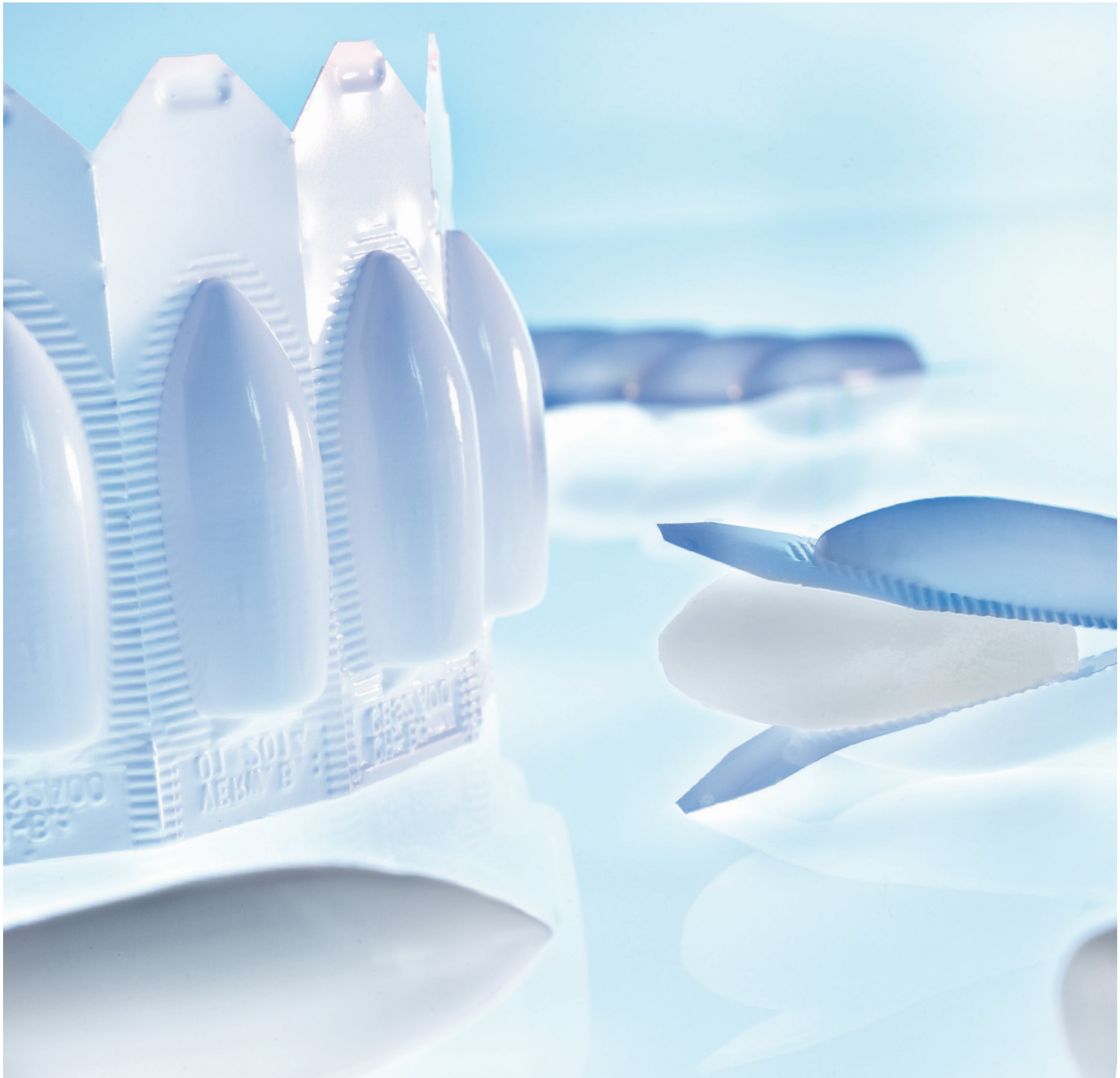
IOI OLEOCHEMICAL

PHARMA

WITEPSOL®

Hard fats for suppositories and ovules

IOI Oleo GmbH



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Abbreviations:
JPE = Japanese Pharmaceutical Excipients
Ph. Eur. = European Pharmacopoeia
USP-NF = United States Pharmacopeia-National Formulary

1 | HARD FACTS ABOUT OUR HARD FATS

The brand name WITEPSOL® is synonym for hard fats mainly used in suppositories and ovules. Development and production of WITEPSOL® started back in the 1950s at the former Chemische Werke Witten, now known as IOI Oleo GmbH.

