



WITEPSOL®

FATTY BASES FOR SUPPOSITORIES



IOI OLEOCHEMICAL

IOI Oleo GmbH
PHARMA

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



IOI OLEOCHEMICAL

Rectal therapy: history and future

The application of remedies via the rectum can be traced back to antiquity.

It is reported that even the ancient Egyptians, ancient Indian physicians and the Mesopotamians used suppositories not only as laxatives but also for the rectal treatment of pain, flatulence and heart spasms. The remedies were mostly mixed with fats and then applied to wool plugs or pieces of linen cloth. As laxatives, these plugs were frequently also dipped in ox gall.

The scientific basis of rectal therapy was only established in the second half of the 19th century. This was based on the investigations of the Stockholm anatomist Retzius, who proved in 1832 that some of the veins leaving the ampulla recti directly lead to the vena cava inferior. This enables direct transportation of large amounts of the rectally administered medicines into the blood circulation, bypassing the liver. With the introduction of cocoa butter as suppository base, systematic investigations could be carried out more easily than before.

The increase of the fund of medicines and the spreading of the knowledge that the excipients also have an important effect on the pharmacological activity of a medicine limited the applicability of cocoa butter for industrial production of suppositories. Particular disadvantages were its chemical instability due to the high proportion of unsaturated glycerides as well as compatibility problems between oxidation products (rancidity) and active compounds. Because of its very complex polymorphic nature, cocoa butter is also not suitable for effective machine production.

The development of suppository compounds based on glycerides of saturated fatty acids of coconut and palm kernel oils in the laboratories of the former Chemische Werke Witten, now IOI Oleo GmbH, made it possible to process a substantially larger number of active compounds according to specific biopharmaceutical and technological aspects.

The use of hard fats based on glycerides of saturated C12-C18 fatty acids is very common nowadays because of their excellent chemical and physical stability, their broad compatibility with nearly all active compounds, their neutrality towards mucous membranes and their favorable processing properties even in high performance machines.

Water-soluble carriers (e.g. polyethylene glycols) are now only used in vaginal or ovular applications due to their irritation potential on mucous membranes.

The suppository bases are described in Pharmacopoeias as Hard Fat, Adeps solidus (European Pharmacopoeia) or as Hard Fat (USP-NF). As a result of numerous scientific investigations and publications, the tradename WITEPSOL® has become a synonym for modern suppository compounds.

Today, scientific interest in rectal therapy is still focused on several areas. It plays a role in the context of dissolution and absorption of active compounds from suppositories, particularly in respect of sustained release and absorption promotion. Additionally, it is a more convenient alternative to injections for patients. Following the latest scientific literature, rectal therapy has also proven to be a good choice for people with swallowing problems (e.g. children and elderly patients).

Therefore, it can be concluded that suppositories are still a valuable dosage form – also for the future.

2 Product range

For the preparation of an optimal form of rectal medicine which has the required therapeutic action but can also be prepared without difficulty in a pharmacy or on an industrial scale, a single grade is not sufficient. A range of WITEPSOL® grades is therefore available to meet the requirements in pharmaceutical technology, production, and also in biopharmacy, so as to achieve the best possible effect in each case. To allow for a better overview of this huge variety, 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 addition of a non-ionic ethoxylated emulsifier.
■ 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) (see page 35) 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 (ASS, 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 pharmacopocias.

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. 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 = 60–70

2

■ WITEPSOL® E

WITEPSOL® products of series E are hard fat compounds having a melting point above body temperature. They are used if active compounds lower the melting point of the excipient because of their fat solubility.

They are characterized by their melting point and hydroxyl value. WITEPSOL® E 75 additionally contains 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® suppository compounds consist of glycerol esters of vegetable saturated fatty acids, mainly lauric acid.

Starting materials are purified, specially selected coconut and palm kernel oils from tropical plantations.

After preliminary purification, the oils are cleaved in their fatty acids and glycerol by means of water at high pressure. The fatty acid mixture is subjected to catalytic hydrogenation and subsequently to fractional vacuum distillation, and the low molecular weight caproic, caprylic, and capric acids (C6–C10) are removed. The C12–C18 fatty acids are adjusted to the correct mixture for the grade and esterified batchwise with purified and distilled glycerol. 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 which are not found in natural fats; 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

100% batch testing and GMP-compliant documentation ensure complete traceability of our products.

For release testing, the chemical parameters of fats according to the requirements of the European Pharmacopoeia 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.



