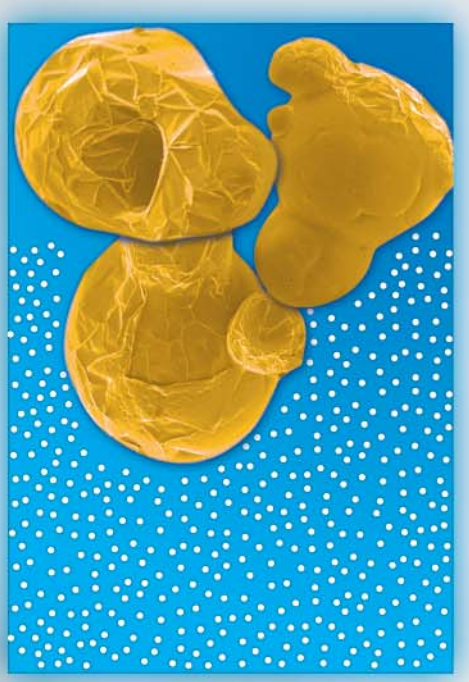
The Preface

In recent years an increasing number of poorly soluble substances has been developed.



This requires the addition of solubilizers in order to make those substances bioavailable. As solid oral dosage forms are the preferred formulation, solubilizers are required with special galenical properties.

Poloxamers are compounds with a long history of use in the field of solubilization that have excellent properties. We are now able to offer micronized grades of these monographed compounds, which results in several advantages:



- Effective solubilization and increased bioavailability, elimination of dose dumping
- Low toxicity
- Perfect content uniformity
- Average particle size within the same range as for active ingredients, which results in homogenous mixtures for granulation or tabletting
- Robust production process Compatibility of the active ingredient and excipients
- No need for micronization of active ingredients for better solubility

The Preface

Lutrol® F
+ active

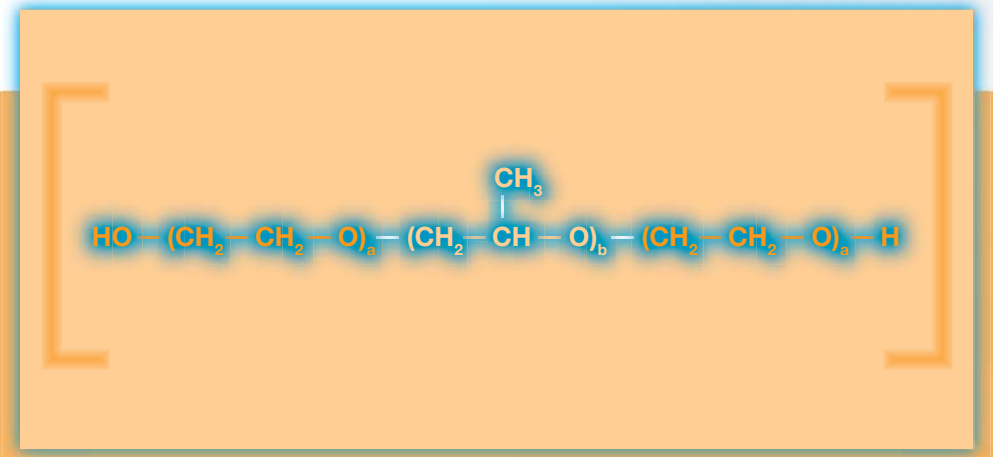
Lμtrol® micro
+ active

The Product

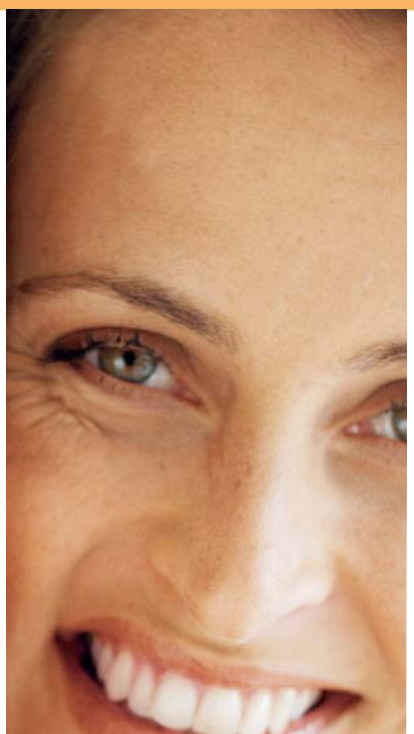
*For **Lµtrol®micro 68**:*
a = approx. 79
and b = approx. 28
The proportion of polyoxyethylene by weight is approx. 70 %

*For **Lµtrol®micro 127**:*
a = approx. 101
and b = approx. 56
The proportion of polyoxyethylene by weight is approx. 80 %

The **Lµtrol®micro** grades are micronized poloxamers working as solubilizing agents. A special micronization process is applied to achieve superior properties.



