WITEPSOL®

Fatty bases for suppositories

CREMER Health

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CONTENTS

Abbreviations:

EP = European Pharmacopeia

JPE = Japanese Pharmaceutical Excipients

Ph. Eur. = European Pharmacopeia

USP-NF = United States Pharmacopeia-National Formulary

RECTAL THERAPY: HISTORY AND FUTURE

The application of remedies via the rectum can, just like peroral and external administration, be traced back to antiquity.

Diepgen reports that even the ancient Egyptians, ancient Indian physicians and the Mesopotamians used anal suppositories not only as laxatives, but also for the rectal treatment of pain, flatulence and heart spasms. The remedies were then 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.

In the middle ages, the rectal application of remedies faded somewhat into obscurity, even though a revival was noted at the medical school of Salerno in the 12th century. But Paracelsus still hardly used a suppository. Until the 18th century the enema was customary, perhaps due to purely commercial considerations by the physicians of the day.

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 lead to the vena cava inferior and thereby offered the possibility of introducing a large part of the rectally administered medicines directly into the blood circulation, bypassing the liver. With the introduction of cocoa butter as suppository base, systematic investigations could be carried out more readily than before.

The increase of the fund of medicines and the spreading of the knowledge that auxiliary materials 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 and compatibility problems between oxidation products (rancidity) and active compounds. Because of a very complex polymorphic nature cocoa butter is also unsuitable for effective machine production.

The development of suppository compounds based on glycerides of saturated fatty acids of coconut and palmkernel oils in the laboratories of Chemische Werke Witten (later part of Dynamit Nobel, HÜLS AG, CONDEA Chemie GmbH, Sasol Germany GmbH now part of CREMER OLEO GmbH & Co. KG) made it possible to process a substantially larger number of active compounds according to specific biopharmaceutical and technological aspects.

Hard fats based on glycerides of saturated C_{12}–C_{18} fatty acids are virtually ubiquitous nowadays because of their chemical and physical stability, their broad compatibility with nearly all active compounds, their neutrality towards mucous membranes and their favourable processing properties even in high performance machines.
Watersoluble vehicles (for example polyethylene glycols) are, not least because of their effect on mucous membranes, now only used in special cases (for example vaginal/ovular).

The fatty suppository bases are described in Pharmacopeiae as adeps solidus (European Pharmacopeia) or as hard

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RECTAL THERAPY: HISTORY AND FUTURE

fat (USP/NF). As a result of the many investigations and publications the tradename WITEPSOL has in the course of time already become a synonym for modern suppository compounds.

Scientific interest in rectal therapy is today focused on two areas. One is the liberation and absorption of active compounds from suppositories, particularly in respect of retardation aims and absorption promotion. The other is the opinion that use of this form of medicine for active compounds based on peptides, to which group many of the new materials now produced by gene technology belong, is a more patientfriendly alternative to injection.

Furthermore, improvements in manufacturing technology are also expected, so as to make the suppository casting procedure even easier and faster.

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Product range

For the preparation of an optimum 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 requirements in pharmaceutical technology, production and also in biopharmacy, so as to achieve the best possible effect in each case. To allow a better survey 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 nonionic 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 are hard fats with hydroxyl values up to 15. They consist mostly of triglycerides with a proportion 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 small tendency to the posthardening phenomenon (maximum 1.5 °C) (see page 35) and can be processed both with automatic casting machines and also 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 OHV 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	OHV = max. 3
WITEPSOL H 12	melting point 32–33.5 °C	OHV = 5–15

Compounds for suspension suppositories having a proportion of solid active compounds of below 25%		
WITEPSOL H 35	melting point 33.5–35.5 °C	OHV = max. 3
WITEPSOL H 5	melting point 34–36 °C	OHV = max. 5
WITEPSOL H 15	melting point 33.5–35.5 °C	OHV = 5–15

Compounds for suspension suppositories and lipophilic active compounds; for melting point correction		
WITEPSOL H 37	melting point 36–38 °C	OHV = max. 3
WITEPSOL H 185	melting point 38–39 °C	OHV = 5–15

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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	OHV = 40–50
WITEPSOL W 25	melting point 33.5–35.5 °C	OHV = 20–30
WITEPSOL W 35	melting point 33.5–35.5 °C	OHV = 40–50
WITEPSOL W 45	melting point 33.5–35.5 °C	OHV = 40–50
WITEPSOL W 31	melting point 35–37 °C	OHV = 25–35

WITEPSOL W 45 is a special grade which is characterized by a higher monoglyceride content 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 pharmacopeiaes.

They are used for the preparation of vaginal and rectal forms of medicines which require greater 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	OHV = 55–70
WITEPSOL S 55	melting point 33.5–35.5 °C	OHV = 50–65
WITEPSOL S 58	melting point 31.5–33.5 °C	OHV = 60–70

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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 or
- for the correction of melting point of low melting compounds.