4 Test methods

The European Pharmacopoeia (Ph. Eur.) requires the following tests for hard fat (Adeps solidus) which are described in the table below:

Identification

Thin-layer chromatography (Ph. Eur. 2.2.27)

Purity tests	Requirements
Acid value (Ph. Eur. 2.5.1)	max. 0.5 mg KOH/g
Hydroxyl value (Ph. Eur. 2.5.3, Method A)	max. 50 mg KOH/g
Iodine value (Ph. Eur. 2.5.4)	max. 3 g J/100 g
Peroxide value (Ph. Eur. 2.5.5)	max. 3 meq O/kg
Saponification value (Ph. Eur. 2.5.6)	210–260 mg KOH/g
Alkaline impurities (Ph. Eur.)	max. 0.75 ml 0.01 N HCl/10.00 g
Sulphated ash (Ph. Eur. 2.4.14)	max. 0.2%
Melting point (Ph. Eur. 2.2.15)	30–45 °C
Nickel (Ph. Eur.)	max. 1 ppm

Physical tests

Open-tube melting point (Ph. Eur. 2.2.15)

Definition

The open-tube melting point is the temperature at which the material starts to rise in the glass capillary.

Comments

Fats are not chemically uniform substances with a sharp melting point. They consist of a range of chemically similar glycerides with sometimes very different melting points. The melting range which can be obtained is really a mixed melting point. The end point of the above method marks the point at which the upward pressure of the fat column becomes greater than the adhesive force of the (molten) sample in the glass tube. At this temperature, the sample may have formed a clear melt, but need not have; an important factor is, inter alia, the lubricating action of the liquid fat components on the fat/glass interface.

The pretreatment of the sample can also have an important influence, since fats are present in different states of crystallization. The transitions between the modifications are temperature and time-dependent. The above method does not necessarily determine the properties of the stable end modification, since transitions below 10 °C take more than 24 hours. Before filling the capillaries, WITEPSOL® should be heated to approx. 60 °C (70 °C maximum temperature should not be exceeded for a longer time) and stirred so as to ensure that all fat components are homogeneously distributed and the memory effect is avoided. The method is proved in practice and is sufficient for identification of suppository bases. The accuracy and reproducibility require exact adherence to the conditions. Results differing by up to 0.8 °C have been observed in ring tests at various laboratories.

4

Test methods

Physical tests

Solidification point (apparatus according to Ph. Eur. 2.2.18)

Definition

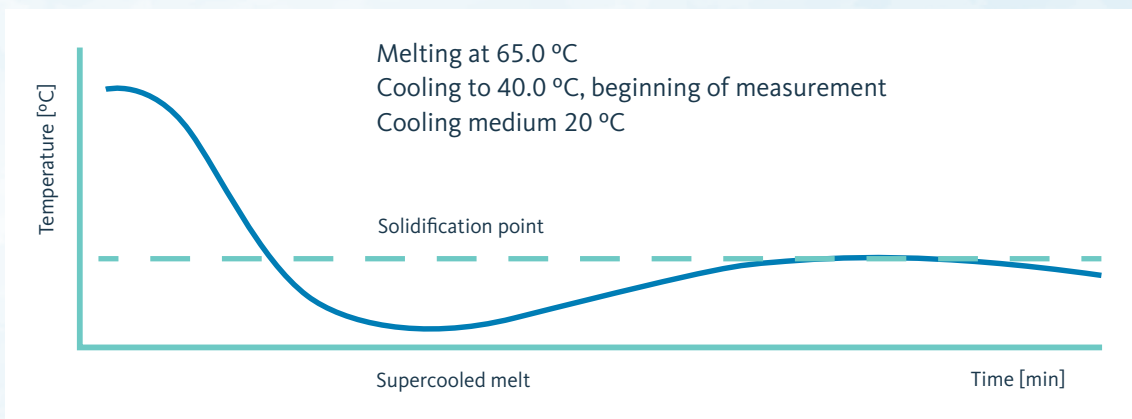
The solidification temperature point is the highest temperature occurring during the solidification of a supercooled liquid.

Comments

An ideal cooling curve (Fig. 1) shows a minimum and a maximum which can be attributed to the cooling medium and the liberation of latent heat of solidification. However, depending on the material and the cooling conditions, it is possible that only a saddle point is obtained. It is advantageous to record the temperature-time curve by means of a temperature sensor and recorder.

This method for determining the phase transition of suppository bases is somewhat less convenient to carry out than the open-tube melting point (see page 13), but more advantageous for some fats.

Fig. 1: Typical solidification curve of WITEPSOL®



Refractive index

Since WITEPSOL® contains only saturated glycerides, the refractive index is not very suitable for differentiation. Only in the case of fats having high proportions of unsaturated fatty acids or partial glycerides, there are characteristic deviations from the values typical for hard fat.