Structural formula: Lµtrol®micro 68 and 127 are polyoxyethylene-polyoxypropylene block copolymers with an average molecular weight of around 8,600 Daltons and 12,200 Daltons, respectively.



Product form:

At room temperature **Lµtrol®micro 68** and **127** appear as white powder prepared by micronization of prilled poloxamer grades. The products are manufactured by alkali-catalyzed polymerization of propylene oxide followed by ethoxylation of the polyoxypropylene unit with subsequent neutralization. The products contain butylhydroxytoluene as an antioxidant and have a weak odor.

Pharmacopoeia:

Both products meet the requirements of the current USP-NF “Poloxamer”, JPE “Polyoxyethylene/Polyoxypropylene Glycol” and Ph. Eur. family monograph “Poloxamers”.

The Product

Chemical nature:

The polymers are block copolymers of polyoxyethylene-polyoxypropylene. Both products have been micronized to an average particle size of approx. 50 µm.

	Lµtrol®micro 68	Lµtrol®micro 127
Molecular weight	7680–9510 g/mol	9840–14600 g/mol
pH-value (2.5 % in water)	5.0–7.5	5.0–7.5
Unsaturation	0.018–0.034 meq/g	0.031–0.065 meq/g
Melting point	52–57 °C	50–56 °C
Polyoxyethylene by weight	79.9–83.7 %	71.5–74.9 %
Heavy metals	max 10 ppm	max 10 ppm
Ethylene oxide	max 1 ppm	max 1 ppm
Propylene oxide	max 5 ppm	max 5 ppm
1,4-Dioxane	max 5 ppm	max 5 ppm
Sulfated ash	max 0.4 g/100 g	max 0.4 g/100 g
Volatile organic compounds	acc. to monographs	acc. to monographs

The test methods are described in the current monographs USP-NF "Poloxamer", JPE "Polyoxyethylene/Polyoxypropylene Glycol" and Ph. Eur. family monograph "Poloxamers".

Solubility:

Both products are readily soluble in water and ethanol (95 %) and other mainly polar solvents. They are insoluble in ether, paraffin and fatty oils.

Rheological properties:

Diluted aqueous solutions of both products show Newtonian flow properties that change to plastic flow properties. For **Lµtrol®micro 68** it changes at a concentration of approx. 60% and for **Lµtrol®micro 127** it changes at concentrations of above 15 %.
Lµtrol®micro F 127 is thermoreversible. **Lµtrol®micro 68** shows a maximum viscosity at 60 to 75 °C whereas **Lµtrol®micro 127** shows the maximum between 30 to 60 °C.