They are characterized by melting point and hydroxyl value. WITEPSOL E 75 additionally contains Cera alba, Ph. Eur.

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

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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 palmkernel oils from tropical plantations.

After preliminary purification, the oils are cleaved into their fatty acids and glycerol by means of water at high pressure. The fatty acid mixture is subjected to catalytic hydrogenation with hydrogen and subsequently to fractional vacuum distillation and the low molecular weight caproic, caprylic and capric acids (C_6– C_{10}) are removed. The C_{12}– C_{18} fatty acids are adjusted to the correct mixture for the grade and are 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 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

The WITEPSOL S and E 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 decolourizing chemical additives which are not found in natural fats; it is produced without solvents and due to the production process means virtually no microorganisms are present.

Quality control

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

100% batch testing and central documentation ensure complete traceability of products.

On final release, the chemical parameters of fats according to the requirements of the European Pharmacopeia are determined.

A supply evaluation system, continuous microbiological monitoring of the products and production plants, long-term stability testing of reserve samples and further testing of properties relating to use back the guarantee that WITEPSOL is always of optimum pharmaceutical quality.

Test methods

The European Pharmacopeia (EP) requires the following tests for hard fat (Adeps solidus), these being described in the subsequent text:

Identification
Thin-layer chromatography (EP 2.2.27)

Purity tests	Requirements
Acid value (EP 2.5.1)	max. 0.5 mg KOH/g
Hydroxyl value (EP 2.5.3, Method A)	max. 50 mg KOH/g
Iodine value (EP 2.5.4)	max. 3g I_2 /100 g
Peroxide value (EP 2.5.5)	max. 3 meq O/kg
Saponification value (EP 2.5.6)	210–260 mg KOH/g
Unsaponifiable matter (EP 2.5.7)	max. 0.6%
Heavy metals (EP 2.4.8)	max. 10 ppm
Alkaline impurities (EP 2.4.19)	max. 0.15 ml 0.01 N HCI/2g
Ash (EP 2.4.16)	max. 0.05%
Melting point (EP 2.2.15)	30–45 °C

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Physical tests

Open-tube melting point

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

Procedure
5 glass capillaries open at both ends (80 mm long, 1.0–1.2 mm internal diameter) are filled with an approximately 10 mm high column of fat by brief dipping into molten WITEPSOL (see comments) and left to stand for 24 hours at, at most, 10 °C. The capillaries are fixed to a thermometer (graduated in 0.1 °C) at the level of the mercury bulb and dipped into a water bath. The distance between the lower ends of the fat columns and the bottom of the bath is 1 cm, the depth of water is 5 cm, and the heating rate is 1 °C/min. The average of 5 determinations is taken.

Comments
Fats are not chemically uniform substances with a sharp melting point. They consist of a range of chemically similar glycerides with some times very different melting points. The melting range which can he 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 timedependent. 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 above 60 °C 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 with various laboratories.

Test methods

Physical tests

Solidification point

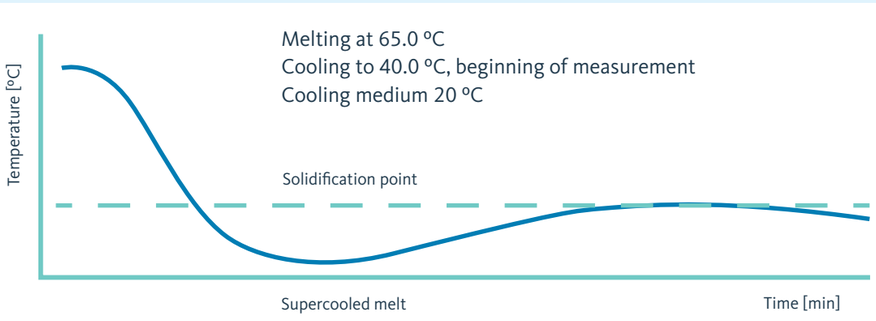
Definition
The solidification temperature is the highest temperature occurring during the solidification of a supercooled liquid.

Procedure
The apparatus described in the European Pharmacopeia 2.2.18, is filled with liquid WITEPSOL. As a guide, a preliminary experiment is carried out to determine the approximate solidification temperature by rapid cooling. Subsequently the material is heated up and allowed to cool slowly while stirring. The temperature is recorded at one minute intervals. The cooling curve normally passes through a minimum which indicates a supercooled melt. Heat is liberated during crystallization and the temperature-time curve rises. The maximum temperature in this phase is the solidification temperature.