Solid fat index (SFI)

Definition

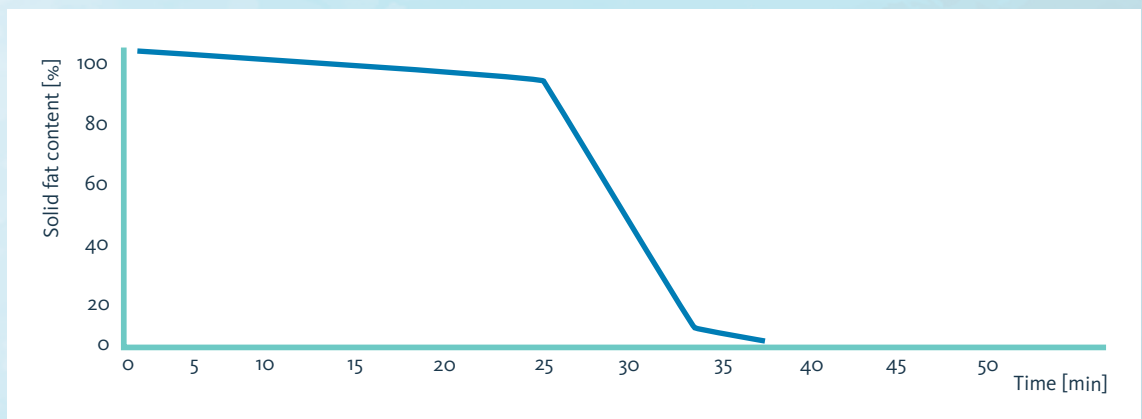
Percentage of solid glycerides in the fat mixture at a certain temperature.

Comments

The solid fat index, in addition to the melting and solidification temperatures, is important in describing the state of aggregation and the phase transition of a fat. Even for the same melting point, the ratio of liquid and solid components below the melting point may be different for various suppository bases: macroscopically the fats feel different. Suppositories should also remain sufficiently hard at 30 °C and should not have a greasy surface (= too many liquid components). The aim should be a SFI curve with the greatest possible gradient (Fig. 2, table 1).

WITEPSOL® meets this requirement, since low melting glycerides of C8 / C10 fatty acids are removed (see pages 17 + 18, gas chromatography).

Fig. 2: Temperature dependence of the solid fat proportion in WITEPSOL® H 15



Test methods

Physical tests

Table 1
Solid Fat Index—proportion of solid components in WITEPSOL® (DSC method) as a function of temperature [°C]

WITEPSOL®	20	25	30	32.5	35	37.5	40	42.5	Open-tube melting point
■ H 5	97	95	57	24	5	0	0	0	34.0–36.0
■ H 12	94	71	23	5	0	0	0	0	32.0–33.5
■ H 15	96	89	48	17	3	0	0	0	33.5–35.5
■ H 35	82	59	27	14	4	0	0	0	33.5–35.5
■ W 25	96	87	44	19	9	0	0	0	33.5–35.5
■ W 32	95	77	26	7	1	0	0	0	32.0–33.5
■ W 35	95	84	36	15	2	0	0	0	33.5–35.5
■ W 45	96	88	32	13	2	0	0	0	33.5–35.5
■ S 55*	93	79	27	12	2	1	0	0	33.5–35.5
■ S 58*	86	68	27	17	2	0	0	0	31.5–35.5
■ E 75*	96	89	55	37	16	4	0	0	approx. 38.0
■ E 76	96	92	61	52	21	7	1	0	37.0–39.0
■ E 85	97	957	85	74	56	35	16	5	42.0–44.0

* Non-pharmacopoeial bases, containing special additives

Thin-layer chromatography (TLC)

For the identification of hard fats, the European Pharmacopoeia describes testing by thin-layer chromatography. The method is suitable for separating mono-, di- and triglycerides from free glycerol. Unsaturated fats and fat-soluble impurities can sometimes be seen alongside the spots typical for hard fats.

The conditions described do not give sufficient separation of the glycerides according to the chain length of their fatty acids. Hard fats having a too high or too low melting point are not detected due to their different lipophilic properties. Likewise, semiquantitative estimations of the partial glyceride content and the hydroxyl value are difficult.

TLC is also suitable for testing water-dispersable components (e.g. emulsifiers). For this purpose, the sample must be shaken with water and separated by using a more polar eluent (e.g. methylene chloride, ethanol, or water). Detection with iodine gas. The various hard fat bases are differentiated in respect of their fatty acid and glyceride distribution by means of gas chromatography.