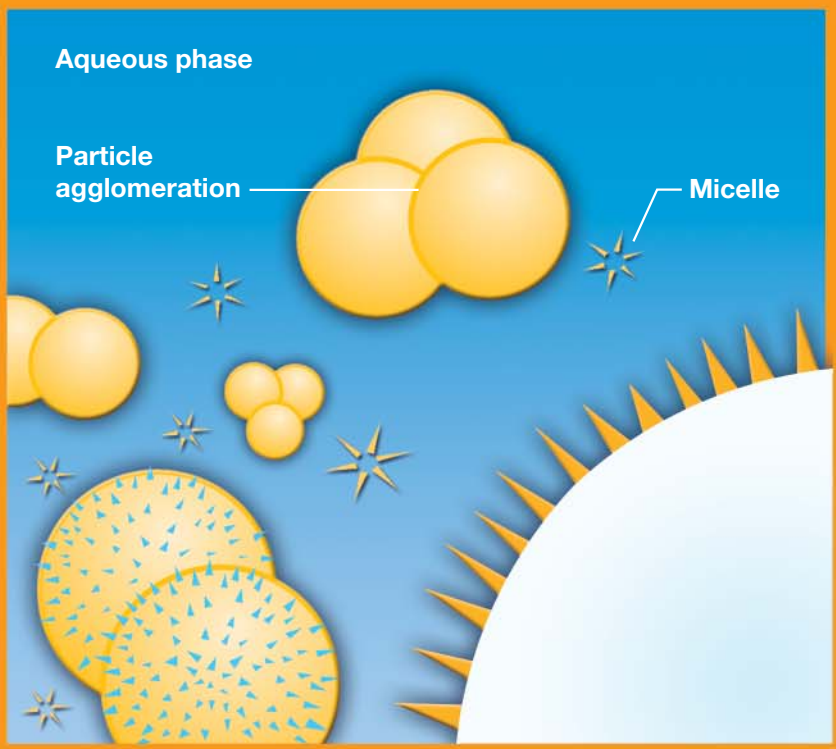
The Application

Lμtrol®*micro* grades are the excipients of choice for your dissolution problems with solid oral dosage forms.

Lμtrol®*micro* grades offer:

- A high HLB value of > 20
- An excellent miscibility
- A wide acceptance of regulatory authorities

Conventional nonionic surfactants are believed to act as a physical barrier to separate particles



Beyond CMC (critical micelle concentration), addition of more surfactant does not provide additional stabilization

Over time, aggregation can occur

The Application

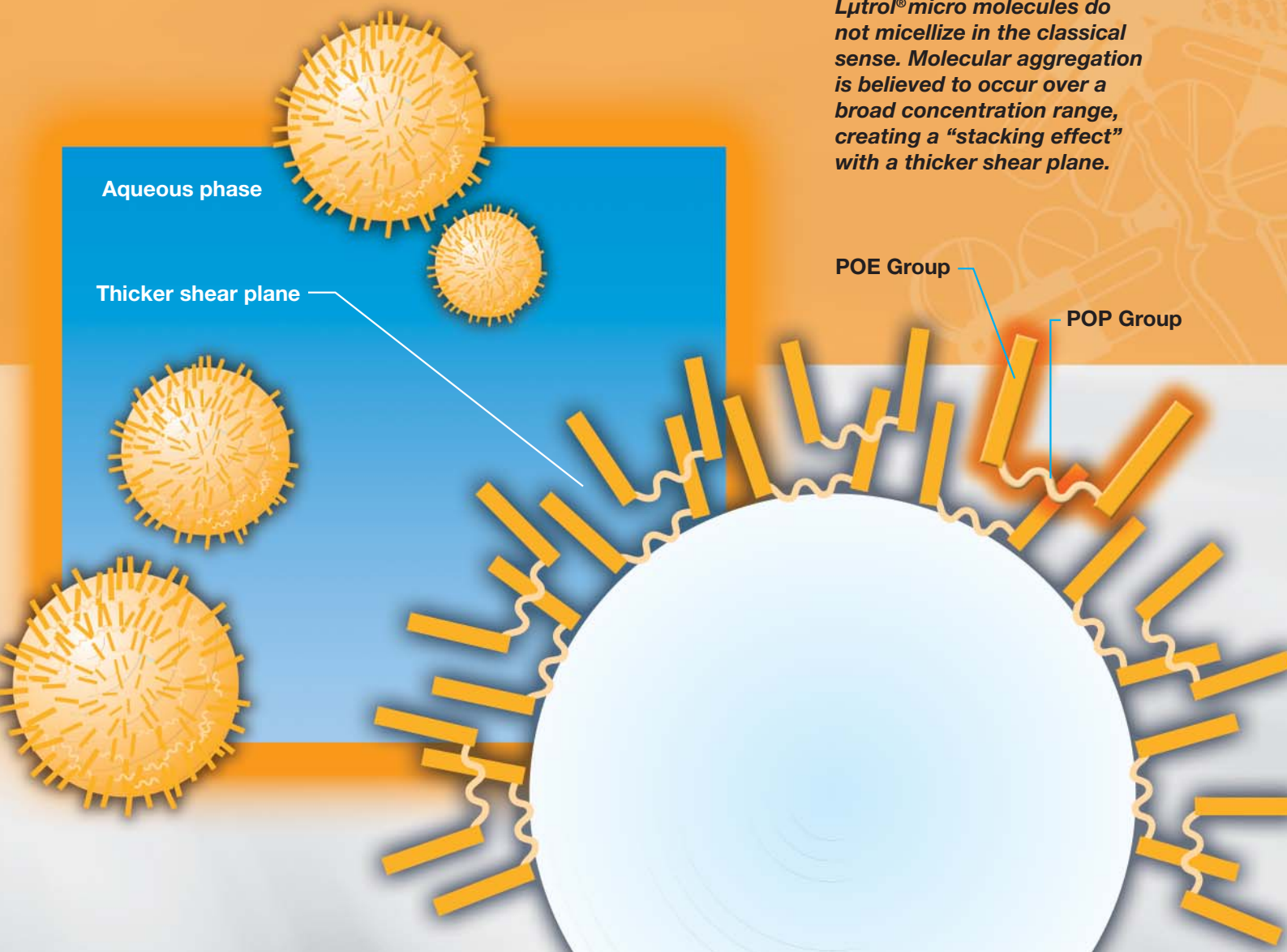
Lμtrol®*micro* grades can be used in several pharmaceutical application fields:

- Dissolution enhancer for actives in tablets and capsules
- Lubricant for actives incompatible with magnesium stearate, e. g. ibuprofen
- Polishing agent for film-coated tablets
- Dispersing/wetting agent
- Water soluble lubricant e. g. for effervescent tablets

Due to the low average particle size that is in the same range as for active ingredients a direct blending with the active is possible with a low tendency of demixing.

This allows a very cost- and time-saving production.

There is evidence that Lμtrol®micro molecules do not micellize in the classical sense. Molecular aggregation is believed to occur over a broad concentration range, creating a "stacking effect" with a thicker shear plane.



The Formulation

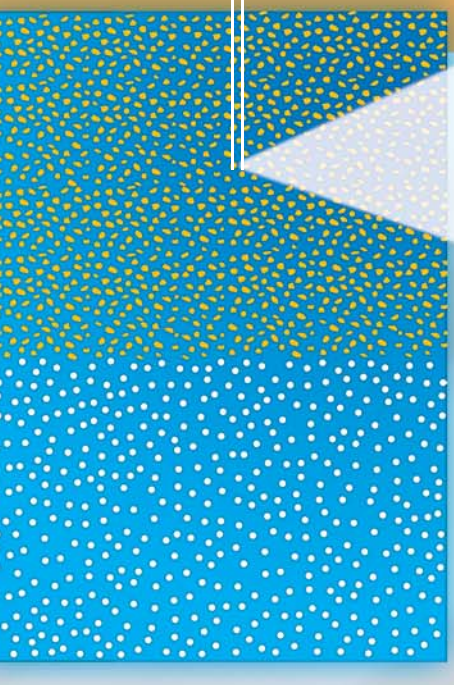
To show the good properties of Lµtrol® micro grades a number of poorly soluble actives was tested.

In this case a very easy manufacturing method was chosen to show only the influence of the solubilizer. Active ingredients and **Lµtrol® micro** were blended for 10 minutes.

After mixing the material was filled into capsules and the dissolution profile was determined in an aqueous dissolution medium.
To give detectable values of the reference material (without solubilizer) the dissolution medium was mixed with ethanol.