Comments
An ideal cooling curve (figure 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 index of refraction 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)

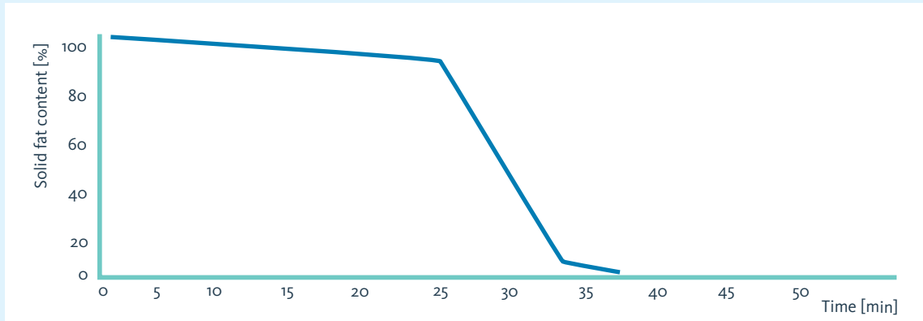
Definition
Percentage of solid glycerides in the fat mixture at a certain temperature.

Procedure
The most important methods for measuring the SFI are dilatation, differential thermal analysis and nuclear magnetic resonance spectroscopy (NMR).

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 (see figure 2, Table 1).

WITEPSOL meets this requirement, since low melting glycerides of C_8 / C_{10} 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	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	ca. 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 Pharmacopeia bases, containing special additives (beeswax, emulsifiers)

Thin-layer chromatography (TLC)

For the identification of hard fats the European Pharmacopeia 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 of hard fat.

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

TLC is also suitable for testing water soluble components (for example emulsifiers). For this purpose the sample must be shaken with water and separated by using a more polar eluent (for example 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 injected directly.

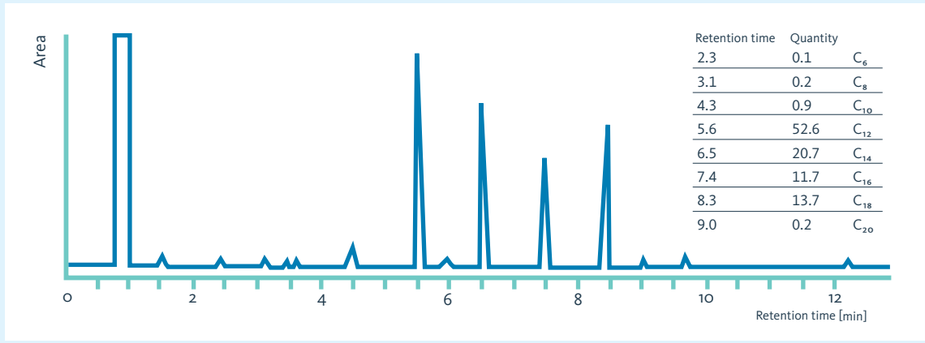
Column: Quartz-glass capillary (for example Carbowax chemically bound) 15–30 m, temperature program to 250 °C, injector/ detector (FID) temperature 320 °C.

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 C_6–C_{10} fatty acids originally present in the coconut/palmkernel oil are removed in the production of WITEPSOL suppository bases. The hardness and the grip-strength of suppositories are thus increased.

Higher melting WITEPSOL grades are distinguished from low melting ones by a displacement of the fatty acid spectrum towards palmitic (C_{16}) and stearic (C_{18}) acids.

Fig. 3: Fatty acid composition of WITEPSOL H 15



Test methods

Physical tests

Gas chromatography (GC)

II. Quantitative determination of glycerides in WITEPSOL

The fat sample is treated with acetic anhydride for 1 hour at 140°C, which acetylates the hydroxyl containing components but does not cleave the fatty acid glycerides. The mixture is injected directly (on column). Quartzglass capillary 5 m, temperature program to 375 °C.

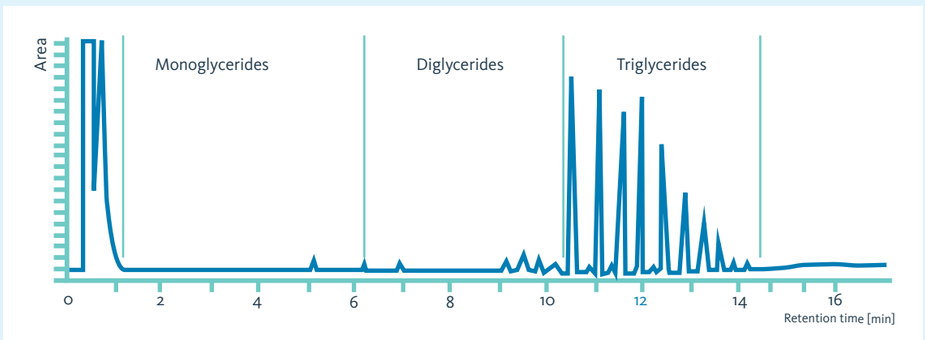
For the C_{12}–C_{18} fatty acids, glyceride peaks from C_{12} (monolaurate) to C_{54} (tristearate) can be expected.