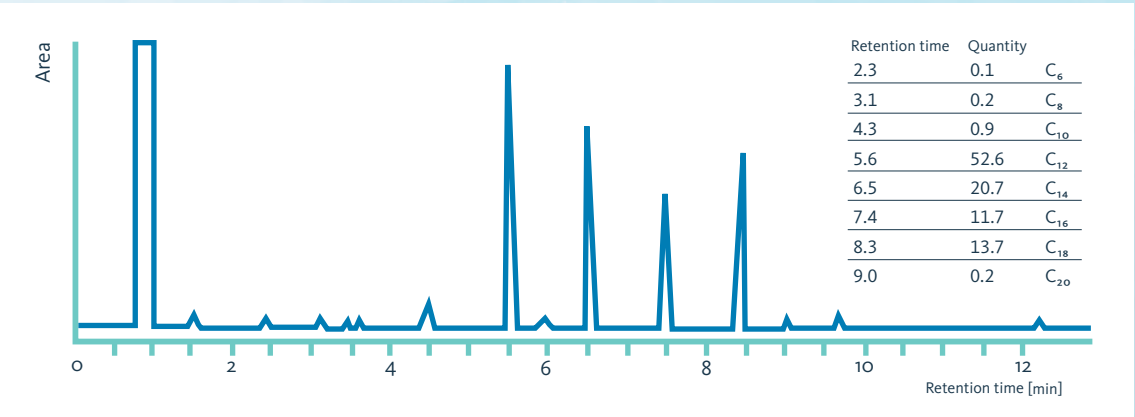
Gas chromatography (GC)

I. Quantitative determination of the fatty acid composition

The sample is transesterified with boron trifluoride/methanol or sodium methoxide to give the methyl esters of the fatty acids. After removal of the water-soluble components, the reaction mixture is directly injected. Column: Quartz-glass capillary (for example Carbowax chemically bound) 15–30 m, temperature program to 250 °C, injector/detector (FID) temperature 320 °C. For an exact quantitative determination of the fatty acid methyl ester peaks, the response factors must be taken into consideration; however, if the percentage areas are equated to the percentages by weight, the error is not greater than 10% relative. The C6–C10 fatty acids originally present in the coconut/palm kernel oil are removed in the production of WITEPSOL® suppository bases. Thus, the hardness and the grip strength of suppositories are increased.

Higher melting WITEPSOL® grades are distinguished from low melting ones by a shift of the fatty acid spectrum towards palmitic (C16) and stearic (C18) acids.

Fig. 3: Fatty acid composition of WITEPSOL® H 15



4

Test methods

Physical tests

Gas chromatography (GC)

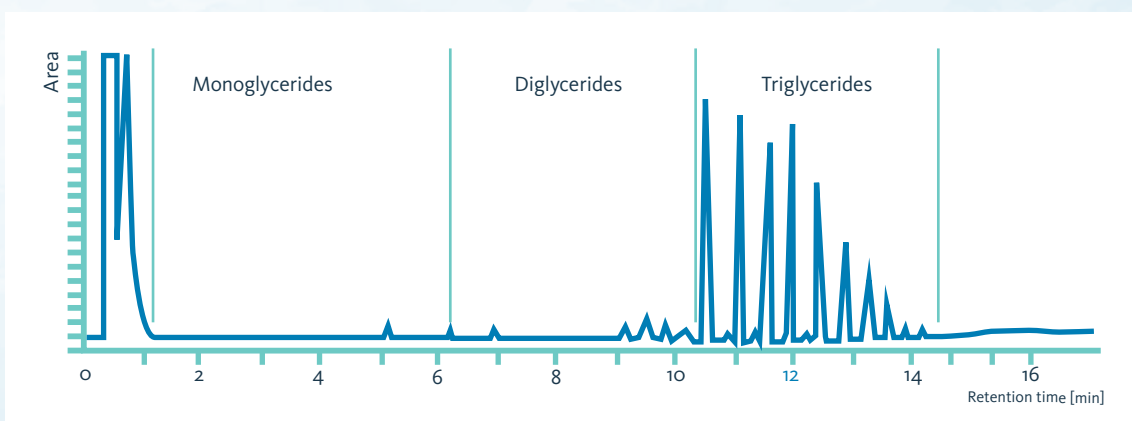
II. Quantitative determination of glycerides in WITEPSOL®

For the C12–C18 fatty acids, glyceride peaks from C12 (monolaurate) to C54 (tristearate) can be expected.

Assignment of the peaks requires reference materials; for an exact quantitative determination of the individual peaks, response factors must be taken into account.

WITEPSOL® H 15 contains – besides triglycerides (C36–C54) – monoglycerides (< 1%) and about 10% of diglycerides, corresponding to a hydroxyl value of about 10. Higher hydroxyl values can be expected due to higher amounts of diglycerides (for example WITEPSOL® W 35) or additionally by means of an increased proportion of monoglycerides (for example WITEPSOL® W 45).