Manufacturing takes place in a fully automated process, including pastillation and packaging line operating under clean room-condition.

This state-of-the-art production guarantees the highest possible standard, and in turn the quality of medicine in our ethical environment.

The site in Witten repeatedly has been granted EU GMP-certification and is US FDA cGMP inspected.

Based on our cGMP production, our regulatory set-up and our experience - quality you can rely on „Made in Germany“.

Packaging line

Pastillation belt

2 | PRODUCT RANGE

For the preparation of an optimal form of rectal medicine or ovule, a single grade is not sufficient. To allow for a better overview of this range, the WITEPSOL® grades are divided into four classes and, within these classes, are arranged in order of increasing melting point.

WITEPSOL® H
WITEPSOL® products of series H are hard fats which are characterized by a low hydroxyl value.

WITEPSOL® W
WITEPSOL® products of series W are hard fats which are characterized by a higher hydroxyl value.

WITEPSOL® S
WITEPSOL® products of series S are special hard fats with a non-ionic ethoxylated emulsifier as main additive.

WITEPSOL® E
WITEPSOL® products of series E are hard fats having melting points above body temperature.

WITEPSOL® H

WITEPSOL® products of series H (except H 19) are hard fats with hydroxyl values up to 15. They mostly consist of triglycerides with a portion of, at most, 15% of diglycerides and not more than 1% of monoglycerides. They are characterized by a very small gap between the melting and solidification temperatures, have only a minor tendency to the posthardening phenomenon (maximum 1.5 °C) and can be processed both with automatic casting machines and, on a small scale, using the cream melting process (precrystallization) at casting temperatures around the stated melting point. Shock cooling should be avoided. This series of grades also includes compounds having hydroxyl values (HV) between 0 and 5 which avoid interactions between the free OH groups and acidic active compounds (ASA, Diclofenac, etc.).

COMPOUNDS FOR SUSPENSION SUPPOSITORIES HAVING A PROPORTION OF SOLID ACTIVE COMPOUNDS OF OVER 25%

WITEPSOL® H 32	melting point 31–33 °C	HV = max. 3
WITEPSOL® H 12	melting point 32–33.5 °C	HV = 5-15
WITEPSOL® H 19	melting point 33.5–35.5 °C	HV = 20-30

COMPOUNDS FOR SUSPENSION SUPPOSITORIES HAVING A PROPORTION OF SOLID ACTIVE COMPOUNDS OF LESS THAN 25%

WITEPSOL® H 35	melting point 33.5–35.5 °C	HV = max. 3
WITEPSOL® H 5	melting point 34–36 °C	HV = max. 5
WITEPSOL® H 15	melting point 33.5–35.5 °C	HV = 5–15

COMPOUNDS FOR SUSPENSION SUPPOSITORIES AND LIPOPHILIC ACTIVE COMPOUNDS; FOR MELTING POINT CORRECTION

WITEPSOL® H 37	melting point 36–38 °C	HV = max. 3

WITEPSOL® W

WITEPSOL® products of series W are hard fats with hydroxyl values of 20–50. They consist of a mixture of triglycerides (65–80%), diglycerides (10–35%), and monoglycerides (1–5%). As a result of their composition, these WITEPSOL® grades have a larger gap between melting and solidification points, they are less sensitive to shock cooling (more elastic), solidify more slowly and can be readily processed both with automatic machines and with small-scale equipment. The partial glyceride content also slows down the sedimentation of solids and promotes the absorption of less readily absorbable active compounds.