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 (C_{36}–C_{54} monoglycerides (< 1%) and about 10% of diglycerides, corresponding to a hydroxyl value of about 10.

Higher hydroxyl values can be caused by more 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 partialglyceride containing W grades. S grades have, due to the emulsifier content, a slightly higher viscosity (see figure 5).

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

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

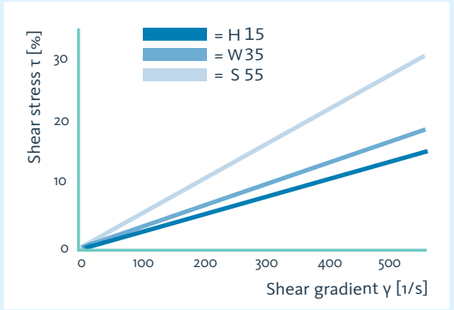
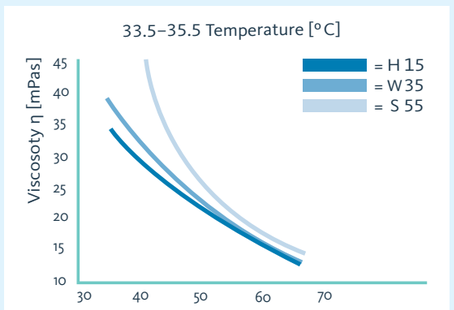
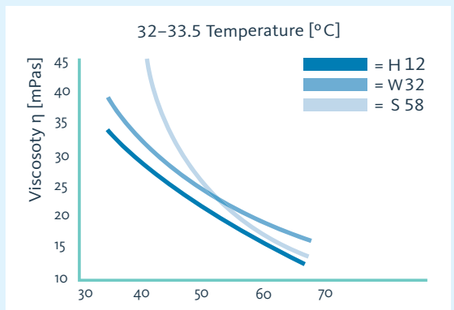


Fig. 5: Comparison of the rheological behaviour of pure WITEPSOL grades

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





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 Pharmacopeia.
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	
10°C	2.0	$\frac{J}{g \cdot K}$
20°C	2.4	
60°C	2.1	

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

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.

Procedure
5 g of WITEPSOL are dissolved in 50 ml of a previously neutralized 1:1 mixture of ether and ethanol, and quickly titrated after addition of phenolphthalein solution with 0.1 N KOH solution until the colour change persists for 15 seconds.

Calculation

$$AV = \frac{5.610 \times \text{titre of 0.1 N KOH in ml}}{\text{amount of WITEPSOL in g}}$$

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 in the hydrolysis of glycerides, the acid value is a measure of 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 (OHV)

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.

Procedure

The sample quantity prescribed in the European Pharmacopeia should be increased because of the low hydroxyl values:

Expected OHV	Sample quantity in g
0–10	12.0
10–15	8.0
15–20	6.0
20–25	4.5
25–30	4.0
30–40	3.0
40–50	2.5
50–100	2.0

The required quantity of material is weighed to an accuracy of ± 0.2% into a 250 ml long-necked flask and 5.0 ml of acetylation mixture (25.0 ml of acetic anhydride + pyridine to 100.00 ml) is added. The flask is provided with a funnel, immersed in a glycerol bath to a depth of 1 cm and left there for 1 hour at 95–100 °C with frequent swirling, After acetylation, 20 ml of a mixture of pyridine and water (4:1 v/v) is added via the funnel and the flask is placed in the glycerol bath for a further 10 minutes. It is then allowed to cool to room temperature, the funnel and neck of the flask are rinsed with 50 ml of methylene chloride, 3–5 drops of phenolphthalein (1% in ethanol) are added and the mixture is titrated with 0.5 N ethanolic KOH solution until the colour change remains for 10 seconds. The acid value of the sample must be determined separately, since it is included in this measurement; it can however be disregarded if it is less than 1% of the OHV.

Calculation

$$\text{OHV} = \frac{0.5 \times 56.11\ (b - a)^*}{\text{amount of WITEPSOL in g}}$$

Comments

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

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

- They alter 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. tendency for the melting point to increase on storage.
- They increase the viscosity of the molten fats.
- They have some surfactant properties: this can give 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.