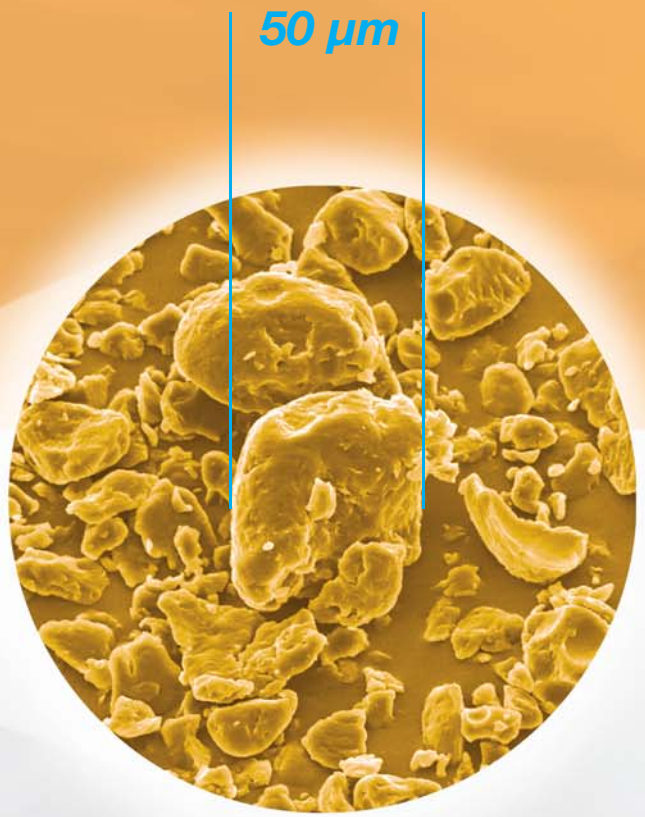
1,000 µm

50 µm



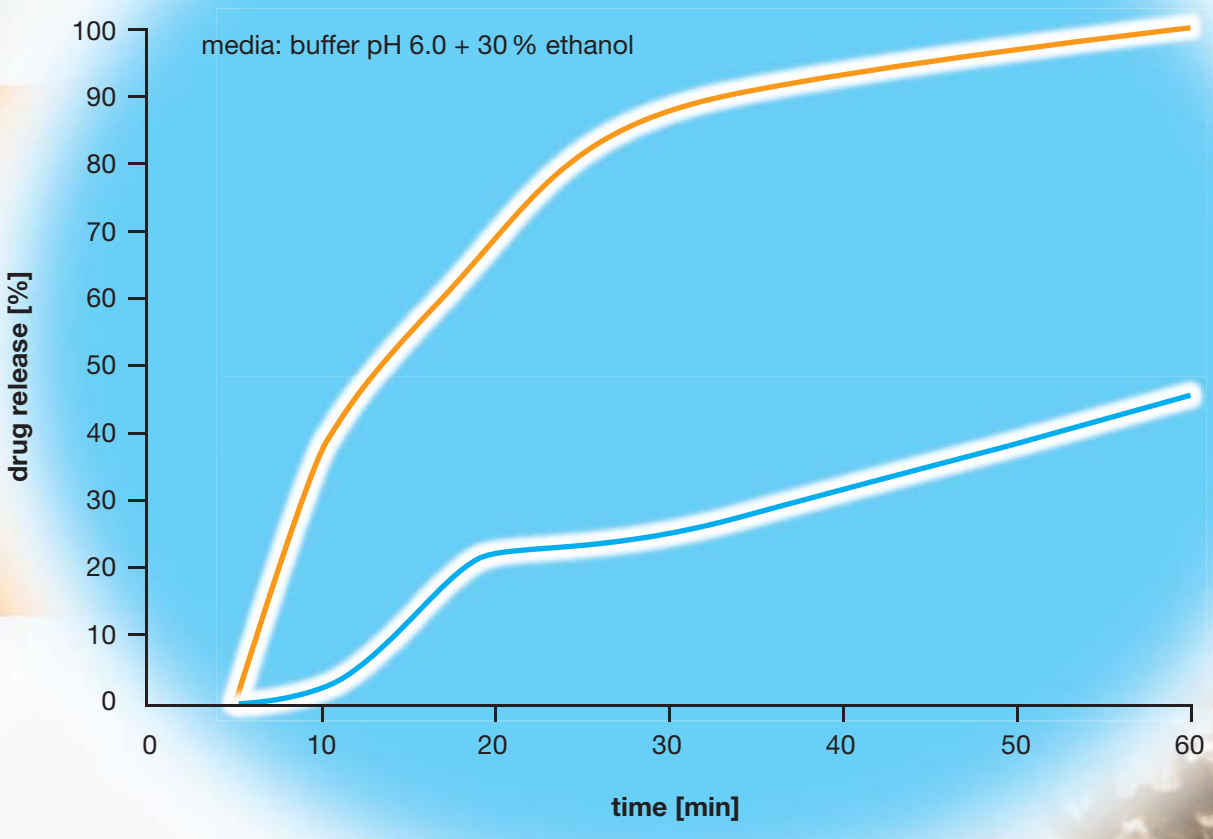
Lutrol® F

Lµtrol® micro



It can be shown that **Lμtrol®*micro* 68** improves the dissolution of ibuprofen significantly. A very high release rate can be achieved by only blending both materials.