Fig. 4: Glyceride distribution of WITEPSOL® H 15



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 emulsifier content (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 largest 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 occur.

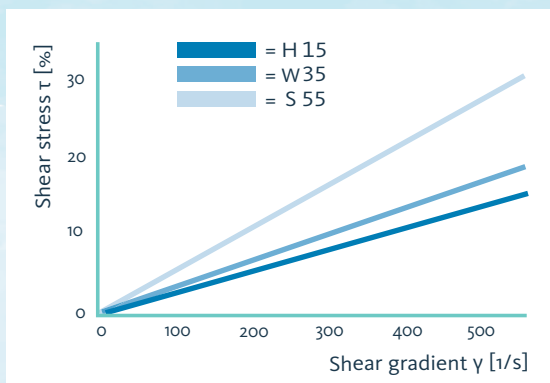
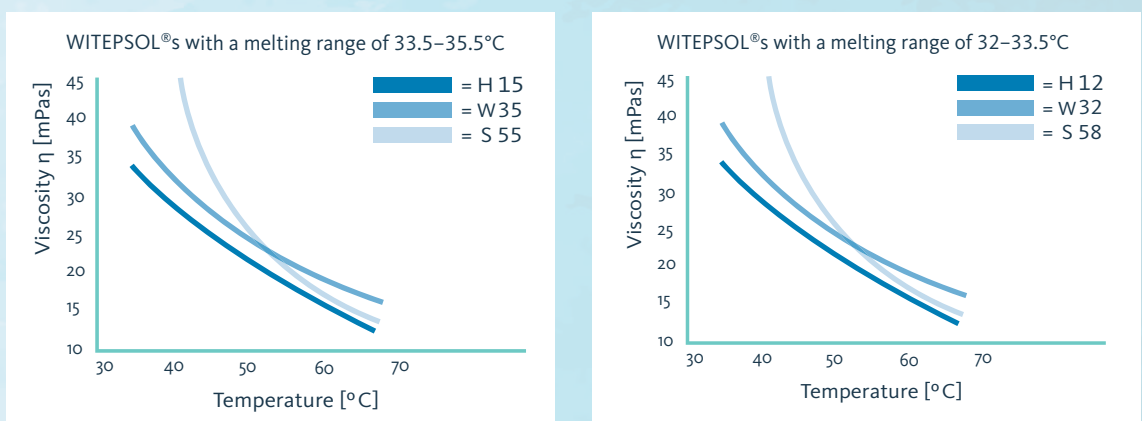


Fig. 5: Comparison of the rheological behavior of pure WITEPSOL® grades

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



4 Test methods

Physical tests

Miscibility

All WITEPSOL[®] grades give clear and homogeneous mixtures with each other. The resulting melting points correspond approximately to the average mean. In practice, various WITEPSOL[®] grades are often mixed, for example to compensate melting point depressions caused by active compounds.

Solubility

As a lipophilic material, WITEPSOL[®] is soluble in petroleum, spirit, acetone, methylene chloride, ether and hot isopropanol; it is insoluble in water, ethanol, glycerol and polyethylene glycol.

Density

Determined by the Archimedes method 2.2.5 in the European Pharmacopoeia.
At 20 °C the density of all WITEPSOL[®] grades is about 0.96 g/cm³.

Caloric data

The specific heat of WITEPSOL[®] is about:

0 °C	1.9	$\frac{\text{J}}{\text{g} \cdot \text{K}}$
10 °C	2.0	
20 °C	2.4	
60 °C	2.1	

The heat of fusion (22–40 °C) is about 138 $\frac{\text{J}}{\text{g}}$.

Chemical tests

Acid value (AV)

Definition

The acid value indicates the quantity, in mg, of KOH required to neutralize the free acids present in 1 g of fat.

Comments

The acid value of the standard WITEPSOL[®] grades is below 0.3. Grades containing beeswax or emulsifier have higher values.

Since free fatty acids are formed during the hydrolysis of glycerides, the acid value can be an indicator for the freshness of the fat. Because of the exceptionally low water content of WITEPSOL[®], a substantial increase in the acid value is not expected even after some years if stored in accordance with directions.

Test methods

Chemical tests

Hydroxyl value (HV)

Definition

The hydroxyl value represents the quantity, in mg, of KOH required to neutralize the amount of acetic acid consumed during acetylation by 1 g of WITEPSOL®.