Procedure

1.0 g of WITEPSOL is weighed to an accuracy of ± 0.1% into a 250 ml flask with ground glass stopper and is completely dissolved in 10 ml of methylene chloride. 25.0 ml of iodine mono-bromide solution (20.0 g of iodine monobromide made up to 1000.0 ml with glacial acetic acid) are added and the stoppered flask is allowed to stand in the dark for about 30 minutes with occasional shaking. After halogenation is complete, 10 ml of a 10% solution of potassium iodide and 100 ml of water are added and titrated with 0.1 N sodium thiosulphate solution with vigorous shaking until the yellow colour has almost disappeared; 2 ml of starch solution (1%) are then added and the solution is titrated until the colour has disappeared (n_1). A blank test is carried out under the same conditions (n_2)

Calculation

$$IV = \frac{1.269}{\text{amount of sample in g}} \times \text{titre in ml } (n_2 - n_1)$$

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 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, as determined by the method described below.

Procedure

5.0 g of WITEPSOL are weighed into a 250 ml flask with ground-glass stopper and dissolved in 30 ml of a mixture of glacial acetic acid and methylene chloride (3:2 v/v), 0.5 ml of saturated potassium iodide solution is added, the mixture is shaken for 1 minute, admixed with 30 ml of distilled water and titrated with 0.01 N sodium thiosulphate solution until the yellow colour has almost disappeared. After addition of 5 ml of starch solution (1%) it is titrated further until the colour has disappeared (n_1). A blank test is carried out under the same conditions (n_2)

Calculation

$$POV = \frac{10}{\text{amount of sample in g}} \times \text{titre in ml } (n_2 - n_1)$$

Comments

The IP is a clue of assessing the oxidative degradation of the fat. It determines, inter alia, hydroperoxides which are formed at the beginning of the reaction chain in the 2-position to double bonds present.

Since other materials and atmospheric oxygen can also oxidize I to I_2, the blank test is important.

The peroxide values of WITEPSOL are very low because of the product's saturated nature and its stability to 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.

4

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.

Procedure
2.0 g of WITEPSOL in a 250 ml flask with ground-glass stopper are saponified with 25.0 ml of 0.5 N ethanolic KOH solution for 30 minutes under reflux and titrated immediately with 0.5 N HCl against phenolphthalein (n_1). A blank test is carried out under the same conditions (n_2).

Calculation

$$SV = \frac{28.05}{\text{amount of sample in g}} \times \text{titre in ml } (n_2 - n_1)$$

Comments
In the case of WITEPSOL the acid value, which is also included in this measurement, is so small as to be of no importance.

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. A comparison of WITEPSOL with natural fats and oils (see survey) shows that the SV of WITEPSOL is substantially higher than for C_{16}/C_{18} rich fats, but somewhat lower than for the C_8/C_{10} containing coconut and palm kernel oil. WITEPSOL is a hydrogenated triglyceride in which the C_8/C_{10} components have been removed so that the suppositories retain sufficient stability of shape and a solid surface even when used at higher temperatures.

Unsaponifiable matter

Definition
Unsaponifiable matter consists of substances which can be extracted with organic solvents after saponification of the fat and which are not volatile at 100–105 °C.

Procedure
Extraction of the alkali-saponified sample with ether in accordance with the European Pharmacopeia.

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.

Heavy metals

Definition
Heavy metals are those elements which, under the prescribed conditions (Ph. Eur. method D 2.4.8), can be precipitated with thioacetamide as sulphides.

Procedure
2 g of hard fat are ignited with MgO at 800 °C, and the residue is taken up in HCl and precipitated with thioacetamide in buffered solution. The reference solution containing 10 ppm of lead is prepared in the same way. The brown coloration of the two samples is assessed visually.

Comments
The method often exhibits positive results which give a false impression, since ignition can be incomplete and there fore the solution can already be dark in colour prior to sulphide precipitation. The intention of the test is the recognition of toxic heavy metals, with lead as the guide material. However, non-toxic metals such as iron are also determined. In fat processing, metal catalysts are used, for example nickel in fat hydrogenation. In the production process for WITEPSOL, there are many procedures for removing traces of catalyst, such as distillation, scrubbing, filtration and adsorption processes, so that the values measured by means of atomic absorption spectroscopy are far below the limit prescribed by the European Pharmacopeia.

Test methods

Chemical tests

Iodine colour number (ICN)

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

Procedure
In elongated glass containers (e.g. test tubes 170 mm long, 25 mm in diameter) a clear melt of WITEPSOL is compared with a concentration series of I_2/KI standard solutions.

The standard solutions are prepared as follows: 10.0 g of KI and 1.00 g of I_2, are dissolved in 1000 ml of water. This stock solution has an ICN of 100, and can be diluted in accordance with the desired differentiation (e.g. 1:50, 1:20, 1:10 etc.). The concentrations can be checked by titration with 0.01 N thiosulphate solution.

A detailed work procedure is contained in the standard methods of the German Association for Fat Science (DGF, method C-IV 4a).