WITEPSOL® W 32	melting point 32–33.5 °C	HV = 40-50
WITEPSOL® W 25	melting point 33.5–35.5 °C	HV = 20-30
WITEPSOL® W 35	melting point 33.5–35.5 °C	HV = 40-50
WITEPSOL® W 45	melting point 33.5–35.5 °C	HV = 40-50

WITEPSOL® W 45 is a special grade which is characterized by a higher monoglyceride content of up to 15%, which supports increased absorption promotion of active compounds and faster solidification.

WITEPSOL® S

WITEPSOL® products of series S are special grades which contain particular auxiliaries in addition to the hard fat of pharmacopoeias.

They are used for the preparation of vaginal and rectal forms of medicines which require better wetting of mucous membranes and enhanced dispersibility and are intended to promote absorption. Besides other ingredients like beeswax or glyceryl ricinoleate the most important auxiliary is an ethoxylated cetylstearyl alcohol.

WITEPSOL® S 51	melting point 30–32 °C	HV = 55–70
WITEPSOL® S 55	melting point 33.5–35.5 °C	HV = 50–65
WITEPSOL® S 58	melting point 31.5–33.5 °C	HV = 60–73

WITEPSOL® E

WITEPSOL® products of series E are hard fat compounds having a melting point above body temperature. Their primary use is as additives for melting point adjustment when active components lower the melting point of the primary hard fat.

They are characterized by their melting point and hydroxyl value. WITEPSOL® E 75 additionally contains beeswax (cera alba).

WITEPSOL® E 75	melting point approx. 38 °C	HV = max. 15
WITEPSOL® E 76	melting point 37–39 °C	HV = 30–40
WITEPSOL® E 85	melting point 42–44 °C	HV = 5–15

3 | PRODUCTION AND QUALITY CONTROL

Production

WITEPSOL® hard fats are de novo synthesized from glycerol and fatty acids of vegetable origin. The fatty acid spectrum, the stoichiometry of the reaction mixture, and the reaction times and temperatures determine the properties of the product, such as melting range, solid fat index, hardness, mono-, di-, triglyceride content (emulsifiability/dispersibility) and viscosity. The crude reaction mixture is subsequently processed as follows:

- Alkali washing to remove free fatty acids (as soaps) and the catalyst (as fat-insoluble basic compounds)
- Neutral washing to remove excess alkali
- Drying in vacuum
- Adsorptive treatment to remove chromogenic products and traces of catalyst
- Steam distillation in vacuum and repeated drying
- Deep-bed filtration under pressure

Some of the WITEPSOL® grades are then mixed with emulsifiers or consistency modifying waxes. Directly prior to conversion into pellets or bulk material, another final fine filtration is carried out.
WITEPSOL® contains no stabilizing or decolorizing chemical additives; it is produced without solvents and virtually no microorganisms are present due to the production process.

Quality control

- Raw material monitoring
- In-process controls
- Finished product analysis

For release testing, the chemical parameters of fats according to the requirements of the European Pharmacopoeia (if applicable) are determined.

A supply evaluation system, continuous microbiological monitoring of the products and production plants, long term stability testing, and further testing of application-oriented properties back the guarantee that WITEPSOL® is always of optimal pharmaceutical quality.

Our high standards are documented and certified.

We practice compliance with various regulations and standards. This is important both for patient safety and for the extensive collaborations we already have in the pharmaceutical world.

- ISO 9001 & ISO 45001
- EMAS
- RSPO SCCS
- EU GMP certified
- US FDA cGMP inspected
- HACCP
- Halal/Kosher

4 | PROCESSING

General guidelines

WITEPSOL® hard fats have been established worldwide decades back as replacements for cocoa butter. They have evident advantages with respect to:

- wide choice of melting points and hydroxyl values
- faster solidification
- smaller melting point differences between crystal modifications
- stability against oxidation
- substantial absence of interactions with active ingredients
- preventing sedimentation by selection of suitable grade
- release and absorption of active ingredients

Processing methods

Suppositories and pessaries are nowadays produced almost exclusively by a casting process on automatic machines. Other previously used pressing processes (extrusion) or melt pressing processes have not remained competitive.

On automatic casting machines, the suppositories are pumped directly into preshaped plastic films or aluminum foils. Casting in metal molds, with subsequent sealing in cellophane, plastic film or aluminum foil is now only used for very small-scale fabrication or on automatic machines which, although widespread in the past, are no longer manufactured today.