Comments

The hydroxyl value indicates the number of free hydroxyl groups in the suppository base. Since WITEPSOL® is washed free of glycerol, the HV is a degree of partial glycerides or hydroxyl groups containing additives (WITEPSOL® S grades) which are present.

Mono- and diglycerides can substantially influence the properties of the fatty base and the suppositories containing active ingredients.

- They have an impact on the crystallization of the triglycerides and increase plasticity. Suppositories based on WITEPSOL® W grades are generally less brittle on shock cooling, but have a tendency towards greater posthardening (see page 35), i.e. a tendency for the melting point to increase.
- They increase the viscosity of the molten fats.
- They have some surfactant properties: this can result in better dissolution, wetting, or dispersion of active compounds; tests must be carried out for chemical interactions with active compounds, in particular those containing carboxyl functions. Furthermore, the mucous membrane of the rectum can be made more permeable (higher bioavailability, absorption promotion).

Test methods

Chemical tests

Iodine value (IV)

Definition

The iodine value represents the number of grams of halogen (calculated as iodine) which are absorbed under the described conditions by 100 g of WITEPSOL®.

Comments

The method determines unsaturated components in fats. Since the standard WITEPSOL® grades contain only saturated fatty acids, the iodine value is below 3. Special grades can have an IV of up to 8 (see list of grades).

Peroxide value (POV)

Definition

The peroxide value represents the quantity of peroxide, in milliequivalents of active oxygen, contained in 1000 g of WITEPSOL®.

Comments

The peroxide values of WITEPSOL® are very low because of the product's saturated nature and its stability against oxidation. The values found are therefore mostly not attributable to classical fat degradation, but to other products with oxidation potential, for example Cetomacrogol in WITEPSOL® S grades.

Test methods

Chemical tests

Saponification value (SV)

Definition

The saponification value represents the quantity, in mg, of KOH required to neutralize the free acids and to saponify the esters present in 1 g of fat.

Comments

The saponification value gives some indication of the fatty acid distribution of the triglyceride: the higher the SV, the lower the average molecular weight, i.e. the more low molecular weight fatty acids are present. In most WITEPSOL® types, the C8/C10 components have been removed.

Unsaponifiable matter

Comments

WITEPSOL® contains very little unsaponifiable matter, since the accompanying materials typically found in plants, such as waxes, sterols, higher alcohols, and hydrocarbons, are largely removed in the reesterification process. Special WITEPSOL® grades (e.g. S 55; E 75) contain beeswax or emulsifiers and therefore more unsaponifiable matter.

Test methods

Chemical tests

Iodine color number (ICN)

Definition

The iodine color number indicates the quantity, in mg, of iodine in an aqueous iodine/potassium iodide solution which shows the same color intensity as a molten fat sample.

Comments

The color of hard fat is caused by traces of chromogenic materials which can be formed by thermal processes during production. These are, for example, aldehydes, ketones, and their condensation products which cannot be completely removed by distillation or by acid or alkali washing.

Such materials are largely removed by adsorption in the production process for WITEPSOL® by treatment with bleaching earth and activated carbon. WITEPSOL® is not chemically bleached and contains no added brighteners which could improve the color but not the purity. The iodine color number can, but need not, be a measure of the pharmaceutical quality of hard fat.

Alkaline impurities

Definition

Alkaline components determined by neutralization with HCl.

Comments

Alkaline components can arise from the refining process by the binding of free fatty acids with excess sodium hydroxide solution.

Due to the many refining steps, WITEPSOL® contains only traces of alkaline impurities.

Sulphated ash

Definition

The sulphated ash test uses a procedure to measure the amount of residual substance not volatilized from a sample when the sample is ignited in the presence of sulfuric acid. The test is commonly used for determining the content of inorganic impurities in an organic substance.

5 Processing

General guidelines

WITEPSOL® suppository bases have been established worldwide 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 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.

Modern automated production machines give, if basic physical properties of the hard fats are taken into account, 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 (70 °C maximum temperature should not be exceeded for a longer time) 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. Avoiding stationary zones within the product stream, since at such points rapidly increasing solidification can interrupt the flow, leading to an interruption in production.
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 temperature of the cast suppositories should not be greater than 15 °C.

Dosage in suppositories

The quantity of WITEPSOL® needed to produce N suppositories can be calculated by means of a so-called displacement factor.

M =	N (C-(f x 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.

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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.

Processing

Testing of suppositories

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.

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 stable β -modification proceeds via intermediate stages and can occur very slowly for example at low storage temperatures.