Comments
The colour 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 scrubbing.

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

Alkaline impurities

Definition
Alkaline components determined by neutralization with HCI.

Procedure
2 g of WITEPSOL are completely dissolved in a mixture of 1.5 ml of 96% ethanol and 3.0 ml of ether. After addition of 0.05 ml of bromophenol blue solution (0.05% in H_2O) the solution is titrated with 0.01 N HCI until the colour changes to yellow. A maximum of 0.15 ml are allowed to be consumed.

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 scrubbing procedures, WITEPSOL contains only traces of alkaline impurities.

Ash

Definition
Ash is taken to mean inorganic components which are not volatile at 600 °C.

Procedure
50 g of WITEPSOL are carefully ashed in a porcelain or platinum crucible over a Bunsen burner flame and the residue is ignited in a muffle furnace at 600 °C ± 25 °C for one hour. After cooling in a desiccator, the ash is weighed.

Water content

Definition
Percentage of H_2O in hard fat.

Procedure
Karl Fischer method (Ph. Eur. 2.5.12 method A).

Comments
Even small amounts of water can cause hydrolysis of fats, which is indicated by an increase in the acid value. WITEPSOL is dried in vacuum after refining. Its stability and long shelf life are, inter alia, due to its very low water content.

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 aluminium foils. Casting in metal moulds, with subsequent sealing in cellophane, plastic film or aluminium 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 with cocoa butter processing, WITEPSOL can be subjected to an initial heat treatment (sterilization or similar) without any noticeable effect on the solidification behaviour.

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

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The prerequisite is the following operating procedure:

1. Melting the compound above 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. Avoiding stationary zones within the product stream, since at such points rapidly increasing solidification can interrupt the flow, leading to an interruption to production.
6. The casting moulds 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 or 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 mould 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.

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 mould (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 moulds are completely ruled. 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. They must, if they are to be used further, be melted again and recast.

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 Pharmacopeia) and uniformity of content (+ 15% of the average content in accordance with 2.9.6 of the European Pharmacopeia)

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

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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 behaviour.

Disintegration

Suppositories and pessaries must melt in as short a time as possible after application. This avoids the sensation of a foreign body and rapidly releases the incorporated active ingredients to act locally or systemically. Testing of the melting behaviour of the finished drugform at body temperature is therefore an important criteria for quality. The measurement of the melting point by capillary does not always correlate with this. The measurement of the melting behaviour of a suppository should be carried out in as narrow a temperature range as possible, i.e. at 37 ± 0.1 °C. The test temperature of 36–37 °C prescribed in the European Pharmacopeia (2.9.2 – disintegration test for suppositories and pessaries) is too broad and is urgently in need of correction. The indicated test method is likewise urgently in need of revision, since it does not give a precisely determinable end point. Recommended methods are that using the suppository penetration tester PM 30 (by SOTAX), according to method 2.9.22 (Softening Time Determination Of Lipophilic Suppositories) of E.P., apparatus B. The testing of the melting behaviour of suppositories also serves to monitor the correct selection of the base. As already mentioned, the melting point is altered by the higher melting crystal modifications which are only slowly formed, which can lead to the desired complete melting time of at most 30 minutes at 37 + 0.1 °C being exceeded. Prior to the measurement, therefore, the suppositories should be maintained at a temperature of 26–28 °C. which leads to a rapid transformation of the unstable lowermelting crystal modifications present into their stable end form. The test is therefore carried out on freshly produced suppositories and then after at least 3 weeks under the above storage conditions.

Processing

Testing of suppositories

The effects of the active compounds can further intensify this 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 optimum melting time of the finished suppository.

Release of active ingredients in vitro

There are numerous methods used for testing the release of active ingredients, which has meant that the Pharmacopeiae still do not contain a procedure. The achievement of a good correlation between in vitro methods and the in vivo results in human beings is the aim. This correlation has so far been found extremely rarely after a critical assessment of all methods, the recommendation is for test arrangements in a closed system and without a membrane between the suppository and acceptor medium.

Challenges in suppository production

Cracks and flaking

Cracks (mostly longitudinal) are caused by stresses in the solid fat which arise from the different cooling rates at the exterior and within the moulding. This visible damage 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 mould 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 centre solidifies more slowly and draws as a result of its contraction, material from above into the core.

Mat 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) then this phenomenon – typical for fats – can usually not develop. It is therefore advantageous to use compounds having 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).

Post hardening

The melting point of cast suppositories can increase as a function of the fat type, the active ingredients, the method of production, 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.

To prevent stored suppositories from failing to melt in the rectum, account must be taken of the phenomenon in the initial formulation and the selection of fatty base. Ageing tests at elevated temperatures (e.g. 3–5 °C below the melting point) are necessary for the development of this form of administration.