In contrast to cocoa butter processing, WITEPSOL® can be subjected to an initial heat treatment (sterilization or similar) without any noticeable effect on the solidification behavior.

If basic physical properties of the hard fats are taken into account, modern automated machines generate finished products which meet the requirements of a desired drug form:

- high content uniformity
- uniform texture

The prerequisite is the following operating procedure:

1. Melting the compound to approx. 60 °C while stirring continuously to avoid memory effects caused by remaining crystalline structures.
2. Cooling to a temperature which ensures ready suspension of the active ingredients. Depending on the quantity, particle size and surface area of the active ingredients, this is 35–40 °C.
3. Incorporating the active ingredients into the melt while stirring continuously.
4. Reducing the temperature until the viscosity increases appreciably. The pumpable consistency of the melt must be maintained by continuous stirring. This temperature can be equal to or a few degrees above the melting point of the fat.
5. Stationary zones within the product stream should be avoided, since at such points rapidly increasing solidification can interrupt the flow, or can lead to a complete production stop.
6. The casting molds should be at room temperature.
7. After the filling procedure, the foil or film strips must not be cooled suddenly, since a crystalline surface on the suppositories can lead to the formation of cracks or “casting channels”. The temperature difference between the pumpable material and the first cooling zone should not exceed 15 °C.

Dosage in suppositories

The quantity of WITEPSOL® needed to produce N suppositories can be calculated by means of the following formula:

$$M = N\,(C-(f \times A))$$

M = quantity of base required for N suppositories in g
N = number of suppositories
C = average capacity of a casting mold for pure base in g
f = displacement factor of the undissolved active ingredient
A = quantity of active compound per suppository in g

The displacement factor indicates the number of grams of suppository bases which are displaced by 1 g of active ingredient.
f is the quotient of the densities of auxiliary and active ingredient.

VISCOSITY

Molten WITEPSOL® behaves approximately like a Newtonian liquid; the measured shear stress is almost linearly dependent on the applied shear rate. The viscosity is lower for the H grades than for the partial glycerides containing W grades. S grades have a slightly higher viscosity due to the contained additives *(see Fig. 5)*.

The temperature dependence of the viscosity of WITEPSOL® grades with the same melting range is shown in *Fig. 6*.
The differences are the biggest in the area of casting temperatures, since proportions of solid glycerides become noticeable here (SFI).

An incorporated active compound can considerably change the viscosity behavior of the system, since dose-dependent physical interactions may occur.

Fig. 5: Comparison of the rheological behavior of pure WITEPSOL® grades

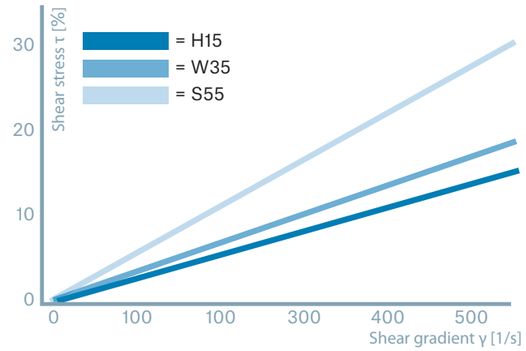
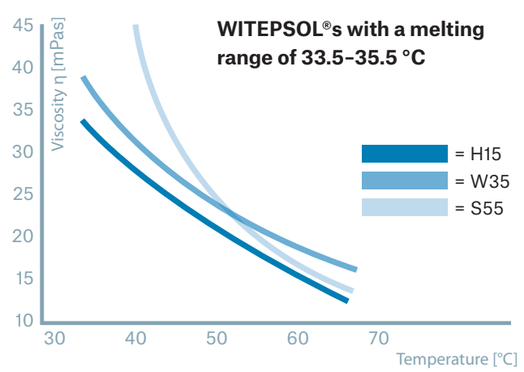
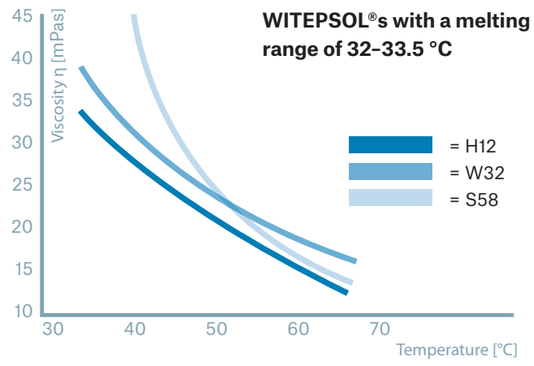