Processing

Challenges in suppository production

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] Diepgen, P. “Das Analzäpfchen in der Geschichte der Therapie” [The anal suppository in the history of therapy] G. Thieme Verlag, Stuttgart 1953
- [2] Thoma, K. “Arzneiformen zur rektalen und vaginalen Applikation” [Drugforms for rectal and vaginal application] Werbe- u. Vertriebsges. Dtsch. Apoth. [Advertising and Business Association of German Pharmacists], Frankfurt 1980
- [3] Nünberg, E. (Editor) “Hagers Handbuch der pharmazeutischen Praxis”, Band 2 “Methoden” [Hagers Handbook of Pharmaceutical Practice, Volume 2 “Methods”] Springer Verlag, Berlin, Heidelberg 1991
- [4] 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)]



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Overviews

WITEPSOL® grades

Description

Suppository bases according to the current monographs Hard Fat, Adeps solidus Ph. Eur. and Hard Fat USP-NF. They are white, odorless hard fats in pastille shape which comprise of glycerides of plant origin; tailored to the point by de novo synthesis.

	Ascending melting point [°C]	Hydroxyl value [mg KOH/g]	Acid value [mg KOH/g]	Iodine value [g I/100g]	Peroxide value [meq O/kg]
Method	Ph. Eur. 2.2.15	Ph. Eur. 2.5.3	Ph. Eur. 2.5.1	Ph. Eur. 2.5.4	Ph. Eur. 2.5.5
■ WITEPSOL® H 5	34.0–36.0	max. 5	max. 0.2	max. 2	max. 1
■ WITEPSOL® H 12	32.0–33.5	5–15	max. 0.2	max. 3	max. 1
■ WITEPSOL® H 15	33.5–35.5	5–15	max. 0.2	max. 3	max. 1
■ WITEPSOL® H 19*	33.5–35.5	20–30	max. 0.2	max. 7	max. 3
■ WITEPSOL® H 32	31.0–33.0	max. 3	max. 0.2	max. 3	max. 1
■ WITEPSOL® H 35	33.5–35.5	max. 3	max. 0.2	max. 3	max. 1
■ WITEPSOL® H 37	36.0–38.0	max. 3	max. 0.2	max. 3	max. 1
■ WITEPSOL® W 25	33.5–35.5	20–30	max. 0.3	max. 3	max. 1
■ WITEPSOL® W 32	32.0–33.5	40–50	max. 0.5	max. 3	max. 1
■ WITEPSOL® W 35	33.5–35.5	40–50	max. 0.3	max. 3	max. 1
■ WITEPSOL® W 45	33.5–35.5	40–50	max. 0.3	max. 3	max. 1
■ WITEPSOL® S 51*	30.0–32.0	55–70	max. 0.5	max. 8	max. 4
■ WITEPSOL® S 55*	approx. 35**	50–65	max. 1.0	max. 3	max. 3
■ WITEPSOL® S 58*	31.5–33.0	60–70	max. 1.0	max. 7	max. 4
■ WITEPSOL® E 75*	approx. 38**	max. 15	max. 1.3	max. 3	max. 1
■ WITEPSOL® E 76	37.0–39.0	30–40	max. 0.3	max. 3	max. 1
■ WITEPSOL® E 85	42.0–44.0	5–15	max. 0.3	max. 3	max. 1
Monographs					
Ph. Eur.	30–45	max. 50	max. 0.5	max. 3	max. 3
USP	27–44	max. 70	max. 1.0	max. 7	
JPE	30–45	max. 70	max. 2.0	max. 3	

* WITEPSOL® grades H19, S51, S55, S58 and E75, respectively, are mixtures of hard fats (according to Ph. Eur.) and additives.
** Due to additive beeswax, the ascending melting points are hard to reproduce (adhesion at the glas capillary). The solidification points are more precise.
They are for WITEPSOL® E 75 = 34–36.5 °C, for WITEPSOL® S 55 = 28–33 °C.