Ibuprofen dissolution with and without Lμtrol®micro



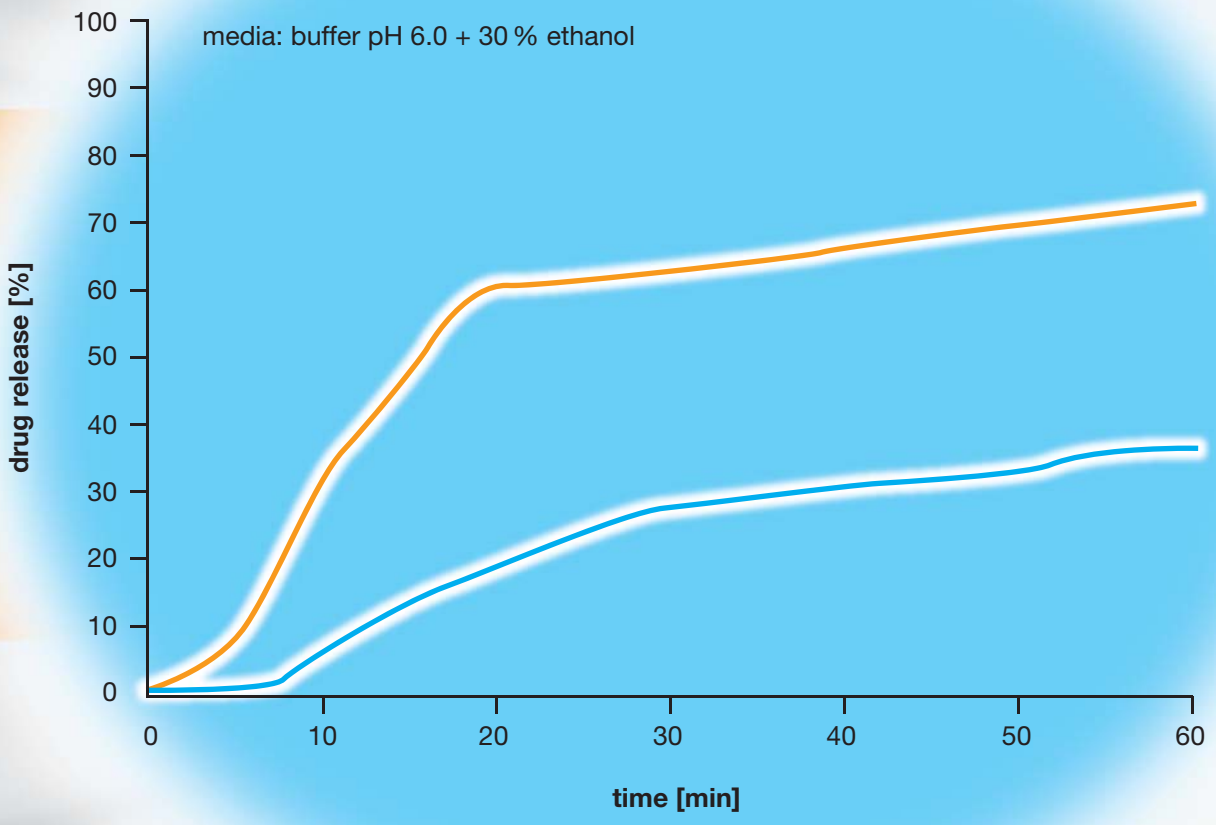
● **Ibuprofen 40 mg + 200 mg Lμtrol®*micro* 68**
● **Ibuprofen 40 mg**

Ibuprofen crystals

The Formulation

The same behavior can be shown with the very poorly soluble active 17-ß-estradiol. The addition of **L*µ*trol®*micro*** increased the drug release after 20 minutes from 15 % up to approx. 50 %. These results show the good solubilizing properties of **L*µ*trol®*micro***.