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5

Processing

Challenges in suppository production

A stable end modification and a constant melting point can be produced as early as during manufacture by “pre-crystallizing” the molten batch of fat. Precrystallization, an indispensable process step in temperature control in the chocolate industry, is the formation and maintenance of a very high proportion of crystallized fat components in the melt. 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.

References

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

[1] Diepgen “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] Boschee, P. AND 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 (1196)]

Surveys

WITEPSOL

1. Description

Suppository bases according to the current monographs Hard Fat, Adeps solidus E.P. and Hard Fat USP-NF. They are white, odorless hard fats in pastill shape which comprises of glycerides of plant origin.

Method	Ascending melting point [°C] EP 2.2.15	Hydroxyl value [mg KOH/g] EP 2.5.3	Acid value [mg KOH/g] EP 2.5.1	Iodine value [g I_2/100 g] EP 2.5.4	Peroxide value [meq O/kg] EP 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 31	35.5–37.0	25–35	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*	ca. 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*	ca. 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					
EP	30–45	max. 50	max. 0.5	max. 3.0	max. 3
USP	27–44	max. 70	max. 1.0	max. 7.0	
JPE	30–45	max. 70	max. 2.0	max. 3.0	

2. Characteristic values

Each of the following products is characterized by 10 parameters. The sorting is oriented at the meaning for the suppository formulation.

Saponification value [mg KOH/g] EP 2.5.6	Alkaline [ml HCI/2g] EP 2.4.19	Heavy metals [ppm] EP 2.4.8	Ash [%] EP 2.4.16	Unsaponifiable matter [%] EP 2.5.7	Method
235–245	max. 0.15	max. 10	max. 0.05	max. 0.3	WITEPSOL H 5
240–255	max. 0.15	max. 10	max. 0.05	max. 0.3	WITEPSOL H 12
230–245	max. 0.15	max. 10	max. 0.05	max. 0.3	WITEPSOL H 15
230–240	max. 0.15	max. 10	max. 0.05	max. 0.3	WITEPSOL H 19*
240–250	max. 0.15	max. 10	max. 0.05	max. 0.3	WITEPSOL H 32
240–250	max. 0.15	max. 10	max. 0.05	max. 0.3	WITEPSOL H 35
225–245	max. 0.15	max. 10	max. 0.05	max. 0.3	WITEPSOL H 37
225–240	max. 0.15	max. 10	max. 0.05	max. 0.3	WITEPSOL W 25
225–240	max. 0.15	max. 10	max. 0.05	max. 0.5	WITEPSOL W 31
225–245	max. 0.15	max. 10	max. 0.05	max. 0.3	WITEPSOL W 32
225–235	max. 0.15	max. 10	max. 0.05	max. 0.3	WITEPSOL W 35
225–240	max. 0.15	max. 10	max. 0.05	max. 0.3	WITEPSOL W 45
215–230	max. 0.15	max. 10	max. 0.05	max. 0.5	WITEPSOL S 51*
215–230	max. 0.15	max. 10	max. 0.05	max. 2.0	WITEPSOL S 55*
215–225	max. 0.15	max. 10	max. 0.05	max. 2.0	WITEPSOL S 58*
220–230	max. 0.15	max. 10	max. 0.05	max. 3.0	WITEPSOL E 75*
220–230	max. 0.15	max. 10	max. 0.05	max. 0.5	WITEPSOL E 76
220–240	max. 0.15	max. 10	max. 0.05	max. 0.5	WITEPSOL E 85
210–260	max. 0.15	max. 10	max. 0.05	max. 0.6	EP
215–255	max. 0.15		max. 0.05	max. 3.0	USP
210–255				max. 3.0	JPE

* „WITEPSOL grades H19, S51, S55, S58 and E75 respectively are mixtures of Hard Fats (according to Ph. Eur.) and additives. Currently these products do not comply with Ph. Eur. requirements. However, EP prepare a new monograph – Hard Fat with Additives – which will hopefully be available in the near future."

** Due to additive beeswax the ascending melting points are hard to reproduce (adhesion at the glas capillary). The solidification points are more precisely. They are for WITEPSOL E 75 = 34–36,5 °C, for WITEPSOL S 55 = 28–33 °C.