Fig. 6: Viscosities as a function of temperature for suppository bases, exhibiting an open-tube melting point of:





4 | PROCESSING

Dosage in suppositories

The displacement factor of unknown materials is determined according to the formula:

$$f = \frac{C - W}{W \times X} + 1$$

W = average weight of a suppository containing X% of active ingredient

To determine the capacity (C) of the casting mold (also known as the calibration value), WITEPSOL® can be melted to a clear melt, while the determination of W should be carried out by the cream melting process (avoidance of sedimentation in the vessel containing the batch). The greater solubility of active ingredients at high temperatures can also affect the result.

The displacement factor is not a constant of a material, but is dependent on the particle size, the crystal form, the wettability, the solubility, and the concentration of the active ingredient.

Another dosage method (that of Münzel) is as follows: The total active ingredient is mixed with a quantity of molten base which is less than that required for the production of the intended number of suppositories and cast in such a way that none of the casting molds are completely filled. Subsequently, the remaining volume is made up with pure base, the total weight of the suppositories is determined and the average weight is calculated. Subtraction of the weight of active ingredient used gives the required quantity of base for one suppository. The suppositories produced in this way have an inhomogeneous distribution of active ingredient. Therefore, the suppositories must be melted again and recasted, if they are to be further used.

Testing of suppositories

In addition to visual examination for a uniform exterior, the absence of cracks, air bubbles, and other surface irregularities, testing is carried out for uniformity of mass (max. 5% of the average mass in accordance with 2.9.5 of the European Pharmacopoeia) and uniformity of content (+ 15% of the average content in accordance with 2.9.6 of the European Pharmacopoeia).

Additional tests are:
- consistency
- disintegration
- release of active compound in vitro

CONSISTENCY

Suppositories must have a sufficiently hard consistency to allow manual insertion, i.e. they should not start to melt at a room temperature of about 20 °C, even with the heat of the hand. In addition, it must be ensured that the suppositories remain stable in shape at elevated room temperatures up to about 30 °C and that sedimentation of the suspended active compound is avoided.

WITEPSOL® therefore specifically contains only those fatty acid esters which prevent softening below 30 °C.

Transesterified bases from coconut and palm kernel fats show distinctly lower hardness in this context. The medium-chain length fatty acid glycerides which are present here produce a negative effect because of their lower melting point.

The desired small gap between good applicability and shelf life at elevated temperatures and rapid disintegration at body temperature is also shown by the steep curves in the determination of the temperature-dependent solid-liquid behavior.

DISINTEGRATION

Suppositories and pessaries must melt as quickly as possible after application. This avoids the sensation of a foreign body and rapidly releases the incorporated active ingredient to act locally or systemically. Testing of the melting behavior of the finished dosage form at body temperature is therefore an important criterion for quality. The measurement of the melting point by capillary does not always correlate with this. The measurement of the melting behavior or – more specifically – the disintegration time (Ph. Eur. 2.9.2) should be carried out at a very narrow temperature range of e.g. 37 ± 0.1 °C. Recommended instrument is the suppository penetration tester PM 30 (by SOTAX), according to method 2.9.22 (Softening Time Determination of Lipophilic Suppositories) of Ph. Eur., apparatus B. The testing of the melting behavior of suppositories also serves to choose the correct WITEPSOL® type.

The effects of the active compounds can further intensify the crystallographic change in the excipient fat, so that suppository bases having different melting points should always be used at the beginning of formulation work.

The use of a WITEPSOL® grade having a melting point below 33.5 °C can be important for the optimal melting time of the finished suppository.