17-ß-estradiol dissolution with and without L*µ*trol®micro

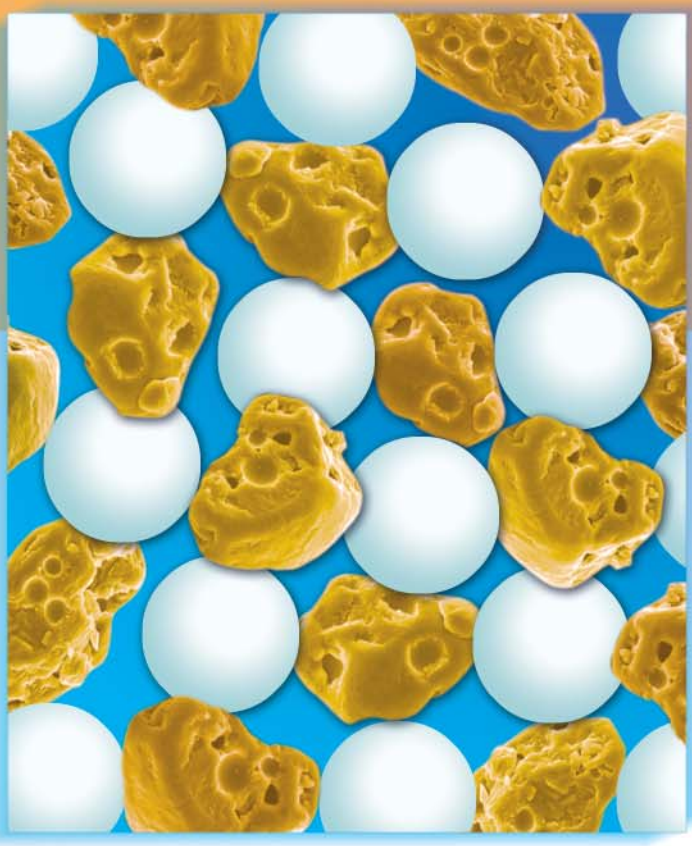


20 mg 17-ß-estradiol + 100 mg L*µ*trol®*micro* 68
20 mg 17-ß-estradiol

The Summary

- Poloxamers can be used in controlled drug delivery systems leading to optimized bioavailability.
- The particle size of the micronized poloxamer is close to that of active ingredients. That perfects content uniformity.
- Micronized poloxamers can be used effectively in dry granulation and to minimize process related problems.

Lµtrol®micro *grades are mostly applicable in solid dosage forms.*



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Please complete, copy and fax to us, or detach the postcard and send it to us.

Please send the following information.

- Technical information on **Lμtrol®*micro***.
- Sample of **Lμtrol®*micro* 68**, 0.5 kg.
- Sample of **Lμtrol®*micro* 127**, 0.5 kg.
- Please contact me, I would like to know more about **Lμtrol®*micro***.
- Technical information on Kollicoat® IR White.
- Technical information on Kollicoat® Protect.
- Technical information on Kollicoat® IR.
- DVD “Pharmaceutical Excipients by BASF Fine Chemicals”.
- Newsletter “ExAct” (Excipients & Actives for Pharma).

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- Sample of **Lμtrol®*micro* 127**, 0.5 kg.
- Please contact me, I would like to know more about **Lμtrol®*micro***.
- Technical information on Kollicoat® IR White.
- Technical information on Kollicoat® Protect.
- Technical information on Kollicoat® IR.
- DVD “Pharmaceutical Excipients by BASF Fine Chemicals”.
- Newsletter “ExAct” (Excipients & Actives for Pharma).

We look forward to answering any questions you may have. Please fill in the postcard, detach it and return it to the address overleaf.

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■ Excipients

Kollidon® grades
Group of povidone and copovidone products suitable mainly as tablet binders, crospovidone as tablet disintegrant and dissolution enhancer.

Kollidon® SR
Matrix sustained release polymer.

Ludipress® grades
Direct tabletting aids for faster product development and speedier processing.

Kollicoat® grades
Range of aqueous based film formers, cost efficient and ecological.

Cremophor® grades and Solutol® HS 15
Range of different ethoxylated emulsifiers and solubilizers suitable for topical, oral and parenteral formulations.

Soluphor® P
2-pyrrolidone.

Lutrol® grades
Range of PEGs (Lutrol® E range) and poloxamers (Lutrol® F range) for a wide variety of pharmaceutical dosage forms.

■ Actives

Ephedrines
Pseudoephedrines
Theophylline
Caffeine
Isotretinoin
Tretinoin
Ibuprofen
Dobutamine
Dopamine
Isometheptene mucate
Oxymetazoline
PVP-Iodine
Selegiline
Xylometazoline

APIs by Orgamol

Vitamins

■ Contract Manufacturing

■ Value Added

BASF
The Chemical Company

Pharma Solutions by BASF

BASF offers more than cGMP quality and supply safety: *technical expertise.* Our technical service is always at your side.

BASF wishes to create a prosperous and sustainable future with you as our customer – ***and partner.***

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BASF – the world's leading chemical company – can look back on well over 140 years of success and has attained an outstanding position as a reliable partner.

Our portfolio for the pharmaceutical industry comprises a comprehensive range of major and new active ingredients and excipient brands.

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