Surveys

Excipients for the pharmaceutical industry

Applications and functions

Topical preparations	Product
Ointment base O/W	SOFTISAN® 601
Fatty bases	SOFTISAN® 154, 378
Oil components	MIGLYOL® 128, 810, 812, 818, 829, 1018
Emulsifiers O/W	IMWITOR® 372 P, 375, 960 K
Emulsifiers W/O	IMWITOR® 491, 600, 618, 900 K, 948, 990
Solubiliziers and wetting agents	SOFTIGEN® 767
Absorption promoters	IMWITOR® 308, 742, 988
Consistency and stability regulators	MIGLYOL® Gel B, T, 840 B • DYNASAN® 110–122 • SOFTISAN® 645, 649
Skin protective agent	SOFTIGEN® 701
Spreading agents	MIGLYOL® 812, 840

Rectal and vaginal preparations	Product
Suppository bases	WITEPSOL® (all grades)
Consistency regulators	MIGLYOL® Gel B, T, 840 B • DYNASAN® 110–122 • SOFTISAN® 645, 649
Crystallization initiators	DYNASAN® 116, 118, 122
Dispersing agents	IMWITOR® 491, 900 K
Absorption promoters	IMWITOR® 308, 742, 988
Protective agent	SOFTIGEN® 701

Oral preparations	Product
Retarding agents	SOFTISAN® 154 • DYNASAN® 110–122 • IMWITOR® 900 K
Tablet lubricants	DYNASAN® 110–122
Polishing agent	MIGLYOL® 812
Fatty bases	SOFTISAN® 154, 378
Oil components	MIGLYOL® 810, 812, 818, 829, 840
Dispersing agents	IMWITOR® 491, 900 K
Absorption promoters	IMWITOR® 308, 742, 988
Consistency regulators	SOFTISAN® 378

Excipients for the pharmaceutical industry

Applications and functions

Injectable preparations (i.m. i.v. intramammary)	Product
Oil components	MIGLYOL® 810, 812
Lipid crystals	DYNASAN® 110–122

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

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Surveys

Typical fatty acid composition of natural fats and oils (in %)

	Cocoa butter	Coconut oil	Palmkernel oil	Peanut oil	Olive oil	Soybean oil	Wheatgerm oil	Sunflower oil	Cottonseed oil	Beef tallow	Lard	Sardineoil
Iodine value [g I_2/100g]	33–42	7–12	10–20	85–105	75–90	117–140	115–130	115–140	96–118	35–50	48–65	150–190
Saponification value [mg KOH/g]	192–197	245–265	188–195	186–198	188–195	185–195	185–195	185–195	190–198	190–200	195–202	185–195
$C_{6.0}$	–	0–1	0–1	–	–	–	–	–	–	–	–	–
$C_{8.0}$	–	3–15	2–6	–	–	–	–	–	–	–	–	–
$C_{10.0}$	–	3–15	3–7	–	–	–	–	–	–	–	–	–
$C_{12.0}$	< 0.1	41–56	41–55	–	–	–	–	–	–	–	–	–
$C_{14.0}$	< 0.2	13–23	14–20	0–1	–	–	–	0–1	0–1	2–7	0–3	4–6
$C_{16.0}$	23–33	4–12	6–11	1–16	7–20	3–14	10–20	3–10	17–31	17–37	20–32	9–14
$C_{18.0}$	30–39	1–5	1–3	1–6	1–3	1–5	1–6	1–10	1–4	6–40	5–24	1–3
$C_{16.1}$	< 1	–	–	0–1	0–2	–	0–1	0–1	0–1	1–5	1–5	10–15
$C_{18.1}$	28–38	3–12	10–23	35–72	56–83	19–30	13–30	14–65	13–44	26–50	35–62	10–24
$C_{18.2}$	2–4	1–4	1–5	13–45	3–20	44–62	44–65	20–75	33–59	1–3	3–16	10–24
$C_{18.3}$	< 1	–	–	0–1	0–2	4–11	2–13	0–1	1–2	1–2	0–1	10–24
$C_{20.0}$	< 1	–	–	2–9	0–1	1–3	0–1	1–2	0–2	0–2	0–2	20–50
$C_{15/17}$	< 0.1	–	–	< 0.2	–	< 0.1	< 0.1	–	< 0.2	1–3	0–1	–

CREMER Health
Compliant with nature

7

WITEPSOL

Hard Fat recommendations for Active Pharmaceutical Ingredients

WITEPSOL H 15 / W 35
Actives for malaria treatment
Anesthetics
Anti inflammatory substances
Antidepressants (alkaloids)
Antiemetics
Antiepileptica (barbiturates)
B-Vitamins
β-Lactam Antibiotics
Broncho dilatators
Expectorants
Male hormons
Non steroidal antirheumatics
Steroidal antirheumatics (corticosteroids)

WITEPSOL W 45
Actives for hemorrhoidal treatment
Anti inflammatory substances for morbus crohn treatment and related indications
Antimycotics
β-Lactam Antibiotics
Laxatives
Non steroidal antirheumatics
Opioids such as Tramadol and related substances

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

WITEPSOL S 51 / S 58
Female hormons
Spermicides

CREMER Health
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