Saponification value [mg KOH/g]	Alkaline impurities [ml HCl/2g]	Nickel [ppm]	Sulphated ash [%]	Unsaponifiable matter [%]	
Ph. Eur. 2.5.6	Ph. Eur.	Ph. Eur.	Ph. Eur. 2.4.14	Ph. Eur. 2.5.7	Method
235–245	max. 0.15	max. 1	max. 0.05	max. 3.0	WITEPSOL® H 5 ■
240–255	max. 0.15	max. 1	max. 0.05	max. 3.0	WITEPSOL® H 12 ■
230–245	max. 0.15	max. 1	max. 0.05	max. 3.0	WITEPSOL® H 15 ■
230–240	max. 0.15	max. 1	max. 0.05	max. 0.6	WITEPSOL® H 19* ■
240–250	max. 0.15	max. 1	max. 0.05	max. 3.0	WITEPSOL® H 32 ■
240–250	max. 0.15	max. 1	max. 0.05	max. 3.0	WITEPSOL® H 35 ■
225–245	max. 0.15	max. 1	max. 0.05	max. 3.0	WITEPSOL® H 37 ■
225–240	max. 0.15	max. 1	max. 0.05	max. 3.0	WITEPSOL® W 25 ■
225–245	max. 0.15	max. 1	max. 0.05	max. 3.0	WITEPSOL® W 32 ■
225–235	max. 0.15	max. 1	max. 0.05	max. 3.0	WITEPSOL® W 35 ■
225–240	max. 0.15	max. 1	max. 0.05	max. 3.0	WITEPSOL® W 45 ■
215–230	max. 0.15	max. 1	max. 0.05	max. 0.5	WITEPSOL® S 51* ■
215–230	max. 0.15	max. 1	max. 0.05	max. 2.0	WITEPSOL® S 55* ■
215–225	max. 0.15	max. 1	max. 0.05	max. 2.0	WITEPSOL® S 58* ■
220–230	max. 0.15	max. 1	max. 0.05	max. 3.0	WITEPSOL® E 75* ■
220–230	max. 0.15	max. 1	max. 0.05	max. 3.0	WITEPSOL® E 76 ■
220–240	max. 0.15	max. 1	max. 0.05	max. 3.0	WITEPSOL® E 85 ■
210–260	max. 0.15	max. 1	max. 0.2		Ph. Eur.
215–255	max. 0.15		max. 0.05	max. 3.0	USP
210–255				max. 3.0	JPE

6 Overviews

Hard fat recommendations for commonly used active pharmaceutical ingredients

WITEPSOL® H 15 / W 35	WITEPSOL® E 75 / E 85
Actives for malaria treatment	Analgesics
Anesthetics	Anesthetics
Anti-inflammatory substances	Antihypertonics
Antidepressants (alkaloids)	Steroidal antirheumatics (corticosteroids)
Antiemetics	
Antiepileptics (barbiturates)	WITEPSOL® S 51 / S 58
B vitamins	Female hormones
β-lactam antibiotics	Spermicides
Bronchodilators	
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



6 Overviews

Excipients for the pharmaceutical industry, also manufactured by IOI Oleo GmbH

Applications and functions

Topical preparations	Product
Ointment base O/W	SOFTISAN® 601
Fatty bases	SOFTISAN® 154, 378
Oil components	MIGLYOL® 128 NON-GMP, 810 N, 812 N, 818, 829
Emulsifiers O/W	IMWITOR® 372 P, 375, 960 K
Emulsifiers W/O	IMWITOR® 491, 600 NON-GMP, 900 K, 900 (F) P, 948, 990 NON-GMP
Solubilizers and wetting agents	SOFTIGEN® 767
Absorption promoters	IMWITOR® 308 NON-GMP, 742, 988
Consistency and stability regulators	MIGLYOL® Gel B, T, 840 B • DYNASAN® 110–118 • SOFTISAN® 645, 649
Skin-protective agent	SOFTIGEN® 701
Spreading agents	MIGLYOL® 812 N, 840

Rectal and vaginal preparations	Product
Suppository bases	WITEPSOL® (all grades)
Consistency regulators	MIGLYOL® Gel B, T, 840 B • DYNASAN® 110–118 • SOFTISAN® 645, 649
Crystallization initiators	DYNASAN® 116, 118
Dispersing agents	IMWITOR® 491, 900 K, 900 (F) P
Absorption promoters	IMWITOR® 308 NON-GMP, 742, 988
Protective agent	SOFTIGEN® 701

Oral preparations	Product
Retarding agents	SOFTISAN® 154 • DYNASAN® 110–118 • IMWITOR® 900 K, 900 (F) P
Tablet lubricants	DYNASAN® 110–118
Polishing agent	MIGLYOL® 812 N
Fatty bases	SOFTISAN® 154, 378
Oil components	MIGLYOL® 810 N, 812 N, 818, 829, 840
Dispersing agents	IMWITOR® 491, 900 K, 900 (F) P
Absorption promoters	IMWITOR® 308, 742, 988
Consistency regulators	SOFTISAN® 378

Injectable preparations (i.m., i.v., intramammary)	Product
Oil components	MIGLYOL® 810 N, 812 N
Lipid crystals	DYNASAN® 110–118

Eye and nasal preparations	Product
Fatty bases	SOFTISAN® 378, 601
Oil components	MIGLYOL® 810 N, 812 N, 818, 829, 840
Emulsifiers O/W	IMWITOR® 372 P, 375, 960 K
Emulsifiers W/O	IMWITOR® 491, 900 K, 900 (F) P

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