Dissolution testing of active ingredients in vitro
For dissolution testing, methods described in Ph. Eur. 2.9.3 can be adapted for suppositories.

Dissolution Tester

4 | PROCESSING

Challenges in suppository production

CRACKS

Cracks (mostly longitudinal) are caused by stresses in the solid fat which arise from the different cooling rates at the exterior and within the mold. These visible damages can be avoided by

- selecting an elastic fat or
- lowering the casting temperature and increasing the cooling temperature, which makes the fat solidify more homogeneously.

Transverse cracks can also be caused by mechanical stressing of the solidifying suppository, for example in the sealing process, if the mold is filled excessively and pressure is applied to the compound.

DIMPLES, SINK HOLES

This fault in appearance occurs frequently and has the same causes as mentioned above: the fat in the center solidifies more slowly and draws, as a result of its contraction, material from above into the core.

MATT SURFACE

Fat bloom consists of crystalline fat formed by diffusion on the surface. If the gap between surface and packing film or foil is small (low contraction), this phenomenon – typical for fats – can usually not develop. It is therefore advantageous to use compounds showing low contraction or a process method using precrystallized fat (see above).

INHOMOGENEOUS DISTRIBUTION OF ACTIVE INGREDIENTS

If sedimentation of the active ingredient occurs despite stirring, the viscosity of the melt is usually too low. Reducing the temperature of the mixture or increasing the cooling after casting or adding viscosity enhancers (e. g. Aerosil) may solve the problem.

THICKENING OF THE MOLTEN MIXTURE

Some active ingredients can, in high doses, form gel-like masses with fat which do not solidify well. This phenomenon, which has not been fully explained, is probably caused by dissolution of the crystal surface by partial glycerides. Possible solutions are fatty bases having a low hydroxyl value, different particle size distributions of the active compound, or viscosity-lowering additives (e. g. lecithin).

POSTHARDENING

The melting point of cast suppositories can increase as a function of the fat type, the active ingredients, the method of production, and the storage conditions and time. The cause is a change in the crystal modification of the solid fat. The transition from the unstable α-modification which is predominant in the fresh state, to the stableββ-modification proceeds via intermediate stages and can occur very slowly for example at low storage temperatures.

A stable end modification and a constant melting point can be achieved by applying a suitable tempering process during manufacturing. The cream melting process, long known in the preparation of pharmaceuticals, has not lost its significance in the industrial mass production of suppositories: the lowest possible casting temperature of the stirred compound and the highest possible cooling temperature are ideal. In this way, a high proportion of the stable end modification is produced from the beginning, and posthardening is thereby reduced.

Further reading

Recommended books with further references relating to pharmacological and technological aspects of rectal therapy:

[1] Nünberg, E. (Editor) “Hagers Handbuch der pharmazeutischen Praxis“, Band 2 “Methoden” [Hagers Handbook of Pharmaceutical Practice, Volume 2 “Methods”] Springer Verlag, Berlin, Heidelberg 1991

[2] Bosché, P.; Loth, H. “Solidification of Molten Hard Fats in Dependence on the Chemical Composition and Thermal Pretreatment“, [Die Pharmazeutische Industrie, EditioCantor Verlag, Pharm. Ind. 58, 2, 161–166 (1996)]

5 | OVERVIEWS

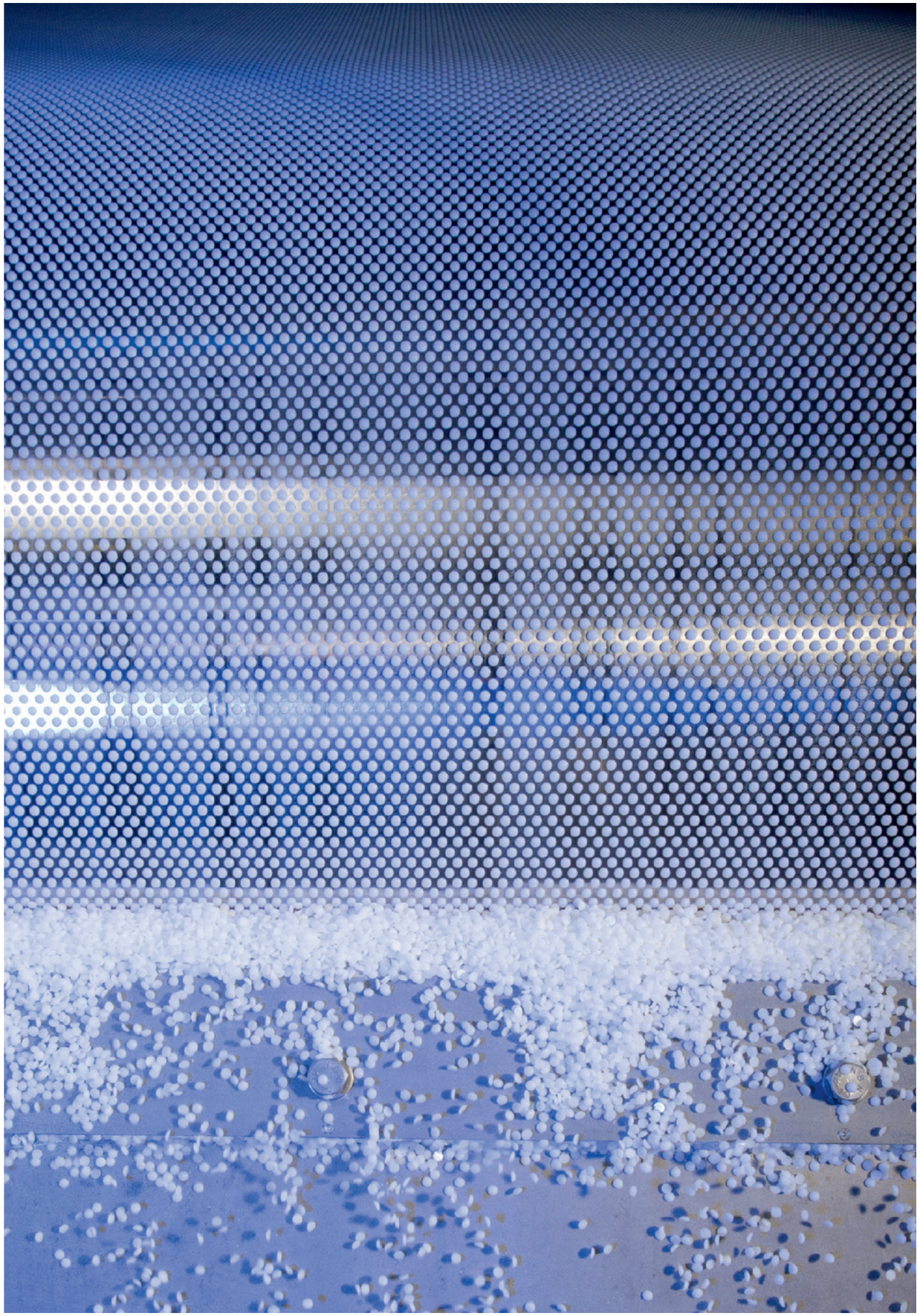
Hard fat recommendations for commonly used active pharmaceutical ingredients

WITEPSOL® H 15 / W 35
Actives for malaria treatment
Anesthetics
Anti-inflammatory substances
Antidepressants (alkaloids)
Antiemetics
Antiepileptics (barbiturates)
B vitamins
β-lactam antibiotics
Bronchodilatators
Expectorants
Male hormones
Nonsteroidal anti-inflammatory drugs
Steroidal antirheumatics (corticosteroids)

WITEPSOL® W 45
Actives for hemorrhoidal treatment
Anti-inflammatory substances for treatment of Crohn´s disease and related indications Antimycotics
β-lactam antibiotics
Laxatives
Nonsteroidal anti-inflammatory drugs
Opioids such as Tramadol and related substances

WITEPSOL® E 75 / E 85
Analgesics
Anesthetics
Antihypertonics
Steroidal antirheumatics (corticosteroids)

WITEPSOL® S 51 / S 58
Female hormones
Spermicides



WITEPSOL®

NOTES

Leading global expert and innovator of functionalised ester-based lipids with added value for pharma solutions.

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